International Journal of Clinical Urology
2022; 6(2): 95-113
http://www.sciencepublishinggroup.com/j/ijcu
doi: 10.11648/j.ijcu.20220602.16
ISSN: 2640-1320 (Print); ISSN: 2640-1355 (Online)

A Detailed Analysis of a Pharmacokinetic Model for Testopel® Implants

David T. Seitman M. S. BME, M. D.[1, *], Joe J. Fallon M. D.[2]

[1]Retired Anesthesiologist, Galloway, NJ, United States

[2]Department of Medicine, Rowan University, Stratford, NJ, United States

Email address:

seitmand@comcast.net (David T. Seitman), jjfjr426@aol.com (Joe J. Fallon)

[*]Corresponding author

To cite this article:

David T. Seitman M. S. BME, M. D., Joe J. Fallon M. D. A Detailed Analysis of a Pharmacokinetic Model for Testopel® Implants. *International Journal of Clinical Urology*. Vol. 6, No. 2, 2022, pp. 95-113. doi: 10.11648/j.ijcu.20220602.16

Received: September 1, 2022; **Accepted**: October 12, 2022; **Published**: October 29, 2022

Abstract: A novel pharmacokinetic model used to titrate therapy for implantable testosterone pellets (Testopel®) in a clinical patient is presented. The model accurately reflects measurements by the Esoterix Laboratory's serum testosterone assay. The difference between the model's predictions and the measured levels were clinically insignificant (mean absolute % difference = 2.9%, mean % difference = 0.40%, SD = 4.6%, n = 9), during the early, development phase of the model, and remained small (mean absolute % difference = 5.2%, mean % difference = -1.3%, SD = 7.7%, n = 13) even when newer data points were included. The model was used to predict the peak (900-1100 ng/dL), trough (>300 ng/dL), and average total serum testosterone levels at steady state. Subsequently, the model was used to alter the treatment regimen to yield a specific average serum testosterone level ("area under the curve" ~600 ng/dL), to keep the serum peak under a target amount (<800 ng/dL), and to keep the serum trough above a certain amount (> 400 ng/dL). Targeted levels were reached by the next cycle of Testopel® therapy. This represents the first time such a close correlation between a predicted and a measured serum testosterone has been shown using any assay. Because of the accuracy of the model, the authors recommend using it to provide a quantitative approach to the initiation and maintenance of Testopel® therapy instead of the traditional, more qualitative trial-and-error technique. Clinicians can now target average, peak, and trough testosterone levels and we can reach those levels by the second cycle of therapy. It is likely the model can be extended to aid treatment with implantable testosterone pellets other than Testopel®. This paper presents a detailed analysis of our pharmacokinetic model and its usage as a clinical aid.

Keywords: Testosterone Implant, Implantation, Testopel® Pharmacokinetic Model, Testosterone Supplementation, Total Serum Testosterone, Steady State Levels

1. Introduction

The number of men over age 30 taking testosterone supplements has varied widely over the past few years [1]. Approximately 3.1% to 7.0% of men aged 70 years and approximately 18.4% of men older than 70 require testosterone supplements because of late onset hypogonadism [2].

Our ability to assess the need for treatment and to monitor the therapy is dependent upon the accuracy and reproducibility of the assays measuring the serum testosterone levels. Recently, the CDC endorsed certain assays believed to be more accurate and more consistent than others [3-6].

Implantable testosterone (75mg) pellets (Testopel®, Endo Pharmaceuticals, Inc., Malvern, PA 19355 USA), were approved by the FDA in 1972 without any pharmacokinetic studies to support the use of the pellets. The product was not actively marketed until 2008. To date, only a few studies looking at the pharmacokinetics have been published [7].

We present a pharmacokinetic model which has recently been validated using real-time patient data [8]. Although this model has been validated with data from only one patient, the predicted data is as reliable as the accuracy of the assays used, which implies real-time accuracy of the model. This model provides a quantitative approach to testosterone therapy. To our knowledge, there are no validated pharmacokinetic models for Testopel® absorption and elimination which predict values as close as our model.

Therapy can now reach targeted testosterone peak, trough, and average levels more efficiently and accurately compared with the current, more qualitative (check-level-and-guess at next dose) approach.

2. Methods

2.1. The Model

The authors modified a classic two-compartment model to represent the pharmacokinetics of testosterone (Testopel®) absorption and elimination [Figure 1]. In a classic two-compartment model, drug is inserted into a central compartment and from there redistributes into a peripheral compartment [9]. Our model takes into account an initial absorption of testosterone from the pellet depot into the central circulation and then its elimination from the body. Both processes are assumed to follow first order kinetics, which means that the rates of absorption and elimination are determined by the concentration differences between the appropriate compartments.

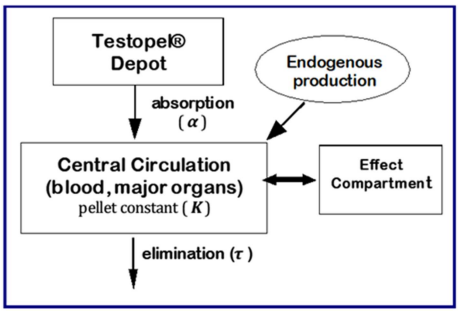

Figure 1. *Testopel® Multi-compartment Model.*

The Effect Compartment is shown for completeness, as it has no influence on the model's pharmacokinetic calculations. The endogenous contribution adds testosterone to the central compartment in a manner described later.

2.2. Model Parameters

The model has three adjustable parameters: the absorption time constant (**α**), the elimination time constant (**τ**), and the pellet constant (***K***). The absorption time constant (**α**) and the elimination time constant (**τ**) are related to their corresponding half-lives, the time it takes in days for half the testosterone to be absorbed from the pellet depot or to be eliminated from the body. The time constant multiplied by ln (2) (approximately 0.693) equals the corresponding half-life. For the purposes of this paper and unless otherwise stated, all **α** and **τ** parameters are shown as time constants, not as half-lives. In addition, all parameters are assumed empirically to have no more than three digits of precision. In actual practice, these parameters would not be expected to have more than two digits of precision.

The pellet constant (***K***) determines the relationship between the serum testosterone concentration and each pellet. The units for this constant are ng/dL/pellet. This constant is probably a function of the patient's weight or Body Mass Index (BMI), and is classically related to the volume of distribution of the testosterone. Because all data comes from one patient, the exact relationship has not been explored.

Under ideal conditions to validate the model, multiple serum testosterone levels would be obtained over numerous cycles using multiple patients. Because of time constraints, data was accumulated from only one patient. The initial data was used as a "training set" to determine the parameters (**α**, **τ**, ***K***) which fit the data best. Subsequent measurements were compared to the model's predictions, and an analysis of the predictions followed.

Because testosterone therapy was started before plans for a formal study were created, data was obtained retrospective to or concurrent with the analysis. Initial parameters were estimated after nine reliable measurements had been obtained. The testosterone levels predicted and the values measured in the laboratory were closer than expected, and clinically indistinguishable from each other. A case report was generated [8] and plans to generate a training set were then formalized.

When fitting a model, it is standard procedure to minimize the sum of the squares of the difference between the predicted values and the measured values (***SSE***). This process is well-described when the model's equations can be solved to calculate the parameters from the measured values, but requires computer assistance otherwise [9]. Because of the double exponential terms in the model's equations, there is no quick "reverse" solution such as might be found when performing standard linear regression. An often-used "trick" to use the logarithm of the values (in an effort to linearize the relationship) will not work here either. Luckily, we were able to minimize the ***SSE*** via a computer spreadsheet which varied tentative values of the parameters in a methodical fashion until the best values were determined.

The ***SSE*** is defined mathematically as

$$SSE = \sum_{0}^{m-1} \left(ST_{measured} - ST_{predicted} \right)^2 \Big/ m \qquad (1)$$

where: ***m*** is the number of data points used,

ST is the measured or predicted serum testosterone level

A Corel® Quattro Pro X7 or X8 spreadsheet macro was used to determine the best parameters. The parameters with a minimum ***SSE*** were assumed to be the best parameters.

More details on the use of this macro can be found in Appendix A, and confirmation of the validity of the macro can be found in Appendix B.

Once parameters were chosen, the model's primary equation (see below) was used to predict the daily serum testosterone levels, the trough values of each cycle, the peak values of each cycle, and the average levels of each cycle. A spreadsheet is especially suited to compute the day-to-day and cycle-to-cycle serum testosterone levels, especially when therapy is altered by changing the interval between implantations (***T***) and/or the number of pellets inserted (***n***) for each cycle. All the model's equations derived below were verified with day-to-day calculations from the spreadsheet.

Steady state conditions are expected after multiple, regularly scheduled pellet implantations. It is possible to

derive equations specifically for steady state conditions. Equations predicting the steady state values such as daily levels, the trough value, the peak value, and the average serum level eliminate the need for day-to-day spreadsheet computations. These values are the targets of personalized, long-term testosterone therapy.

2.3. Daily Serum Levels

The model's primary equation computes the daily serum testosterone level ($\boldsymbol{ST}_{\text{predicted}}(\boldsymbol{t})$). The serum level on day $\boldsymbol{t}$ arises from a few sources. It is the sum of the contribution from the most recent implantation ($\boldsymbol{ST_0}$), the contributions from all previous implantations ($\boldsymbol{ST_1} + \boldsymbol{ST_2} + \boldsymbol{ST_3}$ + etc.), and the patient's endogenous production (if any).

According to the model, if $\boldsymbol{n}$ pellets are placed into the pellet compartment on day 0, the increase in the serum level of testosterone due to that (one) implantation is:

$$ST_0(t) = K \cdot n \cdot e^{-t/\tau} \cdot (1 - e^{-t/\alpha}) \tag{2}$$

where: $\boldsymbol{ST_0(t)}$ is the total serum testosterone level as a function of time $\boldsymbol{t}$,

$\boldsymbol{K}$ is a constant relating pellet dosage (75mg/pellet) to the serum level (ng/dL) for each patient,

$\boldsymbol{n}$ is the number of pellets inserted,

$\boldsymbol{\tau}$ is related to the elimination half-life from the central compartment (circulating blood), and

$\boldsymbol{\alpha}$ is related to the absorption half-life from the pellet compartment to the central compartment.

Similarly, the serum contribution from $\boldsymbol{n}$ pellets inserted $\boldsymbol{t}$+$\boldsymbol{T}$ days ago (where $\boldsymbol{T}$ is the interval in days between this implantation and the most recent previous implantation) is:

$$ST_1(t) = ST_0(t+T) = K \cdot n \cdot e^{-(t+T)/\tau} \cdot (1 - e^{-(t+T)/\alpha})$$

If the interval between implantations is the same, the serum contribution from $\boldsymbol{n}$ pellets inserted two cycles ($\boldsymbol{t}$+2$\boldsymbol{T}$ days) ago is:

$$ST_2(t) = ST_0(t+2T) = K \cdot n \cdot e^{-(t+2T)/\tau} \cdot (1 - e^{-(t+2T)/\alpha})$$

A baseline level ($\boldsymbol{BL}$) is measured before any therapy is instituted, and the patient's ability to generate this level is assumed to not change during the course of therapy. The $\boldsymbol{BL}$ represents the maximal possible endogenous testosterone contribution ($\boldsymbol{EC(t)}$).

The endogenous testosterone production drops to zero when therapy increases the serum testosterone to the suppression level ($\boldsymbol{SL}$). The suppression level was arbitrarily set at twice the baseline level. Furthermore, it was assumed that the dose-response relationship was linear with a delay of one day.

Mathematically, this can be expressed as:

$$EC(t) = \left(1 - \min\left[\frac{ST(t-1)}{SL}, 1\right]\right) \cdot BL \tag{3}$$

where: $\boldsymbol{t}$ is the number of days since the last implantation,

$\boldsymbol{ST}$ is the serum testosterone level due to the pellets.

2.4. Steady State Levels

The goal of therapy is to achieve reliable and repeatable levels as soon as possible after treatment is started. At steady state, the testosterone levels are exactly the same for each cycle, although in clinical practice, there will always be some variation from cycle to cycle.

In engineering realms, a steady state is deemed to be reached after 5 half-lives, because the value is (theoretically) within about 3% of the "true" endpoint. However, in clinical medicine, such accuracy is often impossible to achieve, and a better estimate of the time needed to reach a final or steady state hormone level is about 4 half-lives. After 4 half-lives, the level is 93.75% of the theoretical final value, and it is likely to be indistinguishable from the final value. Note that after 3 half-lives, the level achieved is only 87.5% of the final value, and it probably will be recognized as different from the target value.

If steady state conditions exist, the serum level on any day in the cycle can be calculated as follows:

$$\begin{aligned}
ST_{predicted}(t) &= ST_0(t) + ST_1(t) + ST_2(t) + \ldots + EC(t) \\
&= K \cdot n \cdot e^{-t/\tau} \cdot \left(1 - e^{-t/\alpha}\right) + K \cdot n \cdot e^{-(t+T)/\tau} \cdot \left(1 - e^{-(t+T)/\alpha}\right) \\
&\quad + K \cdot n \cdot e^{-(t+2T)/\tau} \cdot \left(1 - e^{-(t+2T)/\alpha}\right) + \ldots + EC(t) \\
&= K \cdot n \cdot e^{-t/\tau} \cdot \left[1 + e^{-T/\tau} + e^{-2T/\tau} + e^{-3T/\tau} + \ldots\right] \\
&\quad - K \cdot n \cdot e^{-t\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} \cdot \left[1 + e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} + e^{-2T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} + e^{-3T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} + \ldots\right] + EC(t) \\
&= K \cdot n \cdot e^{-t/\tau} / \left(1 - e^{-T/\tau}\right) - K \cdot n \cdot e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} / \left(1 - e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) + EC(t)
\end{aligned} \tag{4}$$

See note 1 to clarify how this was reduced. [1]

For ease of this and future computations, let's introduce two new constants, $\boldsymbol{C}$ and $\boldsymbol{D}$:

$$C = 1 - e^{-T/\tau}$$

$$D = 1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}$$

and three new variables, $\boldsymbol{U(t)}$, $\boldsymbol{V(t)}$, and $\boldsymbol{W(t)}$:

$$U(t) = e^{-t/\alpha}$$

$$U(t)^{\alpha/\tau} = V(t) = e^{-t/\tau}, \quad where\ C = 1 - V(T)$$

$$U(t) \cdot V(t) = W(t) = e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}, \quad where\ D = 1 - W(T)$$

Rewriting (4), the equation for the predicted serum levels at steady state,

---

1 Note 1: To reduce this infinite series of exponential terms into a simple equation, set

$$X = 1 + e^{-T/\tau} + e^{-2T/\tau} + e^{-3T/\tau} + \ldots, \quad now\ multiply\ by\ e^{-T/\tau}$$

$$X \cdot e^{-T/\tau} = \quad e^{-T/\tau} + e^{-2T/\tau} + e^{-3T/\tau} + \ldots, \quad now\ subtract$$

$$X \cdot \left(1 - e^{-T/\tau}\right) = 1, \quad therefore,$$

$$1/\left(1 - e^{-T/\tau}\right) = 1 + e^{-T/\tau} + e^{-2T/\tau} + e^{-3T/\tau} + \ldots, \quad Similarly,$$

$$1/\left(1 - e^{-T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}\right) = 1 + e^{-T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)} + e^{-2T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)} + e^{-3T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)} + \ldots$$

$$ST_{predicted}(t) = K \cdot n \cdot V(t) / C - K \cdot n \cdot W(t) / D + EC(t) \quad (5)$$

Alternatively, this equation can be rewritten as:

$$ST_{predicted}(t) = \frac{K \cdot n \cdot V(t) \cdot \left(D - CU(t)\right)}{C \cdot D} + EC(t)$$

Calculating the peak, trough, and average serum levels are relatively easy for the first-time pellet recipient and for the patient who has reached steady state (after four cycles). Spreadsheet modeling is needed to compute the levels during the interim cycles before a steady state is reached or when the therapy regimen is changing.

2.5. Trough Level

The trough level is measured just prior to implanting new pellets. It is also the baseline level present before any therapy is started. $\boldsymbol{BL}=\boldsymbol{EC}(0)$.

The trough level at the end of the first cycle is $\boldsymbol{ST_0(T)} + \boldsymbol{EC(T)}$. Successive trough levels are closer and closer to the steady state trough level.

The steady state trough level can be calculated explicitly. At steady state after 4 cycles, successive trough levels are essentially equal. Therefore, $\boldsymbol{ST_{predicted}}(4\boldsymbol{T}) = \boldsymbol{ST_{predicted}}(5\boldsymbol{T})$ and it should be obvious that $\boldsymbol{EC}(4\boldsymbol{T}) = \boldsymbol{EC}(5\boldsymbol{T})$ also. The trough value at steady state comes directly from (5),

$$\begin{aligned}
ST_{predicted}(0) &= ST_{predicted}(T) \\
&= K \cdot n \cdot V(T) / C - K \cdot n \cdot W(T) / D + EC(T) \\
\text{for } t = 0,\ ST &= K \cdot n \cdot \left[\frac{D - C}{C \cdot D}\right] + EC(0) = K \cdot n \cdot \left[\frac{1}{C} - \frac{1}{D}\right] + EC(0) \\
\text{for } t = T,\ ST &= K \cdot n \cdot \left[\frac{\left(1 - e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) \cdot e^{-T/\tau} - \left(1 - e^{-T/\tau}\right) \cdot e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}}{C \cdot D}\right] + EC(T) \\
&= K \cdot n \cdot \left[\frac{e^{-T/\tau} - e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}}{\left(1 - e^{-T/\tau}\right) \cdot \left(1 - e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right)}\right] + EC(T) \\
&= K \cdot n \cdot \left[\frac{D - C}{C \cdot D}\right] + EC(0)
\end{aligned} \quad (6)$$

Recognizing that the quantity $e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}$ is a very small number and it can be ignored, the value for the trough level can be approximated as:

$$ST_{predicted}(T) \approx K \cdot n \cdot e^{-T/\tau} \Big/ \left(1 - e^{-T/\tau}\right) + EC(T) \quad (7)$$

To calculate $\boldsymbol{EC}(\boldsymbol{T})$, the pellet contribution on day $\boldsymbol{T}$-1 must be calculated. Using the same approximation as above,

$$ST_{predicted}(T-1) \approx K \cdot n \cdot e^{-(T-1)/\tau} \Big/ \left(1 - e^{-T/\tau}\right)$$

We can now substitute for $\boldsymbol{EC}(\boldsymbol{T})$ to complete (7) above.

$$ST_{predicted}(T) \approx K \cdot n \cdot e^{-T/\tau} \Big/ \left(1 - e^{-T/\tau}\right) + \left(1 - \min\left[\frac{K \cdot n \cdot e^{-(T-1)/\tau}}{SL \cdot \left(1 - e^{-T/\tau}\right)}, 1\right]\right) \cdot BL \quad (8)$$

2.6. Peak Level

The peak value is found on the day when the slope of the serum level vs. time curve equals 0. The peak value is likely above the $\boldsymbol{SL}$ and, therefore, we will assume that there is no endogenous testosterone production at peak.

Therefore, when therapy is first initiated, the peak day occurs when the derivative of (2) with respect to time equals zero.

$$\begin{aligned}
0 = \frac{dST_0(t)}{dt} &= \frac{d\left[K \cdot n \cdot V(t) \cdot \left(1 - U(t)\right)\right]}{dt} \\
&= K \cdot n \cdot \frac{d\left[e^{-t/\tau} \cdot \left(1 - e^{-t/\alpha}\right)\right]}{dt} \\
&= -\frac{1}{\tau} \cdot e^{\frac{-t}{\tau}} + \left(\frac{1}{\tau} + \frac{1}{\alpha}\right) \cdot e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} \\
\alpha \cdot e^{\frac{-t}{\tau}} &= (\alpha + \tau) \cdot e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} \quad \text{, now multiply by } \frac{e^{+t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}}{\alpha} \\
e^{t/\alpha} &= (\alpha + \tau)/\alpha \\
t &= \alpha \cdot \ln\left[\frac{\alpha + \tau}{\alpha}\right]
\end{aligned} \quad (9)$$

At steady state, the peak day will occur slightly earlier. Setting the derivative of (7), the $\boldsymbol{ST_{predicted}}$ curve, to zero, and solving for day $\boldsymbol{t}$ will determine the peak day. Note that

$$\frac{dV}{dt} = -\frac{1}{\tau} \cdot V \quad \text{and} \quad \frac{dW}{dt} = -\left(\frac{\alpha + \tau}{\alpha \cdot \tau}\right) \cdot W$$

therefore,

$$\begin{aligned}
0 = \frac{dST_{predicted}}{dt} &= \frac{d\left(K \cdot n \cdot (V/C - W/D)\right)}{dt} \\
&= K \cdot n \cdot \frac{d(V/C - W/D)}{dt} \\
&= -\frac{V}{\tau \cdot C} + \left(\frac{\alpha + \tau}{\alpha \cdot \tau}\right)\frac{W}{D} \\
&= -\frac{1}{\tau} \cdot e^{-t/\tau} \Big/ \left(1 - e^{-T/\tau}\right) + \left(\frac{\alpha + \tau}{\alpha \cdot \tau}\right) e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} \Big/ \left(1 - e^{-T\cdot\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) \\
&\quad \textit{Now multiply by } \alpha \cdot \tau \cdot \left(1 - e^{-T/\tau}\right) \cdot \left(1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) \\
0 = -\alpha \cdot 0 &= -\alpha \cdot \left(1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) \cdot e^{-t/\tau} + \left(1 - e^{-T/\tau}\right) \cdot (\alpha + \tau) \cdot e^{-t\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)} \\
0 &= -\alpha \cdot \left(1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) + \left(1 - e^{-T/\tau}\right) \cdot (\alpha + \tau) \cdot e^{-t/\alpha} \\
e^{t/\alpha} &= \left(1 - e^{-T/\tau}\right) \cdot \left(\frac{\alpha + \tau}{\alpha}\right) \Big/ \left(1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right) \\
t &= \alpha \cdot \ln\left[\left(1 - e^{-T/\tau}\right) \cdot \left(\frac{\alpha + \tau}{\alpha}\right) \Big/ \left(1 - e^{-T\left(\frac{1}{\tau}+\frac{1}{\alpha}\right)}\right)\right] \\
t_{peak} &= \alpha \cdot \ln\left[\frac{C}{D} \cdot \left(\frac{\alpha + \tau}{\alpha}\right)\right]
\end{aligned} \quad (10)$$

The peak value is calculated by inserting the peak day computed from (10) into (5), the equation for the predicted serum testosterone. The endogenous contribution can be ignored, as the peak value will likely be above the suppression level.

$$ST\left(\alpha\cdot\ln\left[\left(C\cdot(1+\tau/\alpha)/D\right)\right]\right) = K\cdot n\cdot e^{-\frac{\alpha}{\tau}\ln\left[\left(C\cdot(1+\tau/\alpha)/D\right)\right]}\cdot\left(\frac{1}{C}-\frac{e^{-\ln\left[\left(C\cdot(1+\tau/\alpha)/D\right)\right]}}{D}\right)$$

$$= K\cdot n\cdot\left[\frac{D}{C}\left(\frac{\alpha}{\tau+\alpha}\right)\right]^{\frac{\alpha}{\tau}}\cdot\left(\frac{1}{C}-\frac{1}{C}\left(\frac{\alpha}{\tau+\alpha}\right)\right)$$

$$ST_{peak} = \frac{K\cdot n}{C}\cdot\left(\frac{\tau}{\tau+\alpha}\right)\cdot\left[\frac{D}{C}\left(\frac{\alpha}{\tau+\alpha}\right)\right]^{\frac{\alpha}{\tau}} \qquad (11)$$

2.7. Average Level

In clinical practice, our primary concern is usually the average level, and the goal of therapy is to reach a targeted level under steady state conditions as soon as possible. The average value is easily determined using a spreadsheet to compute the daily serum levels for a complete cycle, finding the area under this curve, and dividing by the maintenance interval ***T***.

The equations to determine the average value will be shown below; appropriate approximations are used when necessary. The average testosterone level (***ST$_{avg}$***) is calculated by taking the integral of the equation for ***ST$_{predicted}$*** and dividing by ***T***. Looking solely at the pellet contribution during steady state, and ignoring (momentarily) the endogenous contribution, the ***ST$_{avg}$*** is:

$$ST_{avg} = \frac{1}{T}\cdot\int_{t=0}^{T} ST(t)dt$$

$$= \frac{1}{T}\cdot\int_{t=0}^{T}\left[ST_0(t)+ST_1(t)+ST_2(t)+\ldots\right]dt$$

$$= \frac{1}{T}\cdot\int_{t=0}^{\infty} K\cdot n\cdot e^{-t/\tau}\cdot(1-e^{-t/\alpha})dt$$

$$= \frac{K\cdot n}{T}\cdot\left[\left(-\tau\cdot e^{-t/\tau}\right]_0^{\infty}-\left(\frac{-\alpha\cdot\tau}{\alpha+\tau}\cdot e^{-t\left(1/\tau+1/\alpha\right)}\right]_0^{\infty}\right]$$

$$= \frac{K\cdot n}{T}\cdot\left(\tau-\left(\alpha\cdot\tau/(\alpha+\tau)\right)\right)$$

$$= \frac{K\cdot n\cdot\tau^2}{T\cdot(\alpha+\tau)} \qquad (12)$$

This equation implies that when the serum level is above the suppression level (***SL***) for an entire cycle, the average level is directly proportional to ***n***, the number of pellets inserted, and inversely proportional to ***T***, the time interval between insertions. This assertion makes sense as the Law of Conservation of Mass dictates that all the testosterone put into the patient will eventually be metabolized or removed after passing through the central circulation compartment.

The equation to compute the average serum level must be modified to include possible endogenous production. To calculate the endogenous testosterone contribution to the average serum level at steady state, the two specific days when the serum levels equal the ***SL*** must be identified. Define these days as follows:

t$_a$: the day after the peak when the serum level first drops below the ***SL***

t$_b$: the day before the peak when the serum level first exceeds the ***SL***

The integral of the ***EC(t)*** between these two days represents the endogenous contribution. This value is added to the area $\boldsymbol{K\cdot n\cdot\tau^2/(\alpha+\tau)}$ previously calculated by (12), and the total is divided by ***T*** to determine the true average level.

It does not seem possible to obtain an explicit equation for ***t$_a$*** and ***t$_b$***, even though their values are easily computed in a spreadsheet using an iterative equation. The value for ***t$_a$*** or ***t$_b$*** can be calculated by starting with an initial estimate (***t$_0$***) and then solving for ***t$_1$***, ***t$_2$***, ***t$_3$***, ... ***t$_n$***. A judicious choice for ***t$_0$*** significantly reduces the number of iterations needed. When the difference between ***t$_{n-1}$*** and ***t$_n$*** is arbitrarily small, then the value of ***t$_n$*** is arbitrarily close to the actual value of ***t$_a$*** or ***t$_b$***.

To calculate ***t$_a$*** on a computer using an iterative equation, solve (5) for ***V(t)***.

$$V(t_a) = e^{-t_n/\tau} = \frac{C\cdot D\cdot SL}{K\cdot n\cdot\left(D-C\cdot U(t_a)\right)}$$

$$t_{n+1} = -\tau\cdot\ln\left[\frac{C\cdot D\cdot SL}{K\cdot n\cdot\left(D-C\cdot e^{-t_n/\alpha}\right)}\right]$$

$$= \tau\cdot\ln\left[\frac{K\cdot n\cdot\left(D-C\cdot e^{-t_n/\alpha}\right)}{C\cdot D\cdot SL}\right]$$

$$= \tau\cdot\ln\left[\frac{K\cdot n}{SL}\cdot\left(\frac{1}{C}-\frac{e^{-t_n/\alpha}}{D}\right)\right] \qquad (13)$$

A safe starting point for ***t$_0$*** is to set it equal to the interval ***T***. Two or three iterations will be needed to estimate ***t$_a$*** within one day of its actual value. The exact equation is very complex.

An approximate value for ***t$_a$*** can be obtained faster if we use Newton's approximation and a "smart" choice for ***t$_1$*** obtained from (13). Because we have already set ***t$_0$*** = ***T***, and ***T*** >> **α**, $e^{-t_n/\alpha}$ is very small and can be ignored. This allows us to calculate our "smart" choice for ***t$_1$***.

$$t_1 = \tau\cdot\ln\left[\frac{K\cdot n}{SL\cdot C}\right]$$

Newton's approximation is typically written

$$t_{n+1} = t_n - f(t_n)/f'(t_n) \qquad (14)$$

which we can use to calculate ***t$_2$*** from ***t$_1$***. Let ***t$_2$*** be sufficiently close to ***t$_a$***

$$t_a \approx t_2 = t_1 - ST(t_1)/ST'(t_1)$$

$$where\quad ST(t_1) = K\cdot n\cdot e^{-t_1/\tau}\cdot\left(\frac{1}{C}-\frac{e^{-t_1/\alpha}}{D}\right)-SL$$

$$ST'(t_1) = K\cdot n\cdot e^{-t_1/\tau}\cdot\left(-\frac{1}{\tau\cdot C}+\frac{(\alpha+\tau)}{\alpha\cdot\tau}\frac{e^{-t_1/\alpha}}{D}\right)$$

$$So,\quad t_2 = t_1 - \frac{K\cdot n\cdot e^{-t_1/\tau}\cdot\left(\frac{1}{C}-\frac{e^{-t_1/\alpha}}{D}\right)-SL}{K\cdot n\cdot e^{-t_1/\tau}\cdot\left(-\frac{1}{\tau\cdot C}+\frac{(\alpha+\tau)}{\alpha\cdot\tau}\frac{e^{-t_1/\alpha}}{D}\right)}$$

$$= t_1 - \frac{\left(D-C\cdot e^{-t_1/\alpha}\right)-C\cdot D\cdot SL/\left(K\cdot n\cdot e^{-t_1/\tau}\right)}{-\frac{D}{\tau}+\frac{(\alpha+\tau)}{\alpha\cdot\tau}\cdot C\cdot e^{-t_1/\alpha}}$$

$$\begin{aligned}
&\text{Since}\quad e^{-t_1/\tau}=[SL\cdot C/K\cdot n]\qquad \text{and}\qquad e^{t_1/\alpha}=[K\cdot n/SL\cdot C]^{\tau/\alpha}\\
&t_2=\tau\cdot\ln\left[\frac{K\cdot n}{SL\cdot C}\right]-\frac{\left(D-C\cdot[K\cdot n/SL\cdot C]^{\tau/\alpha}\right)-C\cdot D\cdot SL/\left(K\cdot n\cdot[SL\cdot C/K\cdot n]\right)}{-\frac{D}{\tau}+\frac{(\alpha+\tau)}{\alpha\cdot\tau}\cdot C\cdot[K\cdot n/SL\cdot C]^{\tau/\alpha}}\\
&\quad=\tau\cdot\ln\left[\frac{K\cdot n}{SL\cdot C}\right]-\frac{-C\cdot[K\cdot n/SL\cdot C]^{\tau/\alpha}}{-\frac{D}{\tau}+\frac{(\alpha+\tau)}{\alpha\cdot\tau}\cdot C\cdot[K\cdot n/SL\cdot C]^{\tau/\alpha}}\\
&t_2=\tau\cdot\ln\left[\frac{K\cdot n}{SL\cdot C}\right]-\frac{1}{\frac{D\cdot[K\cdot n/SL\cdot C]^{-\tau/\alpha}}{C\cdot\tau}-\frac{(\alpha+\tau)}{\alpha\cdot\tau}}\\
&t_a\approx\tau\cdot\ln\left[\frac{K\cdot n}{SL\cdot C}\right]-\frac{\tau}{\frac{D}{C}\cdot\left[\frac{K\cdot n}{C\cdot SL}\right]^{-\tau/\alpha}-\frac{\alpha+\tau}{\alpha}}
\end{aligned}\tag{15}$$

We can calculate t_b in an analogous manner to the derivation for t_a. The iterative solution uses (5) solved for $U(t)$ (instead of solving for $V(t)$).

$$\begin{aligned}
U(t_b)&=\frac{D}{C}-\frac{SL\cdot D}{K\cdot n\cdot V(t_b)}\\
t_{n+1}&=-\alpha\cdot\ln\left[\frac{D}{C}-\frac{SL\cdot D}{K\cdot n\cdot e^{-t_n/\tau}}\right]
\end{aligned}\tag{16}$$

A good estimate for the start of the iteration is to set $t_0 = 0$. After iterating at least twice, the value of t_n will be no further than one day away from the value of t_b calculated using a spreadsheet. Again, the exact equation is very complex and will not be shown in this paper.

A simpler, non-iterative equation can be found by using (16), the iterative solution, once to calculate t_1 (with $t_0 = 0$), and then using the same Newton approximation (14) as before.

To simplify the appearance of the equations, let us define a new variable:

$$Q=\frac{D}{C}-\frac{D\cdot SL}{K\cdot n}$$

We can use the value of t_2 as an estimate for t_b with about a two day accuracy.

$$\begin{aligned}
&t_1=-\alpha\cdot\ln[Q]\qquad(\textit{iterative solution})\\
&t_2=t_1-\frac{D-C\cdot e^{-t_1/\alpha}-C\cdot D\cdot SL/\left(K\cdot n\cdot e^{-t_1/\tau}\right)}{-\frac{D}{\tau}+\frac{\alpha+\tau}{\alpha\cdot\tau}\cdot C\cdot e^{-t_1/\alpha}}\qquad(\textit{Newton approximation})\\
&\quad\text{Since}\quad e^{-t_1/\alpha}=Q,\quad\text{and}\quad e^{t_1/\tau}=[Q]^{-a/\tau}\\
&t_b\approx t_2=-\alpha\cdot\ln[Q]-\frac{1-\frac{C}{D}\cdot[Q]-\frac{C\cdot SL}{K\cdot n\cdot[Q]^{-a/\tau}}}{\frac{\alpha+\tau}{\alpha\cdot\tau}\cdot\frac{C}{D}\cdot[Q]-\frac{1}{\tau}}\\
&\quad=-\alpha\cdot\ln[Q]-\frac{1-\frac{C}{D}\cdot\left[\frac{D}{C}-\frac{D\cdot SL}{K\cdot n}\right]-\frac{C\cdot SL}{K\cdot n\cdot[Q]^{-a/\tau}}}{\frac{\alpha+\tau}{\alpha\cdot\tau}\cdot\frac{C}{D}\cdot\left[\frac{D}{C}-\frac{D\cdot SL}{K\cdot n}\right]-\frac{1}{\tau}}\\
&\quad=-\alpha\cdot\ln[Q]-\frac{1-\left[1-\frac{C\cdot SL}{K\cdot n}\right]-\frac{C\cdot SL}{K\cdot n\cdot[Q]^{-a/\tau}}}{\frac{\alpha+\tau}{\alpha\cdot\tau}\cdot\left[1-\frac{C\cdot SL}{K\cdot n}\right]-\frac{1}{\tau}}\\
&\quad=-\alpha\cdot\ln[Q]-\alpha\cdot\tau\cdot\frac{\frac{C\cdot SL}{K\cdot n}-\frac{C\cdot SL}{K\cdot n\cdot[Q]^{-a/\tau}}}{(\alpha+\tau)-(\alpha+\tau)\cdot\frac{C\cdot SL}{K\cdot n}-\alpha}\\
&\quad=-\alpha\cdot\ln[Q]-\alpha\cdot\tau\cdot\frac{\frac{C\cdot SL}{K\cdot n}\cdot\left[1-[Q]^{a/\tau}\right]}{\tau-(\alpha+\tau)\cdot\frac{C\cdot SL}{K\cdot n}}\\
&\quad=-\alpha\cdot\ln[Q]-\frac{\alpha\cdot\tau\cdot\left[1-[Q]^{a/\tau}\right]}{\tau\cdot\frac{K\cdot n}{C\cdot SL}-(\alpha+\tau)}\\
&t_b\approx-\alpha\cdot\ln[Q]-\frac{1-[Q]^{a/\tau}}{\frac{K\cdot n}{\alpha\cdot C\cdot SL}-\frac{(\alpha+\tau)}{\alpha\cdot\tau}}
\end{aligned}\tag{17}$$

The process to determine t_a and t_b was tedious, but their approximate values are needed to calculate the endogenous testosterone contribution to the average levels. Since, by definition, there is no endogenous production in the range $t_b < t < t_a$, only the endogenous production at the beginning of a cycle (from t=0 to t_b) and at the end of a cycle (from t=t_a to T) must be calculated. Our model assumes the endogenous production on day t+1 is solely dependent upon the serum testosterone level on day t. Since we are summing the total contribution on every day of the cycle, this one-day offset can be ignored in the calculations.

Use (5) and integrate (3) over the range from 0 to t_b, and from t_a to T to obtain the total contribution of endogenous testosterone to the serum testosterone level.

$$\begin{aligned}
\int EC(t)dt&=\int_{t=0}^{t_b}EC(t)dt+\int_{t=t_a}^{T}EC(t)dt=\int_{t=0}^{t_b}\left(BL-\frac{BL}{SL}\cdot ST(t)dt\right)+\int_{t=t_a}^{T}\left(BL-\frac{BL}{SL}\cdot ST(t)dt\right)\\
&=BL\cdot(t_b-0+T-t_a)+\\
&\quad+\frac{BL}{SL}\cdot\left(\frac{K\cdot n}{C}\right)\cdot\tau\cdot\left(e^{-t_b/\tau}-1\right)-\frac{BL}{SL}\cdot\left(\frac{K\cdot n}{D}\right)\cdot\left(\frac{\alpha\cdot\tau}{\alpha+\tau}\right)\cdot\left(e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-1\right)+\\
&\quad+\frac{BL}{SL}\cdot\left(\frac{K\cdot n}{C}\right)\cdot\tau\cdot\left(e^{-T/\tau}-e^{-t_a/\tau}\right)-\frac{BL}{SL}\cdot\left(\frac{K\cdot n}{D}\right)\cdot\left(\frac{\alpha\cdot\tau}{\alpha+\tau}\right)\cdot\left(e^{-T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}\right)\\
&=BL\cdot\left[(T-t_a+t_b)+\left(\frac{K\cdot n\cdot\tau}{SL}\right)\cdot\left[\frac{e^{-T/\tau}-e^{-t_a/\tau}+e^{-t_b/\tau}-1}{C}-\left(\frac{\alpha}{\alpha+\tau}\right)\cdot\frac{e^{-T\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}+e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-1}{D}\right]\right]\\
&=BL\cdot\left[(T-t_a+t_b)+\left(\frac{K\cdot n\cdot\tau}{SL}\right)\cdot\left[\frac{-e^{-t_a/\tau}+e^{-t_b/\tau}-C}{C}-\left(\frac{\alpha}{\alpha+\tau}\right)\cdot\frac{-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}+e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-D}{D}\right]\right]\\
&=BL\cdot\left[(T-t_a+t_b)+\left(\frac{K\cdot n\cdot\tau}{SL}\right)\cdot\left[\frac{-e^{-t_a/\tau}+e^{-t_b/\tau}}{C}-\left(\frac{\alpha}{\alpha+\tau}\right)\cdot\frac{-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}+e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}}{D}-\frac{\tau}{\alpha+\tau}\right]\right]
\end{aligned}\tag{18}$$

Although further substitutions can be made into (18), the equation's complexity cannot be reduced. Combining (12) and (18), the actual average serum testosterone can be found by substituting the appropriate values into the following equation.

$$\begin{aligned}
ST_{avg}&=\frac{K\cdot n\cdot\tau^2}{T\cdot(\alpha+\tau)}+\frac{BL}{T}\cdot\left[(T-t_a+t_b)+\left(\frac{K\cdot n\cdot\tau}{SL}\right)\cdot\left[\frac{-e^{-t_a/\tau}+e^{-t_b/\tau}}{C}-\left(\frac{\alpha}{\alpha+\tau}\right)\cdot\frac{-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}+e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}}{D}-\frac{\tau}{\alpha+\tau}\right]\right]\\
&=\frac{K\cdot n\cdot\tau^2}{T\cdot(\alpha+\tau)}\cdot\left[1-\frac{BL}{SL}\right]+\frac{BL}{T}\cdot\left[T-t_a+t_b+\left(\frac{K\cdot n\cdot\tau}{SL}\right)\cdot\left[\frac{e^{-t_b/\tau}-e^{-t_a/\tau}}{C}-\left(\frac{\alpha}{\alpha+\tau}\right)\cdot\frac{e^{-t_b\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}-e^{-t_a\left(\frac{1}{\alpha}+\frac{1}{\tau}\right)}}{D}\right]\right]
\end{aligned}\tag{19}$$

Although a computer is not daunted by the complexity of (19), a simpler equation is still desirable. Examining the plot of serum testosterone and its two major components (see Figure 2) shows that the endogenous contributions' curves form two nearly triangular regions. The area of the triangular regions is half the base (t_b or T-t_a) times the height $EC(T)$. This approach yields another, slightly simpler, equation to approximate the average serum testosterone level during steady state conditions.

$$\begin{aligned}
ST_{avg}&\approx\frac{K\cdot n}{T}\cdot\frac{\tau^2}{\alpha+\tau}+BL\cdot\left(1-\frac{K\cdot n}{SL}\cdot\frac{D-C}{C\cdot D}\right)\cdot\frac{\left(T-t_b+t_a\right)}{2\cdot T}\\
&=\frac{K\cdot n}{T}\cdot\left[\frac{\tau^2}{\alpha+\tau}+\frac{BL\cdot\left(T-t_b+t_a\right)}{2\cdot SL\cdot T}\cdot\left(1-\frac{K\cdot n}{SL}\cdot\frac{D-C}{C\cdot D}\right)\right]
\end{aligned}\tag{20}$$

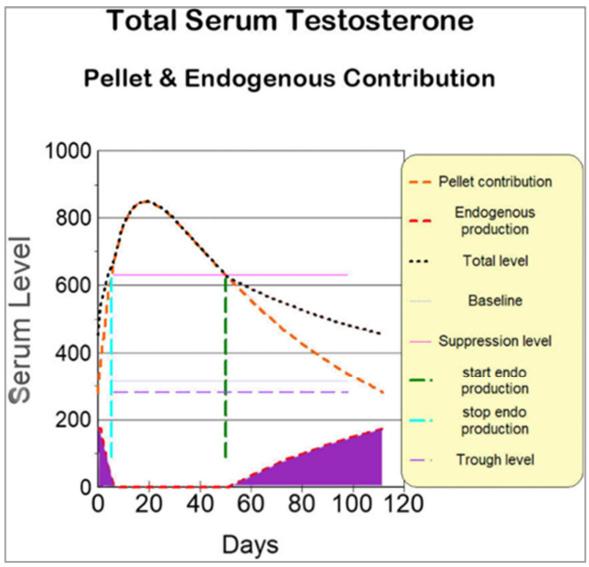

Figure 2. *Sample curves of the pellet and the endogenous contribution to serum testosterone showing the area of the endogenous curve to be approximately that of two triangles whose areas can be computed as described in the text.*

3. Results

3.1. Model Parameters

The model's equations were entered into a Corel Quattro Pro spreadsheet, and the parameter values were determined in a semi-automatic fashion as described in the Methods section and Appendix A.

All blood samples were drawn at Laboratory Corporation of America Holdings ("Labcorp") sites. Because only one to three samples were obtained with each cycle, it was important to assure the most accurate and reliable assay was used. Prior to August, 2017, reliable parameter values could not be calculated because of excessive variation between the calculated values and measured values using the Labcorp assay. However, data from the Esoterix assay used after May, 2017, fit the model's curves more closely.

Early in the therapy, with only 9 accurate measurements, the parameters were calculated with some degree of confidence. Local minimal ***SSE***'s were found using parameters near to the parameters yielding the true minimal ***SSE***. In addition, the mean % difference between the model's prediction and the laboratory values was 0.442% (maximum % difference = -7.7%, SD = 4.58%). To obtain Hormone Standardization (HoSt) certification, the CDC requires that testosterone assays vary less than 6.4% when assaying duplicate samples [3], so our model did not appear to introduce more error than is already inherent in the Esoterix assay. Table 1 shows the data used to generate the training set.

The algorithm used (see Appendix A for more details) identified more than one local minima, probably because of the relatively small number of data points used. All the local minima identified, however, had parameters which varied less than the expected precision of the numbers. Table 2 shows the various local minima identified. The lowest ***SSE*** obtained was used for further analysis.

Table 1. *Calculated and measured levels from Esoterix assay for training set.*

Date	# pellets implanted	Total serum testosterone (ng/dL)	Calculated level (ng/dL)	% change between measured & calculated
Nov 8, 2016	10			
Feb 14, 2017	10			
May 23, 2017	9			
Jun 13, 2017		911	957	5.1%
Aug 8, 2017	9			
Oct 18, 2017		573	583	1.8%
Oct 24, 2017	9			
Nov 8, 2017		1030	1040	0.9%
Jan 9, 2018	9			
Mar 30, 2018		512	511	-0.3%
Apr 3, 2018	9			
Apr 9, 2018		735	782	6.4%
Apr 19, 2018		1038	1010	-2.7%
Jul 3, 2018		458	434	-5.2%
Jul 11, 2018		417	408	-2.3%
Jul 13, 2018	8			
Aug 3, 2018		937	865	-7.7%
Best fit parameters determined to be: pellet constant K = 5270 ng/dL/pellet; absorption half-life $\alpha \cdot ln(2) = 14.8$ days; elimination half-life $\tau \cdot ln(2) = 38.3$ days.				

Table 2. *Parameter estimations for training set using the local minima sum of square errors. Calculations using rounded off parameters.*

Pellet constant K (ng/dL/pellet)	Absorption half-life α·ln(2) (days)	Elimination half-life τ·ln(2) (days)	Minimal SSE found with algorithm
5270	14.8	38.3	1599.8
5300	14.9	38.2	1599.8
5310	14.9	38.2	1602.2
5260	14.8	38.4	1600.3

Table 3. *Calculated and measured levels (Esoterix assay) used for test set.*

Date	# pellets implanted	Total serum Testosterone (ng/dL)	Calculated level (ng/dL)	% change Between measured & calculated
Oct 11, 2018		433	407	-6.1%
Oct 22, 2018	8			
Nov 12, 2018		1006	829	-17.6%
Nov 19, 2008		834	825	-1.1%
Jan 22, 2019		357	396	10.9%
Using best fit training set parameters (pellet constant K =5270 ng/dL/pellet; absorption half-life $\boldsymbol{\alpha} \cdot ln(2) = 14.8$ days; elimination half-life $\tau \cdot ln(2) = 38.3$ days), mean % difference = -1.45%, SD = 11.8%.				

Using the best of the triads to predict serum testosterone, the mean percent difference between the measured values and the predicted values for the "training set" was 0.442% (SD = 4.58%, n = 9). The triad giving these values was $\boldsymbol{\alpha} \cdot \ln(2) = 14.8$ days, $\boldsymbol{\tau} \cdot \ln(2) = 38.3$ days, and $\boldsymbol{K} = 5270$ ng/dL/pellet.

The next data to be analyzed were the serum levels obtained between October 11, 2018, and January 22, 2019. This data is shown in Table 3 and it represents the "test" set. Using the same parameters as the training set, the test set mean percent deviation was -3.45% (SD = 11.8%, n = 4).

Lastly, all the data collected between June 13, 2017, and January 22, 2019, was analyzed using the same parameters.

The mean % deviation was -1.33% (SD = 7.67%, n = 13). These values were well-within clinical significance and still support our assumption that the model is as accurate as the Esoterix assay used.

Unfortunately, the recent COVID-19 pandemic, lead to a shortage of Testopel® pellets, thereby postponing further analysis. However, an analysis was performed on all the data collected so far. Using the early data from June 27, 2017, through January 22, 2019, as a training set, best fit parameters were determined to be $\alpha \cdot \ln(2) = 18.2$ days, $\tau \cdot \ln(2) = 33.7$ days, and $K = 6780$ ng/dL/pellet. The mean % difference was -0.63%, with a standard deviation of 7.26%. The remaining data from May 29, 2019, to June 22, 2020, was then used as the test set. The mean % difference was -3.46%, with a standard deviation of 10.75%. These numbers, while not as close as those predicted earlier, are still clinically indistinguishable from each other.

3.2. Daily Serum Levels

Prior to June, 2017, the standard Labcorp testosterone assay, which was not HoSt certified, was used to measure the serum levels. The best parameter values could not be determined because no clear-cut minimal ***SSE*** could be obtained. Figure 3 shows the original Labcorp assay measurements and the predicted serum levels. The thick red curve represents $ST_{total}(t)$, and the thinner colored curves represent the contribution from each of the previously inserted pellets. The endogenous contribution is not shown because it was suppressed during most of the cycle. The model parameters were adjusted in an attempt to better the fit, but the discrepancy between the measured and the predicted values remained large.

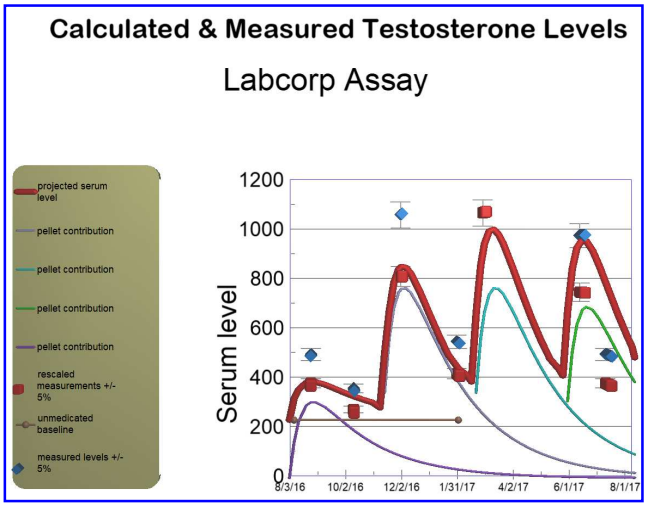

Figure 3. *Calculated testosterone levels and Labcorp measurements.*

Starting June 13, 2017, until the present, nearly every testosterone measurement was obtained using the Esoterix Laboratory assay, which was a HoSt certified assay. This data was graphed in Figure 4. Two data points from January, 2018, were included in the early analysis of the data, but were eliminated from later analysis. Both of these samples were taken in the afternoon (one delay caused by a snowstorm closing the facility; the other because of a morning plane flight). These two data points (marked in Figure 4) are still visually close to the predicted curve supporting the notion that diurnal variation is minimal during suppressive therapy.

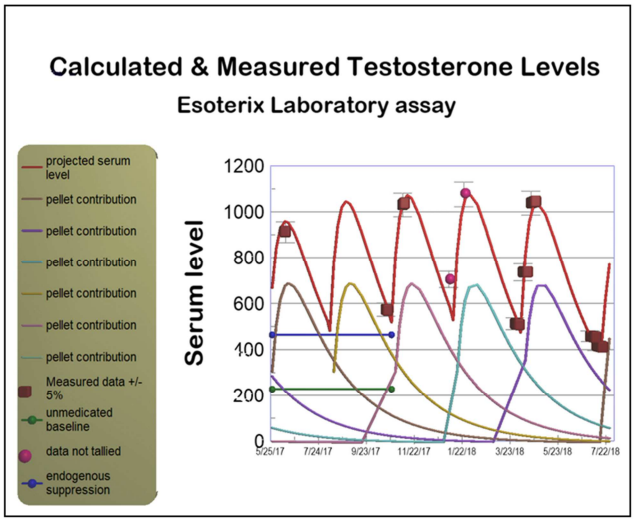

Figure 4. *Calculated testosterone levels and Esoterix laboratory measurement.*

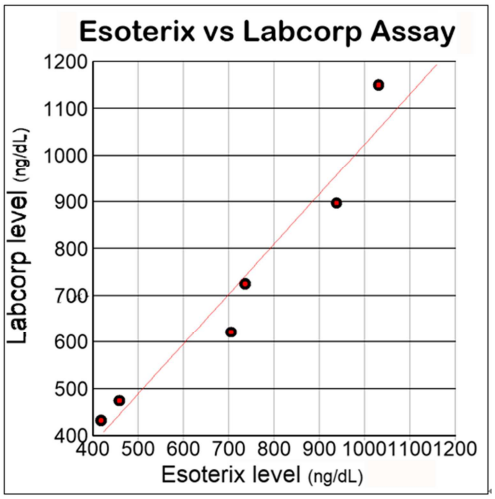

Figure 5. *Calculated testosterone levels and Esoterix laboratory measurement.*

Today's Labcorp assay is now a HoSt certified assay. Using some of the data, the Esoterix assay and the current Labcorp assay are compared in Figure 5. Both assays show close agreement to each other; the correlation coefficient ***r*** is 0.97, and the linear fit equation converting one assay's results to the other is:

$$\text{Labcorp value} = 1.09 \times \text{Esoterix value} - 55.6$$

Although both assays are expected to yield accurate results, the predicted parameters differ for each assay because their best-fit lines are different. Therefore, to obtain the best accuracy, we recommend not switching HoSt certified assays when attempting to find the ideal therapeutic regimen for any given patient.

3.3. Steady State

After sufficient measurements were taken to enable us to compute the model's parameters, a table was created showing the peak, the trough, and the average serum levels with various implant schedules. A sample grid using early parameters estimates (α, τ, and K) = (20.2, 56.12, 5135) is shown in Figure 6. By choosing target values in advance, this grid (customized for each patient) can be used to decide the therapy regimen prior to the start of therapy.

According to the equations, the peak value generally occurs between day 20 and day 25 for pellet insertion frequencies between 10 and 20 weeks. For example, using the triad (16.45, 62.18, 4226), and an injection frequency of 15 weeks (105 days), the peak value (when a steady state has been reached) will be on day

$$t = 16.45 \cdot [\ln(1-e^{-105/62.18}) \cdot (1+62.18/16.45)]$$

$$= 16.45 \cdot [\ln(0.8152) \cdot (4.780)]$$

$$= 22.4$$

Figure 6 shows that the number of pellets implanted is directly proportional to the overall variation (difference between peak and trough levels) during a cycle. The peak values are also increased with shorter intervals between implants. Lower trough values occur with fewer pellets and longer intervals between implants. These relationships can be used to choose the optimal treatment to attain targeted peak, trough, and average testosterone levels.

The grid was developed after therapy had commenced, and it showed that the current regimen (9 pellets every 11 weeks) produced average serum levels higher than desired. Since an average level near 600 was desired, appropriate regimens (taken from Figure 6) were printed (Table 4) so that the best regimen (peak and trough values closest to desired target) could be chosen.

A new schedule of 8 pellets every 14 weeks was chosen. This schedule produces a slightly lower, average serum level of 593 ng/dL, a trough of 301 ng/dL (plus the endogenous contribution of 80 ng/dL equals a measured trough level of 380 ng/dL), and a peak of 828 ng/dL. In order to quickly reach a steady state for this new schedule, pellet implants were delayed until the serum level reached the new steady state trough of 381 ng/dL. By waiting until the serum level equaled the targeted trough of 381, the new steady state was reached by the following cycle.

The more important equations used by this model are summarized in Table 5.

Total Testosterone Serum Levels predicted for different Testopel® insertions at different frequencies

Data generated for case report

printed 13-Sep-2018 NOTE: THIS DATA MAY NOT BE APPLICABLE TO OTHER PATIENTS

FREQUENCY	VALUE	7 pellets	8 pellets	9 pellets	10 pellets
inserted every 10 weeks	peak level	904 @ day 20 (2w 6d)	1034 @ day 20 (2w 6d)	904 @ day 20 (2w 6d)	904 @ day 20 (2w 6d)
	SS average	**741**	**846**	**952**	**1058**
	trough level	*495*	*566*	*636*	*707*
inserted every 11 weeks	peak level	850 @ day 21 (3w 0d)	972 @ day 21 (3w 0d)	1093 @ day 21 (3w 0d)	1215 @ day 21 (3w 0d)
	SS average	**637**	**769**	**866**	**962**
	trough level	*439*	*480*	*540*	*600*
inserted every 12 weeks	peak level	807 @ day 22 (3w 1d)	972 @ day 21 (3w 1d)	1093 @ day 21 (3w 1d)	1215 @ day 21 (3w 1d)
	SS average	**617**	**705**	**793**	**882**
	trough level	*409*	*434*	*460*	*511*
inserted every 13 weeks	peak level	772 @ day 22 (3w 1d)	882 @ day 21 (3w 1d)	992 @ day 21 (3w 1d)	1102 @ day 21 (3w 1d)
	SS average	**570**	**651**	**732**	**814**
	trough level	*384*	*405*	*427*	*448*
inserted every 14 weeks	peak level	743 @ day 23 (3w 2d)	849 @ day 23 (3w 2d)	955 @ day 23 (3w 2d)	1061 @ day 23 (3w 2d)
	SS average	**529**	**604**	**680**	**756**
	trough level	*362*	*381*	*399*	*418*
inserted every 15 weeks	peak level	718 @ day 23 (3w 2d)	821 @ day 23 (3w 2d)	923 @ day 23 (3w 2d)	1026 @ day 23 (3w 2d)
	SS average	**494**	**564**	**635**	**705**
	trough level	*345*	*361*	*377*	*393*
inserted every 16 weeks	peak level	698 @ day 24 (3w 3d)	798 @ day 24 (3w 3d)	898 @ day 24 (3w 3d)	997 @ day 24 (3w 3d)
	SS average	**463**	**529**	**595**	**661**
	trough level	*330*	*343*	*357*	*371*

weight = 180 lb. BMI = 28.6 $t_{1/2}$ absorption = 14.0 days $t_{1/2}$ elimination = 38.9 days baseline level = 233 S/N=18066.520.256.1233513 pellet base = 5135

© David Seitman, M. D. 2018

Figure 6. *Dosage and frequency effects on peak, average, and trough testosterone levels.*

Table 4. *Treatment schedule to produce a specific average testosterone level.*

Number of Testopel® pellets inserted	Injection frequency	Average Total Serum level	Lowest Serum level	Peak Serum level
7 pellets every	13 weeks	570	384	772@day 22 (3w 1d)
9 pellets every	16 weeks	595	357	898@day 24 (3w 3d)
8 pellets every	14 weeks	604	381	849@day 23 (3w 2d)
7 pellets every	12 weeks	617	409	807@day 22 (3w 1d)
weight =180 lbs. BMI=28.6 $t_{1/2}$absorption=14.0 days $t_{1/2}$elimination=38.9 days baseline level=233 pellet base=5135 s/n=18066.520.256.1233513 © David Seitman, MD 2018				
Implanting 8 pellets every 98 days (14.0 weeks) results in an average total serum testosterone level of 604, a trough level of approximately 381, and a peak level of approximately 849 on day # 23.				

Table 5. *Important model equations.*

Value	Equation #	Equation	Notes
Daily levels	2	$ST(t) = K \cdot n \cdot V(t) \cdot (1 - U(t)) + EC(t)$	$V = e^{-t/\tau}$, $U = e^{-t/\alpha}$, ***K*** = pellet constant, ***n*** = # pellets
Steady state levels	5	$ST(t) = \frac{K \cdot n \cdot V(t)}{C} - \frac{K \cdot n \cdot W(t)}{D} + EC(t)$	$W = U \cdot V$, $C = 1 - e^{-T/\tau}$, $D = 1 - e^{-T \cdot \left(\frac{1}{\tau} + \frac{1}{\alpha}\right)}$ ***K*** = pellet constant, ***n*** = # pellets
Endogenous testosterone contribution	3	$EC(t) = \left(1 - \min\left[\frac{ST(t-1)}{SL}, 1\right]\right) \cdot BL$	***BL*** = baseline level, ***SL*** = suppression level ***ST*** = serum testosterone level (from pellets)
Trough, first cycle	-	$ST(T) = K \cdot n \cdot V(T) \cdot (1 - U(T)) + EC(T)$	$EC(t) = \left(1 - \min\left[\frac{ST(t-1)}{SL}, 1\right]\right) \cdot BL$ ***T*** = implant interval, ***K*** = pellet constant, ***n*** = # pellets
Trough, steady state	6	$= K \cdot n \cdot \left[\frac{1}{C} - \frac{1}{D}\right] + EC(0)$	$EC(t) = \left(1 - \min\left[\frac{ST(t-1)}{SL}, 1\right]\right) \cdot BL$ ***T*** = implant interval, ***K*** = pellet constant, ***n*** = # pellets
Peak day, first cycle	9	$t = \alpha \cdot \ln\left[\frac{\alpha + \tau}{\alpha}\right]$	**α** = absorption constant **τ** = elimination constant
Peak day, steady state	10	$t = \alpha \cdot \ln\left[\frac{C}{D} \cdot \left(\frac{\alpha + \tau}{\alpha}\right)\right]$	$C = 1 - e^{-T/\tau}$, $D = 1 - e^{-T \cdot \left(\frac{1}{\tau} + \frac{1}{\alpha}\right)}$ **α** = absorption constant, **τ** = elimination constant
Peak level, first cycle	-	$\left(\frac{K \cdot n \cdot \tau}{\alpha + \tau}\right) \cdot \left[\frac{\alpha}{\alpha + \tau}\right]^{\frac{\alpha}{\tau}}$	***K*** = pellet constant, ***n*** = # pellets, **α** = absorption constant, **τ** = elimination constant
Peak level, steady state	11	$\frac{K \cdot n}{C} \cdot \left(\frac{\tau}{\alpha + \tau}\right) \cdot \left[\frac{D}{C} \cdot \frac{\alpha}{\alpha + \tau}\right]^{\frac{\alpha}{\tau}}$	$C = 1 - e^{-T/\tau}$, $D = 1 - e^{-T \cdot \left(\frac{1}{\tau} + \frac{1}{\alpha}\right)}$
Endogenous testosterone start date	15	$t_a \approx \tau \cdot \ln\left[\frac{K \cdot n}{SL \cdot C}\right] - \frac{\tau}{\frac{D}{C} \cdot \left[\frac{K \cdot n}{C \cdot SL}\right]^{-\tau/\alpha} - \frac{\alpha + \tau}{\alpha}}$	$C = 1 - e^{-T/\tau}$, $D = 1 - e^{-T \cdot \left(\frac{1}{\tau} + \frac{1}{\alpha}\right)}$, ***K*** = pellet constant, ***n*** = # pellets, **α** = absorption constant, **τ** = elimination constant, ***SL*** = suppression level
Endogenous testosterone stop date	17	$t_b \approx -\alpha \cdot \ln[Q] - \frac{1 - [Q]^{\alpha/\tau}}{\frac{K \cdot n}{\alpha \cdot C \cdot SL} - \frac{(\alpha + \tau)}{\alpha \cdot \tau}}$	$C = 1 - e^{-T/\tau}$, $D = 1 - e^{-T \cdot \left(\frac{1}{\tau} + \frac{1}{\alpha}\right)}$, ***K*** = pellet constant, ***n*** = # pellets, **α** = absorption constant, **τ** = elimination constant, ***SL*** = suppression level $Q = \frac{D}{C} - \frac{SL \cdot D}{K \cdot n}$
Average steady state level-pellets only	12	$\frac{K \cdot n \cdot \tau^2}{T \cdot (\alpha + \tau)}$ w/o endogenous contribution	***T*** = implant interval, ***K*** = pellet constant, ***n*** = # pellets, **α** = absorption constant, **τ** = elimination constant
Average testosterone level including endogenous production	19	$ST_{avg} = \frac{K \cdot n \cdot \tau^2}{T \cdot (\alpha + \tau)} \cdot \left[1 - \frac{BL}{SL}\right] + \frac{BL}{T} \cdot \left[T - t_a + t_b + \left(\frac{K \cdot n \cdot \tau}{SL}\right) \cdot \left[\frac{e^{-t_b/\tau} - e^{-t_a/\tau}}{C} - \left(\frac{\alpha}{\alpha + \tau}\right) \cdot \frac{e^{-t_b \cdot \left(\frac{1}{\alpha} + \frac{1}{\tau}\right)} - e^{-t_a \cdot \left(\frac{1}{\alpha} + \frac{1}{\tau}\right)}}{D}\right]\right]$
	20	$ST_{avg} \approx \frac{K \cdot n}{T} \cdot \left[\frac{\tau^2}{\alpha + \tau} + \frac{BL \cdot (T - t_b + t_a)}{2 \cdot SL \cdot T} \cdot \left(1 - \frac{K \cdot n}{SL} \cdot \frac{D - C}{C \cdot D}\right)\right]$ See text for definitions of the variables	

4. Discussion

Testopel® was approved in the USA by the FDA in 1972, but was not marketed until 2008. It is the only testosterone pellets approved by the FDA for use in the USA. There was no published pharmacokinetic data for Testopel® prior to 2009 [6], and very few published studies [10-13] after that date. There are a few studies of other forms of implantable testosterone pellets, but comparing the data from [14-17] to Testopel®'s data should be done cautiously because the pellet matrix is different, the implantation site is different (abdominal, not gluteal), and/or the dosage is different.

4.1. Comparison with Other Data

Our methodology differs greatly from previously published works. All the other studies except Jockenhövel's [15] derive their validation from aggregated data obtained from many patients. Patients were arbitrarily grouped by

weight ranges, and their serum levels, measured at different times, were also aggregated; our study analyzed the data from one patient, with data obtained at specific times post implantation. Other studies used various assays which were neither consistent nor accurate; our study relied upon one CDC-certified specific assay.

The value of the pellet constant ***K*** is likely influenced by the percent of free testosterone and the amount of steroid binding hormone, as both influence the volume of distribution of the testosterone. Neither of these values were specifically included in our analysis because our pellet constant incorporates both effects into the one constant.

Studies [12, 14, 16, 17] infer that pellet absorption follows zero-order kinetics (i.e., absorption rate is a constant), but our data clearly do not support this conclusion. Our data is consistent with first-order absorption kinetics (i.e., absorption rate is dependent upon concentration). This agrees with one study by Jockenhövel [15]. However, we calculated an absorption half-life of 10.3-15.4 days which differs greatly from his determination of 74.7 days. It should be noted that Jockenhövel did not use Testopel® pellets, and he labeled his observed constant percent absorption as zero-order kinetics. However, constant percent absorption is equivalent to an absorption rate dependent upon concentration, so he should have labeled his data to be consistent with first-order kinetics.

The Endo Pharmaceuticals PDR insert suggests that the elimination half-life is between 45 and 52 days, but it is unclear how this data was determined. Our data places the elimination half-life between 37.6 and 46.0 days, which is shorter than other published data. Extrapolating from his graphed data, Pastuzsack's [12] elimination half-life is about 80-90 days. Handelsman [14] states a half-life of 75 days, and this is consistent with [15] who determined an elimination half-life of 70.8 ± 10.7 days.

Elimination half-life is dependent upon the exact composition of the testosterone injected as well as the rate of its metabolism in various tissues of the body. Measurement error will also play a role in its calculation. Analysis of the wide variation in elimination half-life seen in the literature compared to our value was beyond the scope of this investigation.

4.2. Model Assumptions

We acknowledge that our acceptance of a baseline serum testosterone level of 233 ng/dL was measured using the old Labcorp assay; additional baseline assessments using a HoSt certified assay were not done because of ongoing therapy. It is likely that we are over-estimating the baseline level as well as the endogenous contribution. Unless therapy is discontinued long enough for all exogenous testosterone to be completely excreted, the only way to determine if the body is producing testosterone, while in the midst of therapy, is to measure the serum LH level. As the serum testosterone level approaches the trough level, a rising LH production indicates the body's testosterone production is no longer suppressed. While a true baseline level (sans influence of exogenous testosterone) cannot be measured, one can estimate its value by calculating the partially suppressed response (measured serum level minus the predicted) and extrapolating to find the level when the expected endogenous production is maximum (which represents the baseline level). This exercise was not performed because it required more data points near the trough than were collected.

The dose-response curve of endogenous testosterone production to exogenously applied testosterone is not well-known. An approximation was used in the model which did not specifically address the elimination half-life of the endogenous testosterone. This model assumes a linear, inverse relationship between endogenous testosterone production and the prior day's serum level from exogenous sources. Before any therapy is started, the body's testosterone production results in the measured baseline levels. As testosterone is supplied externally, the body's production will diminish. If the serum level is above an arbitrarily chosen suppression level, endogenous testosterone production is completely suppressed and the endogenous contribution to the serum level is zero. We arbitrarily set the suppression level at twice the baseline level. As stated in the preceding paragraph, multiple LH measurements would be needed to support the accuracy of our assumptions.

The model ignores diurnal variation in testosterone production, as well as circadian and circannual rhythms [18, 19]. These rhythms affect and are affected by endogenous production. Since endogenous testosterone production is totally suppressed during most of a treatment cycle, all rhythmic variations are probably non-existent or minimal. If the trough is above the suppression level, the current requirement by many insurance companies to obtain early AM samples can be safely ignored.

During therapy, the LH was measured at 0.1 (1.7-8.6) mIU/mL when the serum testosterone level was 492 ng/dL (default Labcorp assay). Since 492 ng/dL is greater than the predicted suppression level (set at twice the baseline) of 466 ng/dL, this supports our model's assumption of endogenous suppression.

Since peak testosterone levels are reached more than one day after the suppression level is exceeded, our model predicts that the peak level is independent of the baseline level. This conclusion agrees with Pastuszack and others. Our model supports their findings that the peak level is dependent upon the total milligrams implanted and the BMI [12].

As mentioned above, pellet therapy is likely to raise the serum levels significantly above baseline levels. For this reason, the patient's serum level is near baseline for only a small amount of time between implants, and an error in the endogenous calculation is less likely to cause significant error in the overall calculations. The equation which describes the endogenous production of testosterone only needs to be included when the serum level falls beneath the suppression level.

While there is no clinical evidence showing how long it takes to stimulate endogenous production, the authors felt that a one-day delay was reasonable and was likely to yield results within the accuracy of clinical measurement. However, it is likely that prolonged suppression of endogenous testosterone production causes a long-lasting suppression of

the endogenous response to hypogonadal levels. If confirmed, our model may need to be tweaked to include this sluggish response to testosterone production.

While the model addresses the influence of the pellet absorption on the endogenous production, there was no attempt to ascertain the effect of the endogenous production on the diffusion rate of testosterone out of the pellet depot. The model's exponential equation was derived from the assumption that the rate of diffusion from the depot to the central circulation was dependent solely upon the concentration difference between these two compartments. However, when the endogenous compartment contributes testosterone to the central compartment, the concentration difference between depot and central compartment will be reduced, and the rate of diffusion will also be reduced. The model ignores this effect. The goal of therapy is to markedly elevate reduced baseline levels, and the endogenous production is likely to be a minor correction to the values computed.

To prove when the maximal serum level occurs would require testing the day before, the day of, and the day after we expect the peak to occur. This was not done, but a few measurements were taken near the expected peak to confirm our model. Depending how close the levels are to steady state and how frequent the implantations, our model predicts the peak to occur on day 26 after the first implantation and to occur sooner with successive implants. When pellets are implanted every 12 to 16 weeks, the peak level occurs between 21 and 23 days at steady state. Pastuszack [12] predicts the peak levels to occur 2-4 weeks after implantation. Other researchers (Kaminetsky [10], Handelsman [14], and Jockenhövel [15]) were more liberal and suggested the peak occurs several days to weeks after implantation. McMahon's more recent article [13] puts the peak level at about day 14 when 12 pellets were implanted. Our model suggests that the number of pellets changes the peak level, but not the day on which the peak level occurs.

The model's data was calculated to three digits of precision. This corresponds to less than a 1% variance, which is more precise than needed in clinical practice.

The model does not account for changes in production of testosterone due to food intake [18, 20]. Early bloodwork was performed without regard for npo status, and the data was commingled with subsequent data when the patient remained npo.

Our model also totally ignores the interaction between the serum levels and the Effect compartment, and there was no correction for changes in the androgen levels caused by interactions between receptor sensitivity and serum levels [19].

A correction was introduced into the equations (equaling approximately 6 hours) because most lab samples were collected between 9:30am and 10:00am and the pellets were always implanted after 2:00pm. Although more precise accounting could have been performed, this small correction only changed the predicted levels by about 1 ng/dL.

Over time, the model predicted the peaks and troughs less accurately, although the average levels appeared unchanged. Several circumstances were identified to account for this growing discrepancy. During a few of the pellet insertions, blood vessels were nicked and a small hematoma would appear under the skin. It is likely that initial absorption during that insertion was increased. This would increase the subsequent peak and lower the following trough. In addition, scarring and fibrous tissue would likely decrease the early absorption. Lastly, the site of injection was altered when a new provider performed the procedure.

4.3. Patient Management Without a Model

With no therapy, the baseline level constitutes our best guess at the patient's average testosterone level. Clinicians need to rely on the peak and trough levels during testosterone therapy because there is no test, like the HgbA1c which estimates average serum glucose levels, to give us a handle on the average testosterone level. During Testopel® therapy, we can now estimate average levels using (19) or (20).

Several factors need to be considered when using testosterone pellets to treat hypogonadism. Once an average level is targeted (think normal baseline level if patient were not hypogonadal), different therapy plans alter the interval between implants and/or the number of pellets inserted. Increasing the time intervals between implantations allow for more complete healing at prior insertion sites, but may increase the difference between minimum and maximum levels. Likewise, increasing the number of pellets inserted allows one to wait longer between reinsertions but will markedly increase the peak level. Many clinicians start therapy empirically and determine repeat frequency and dosage based upon the serum level measured a few months later. Without a model, intermittent sampling of testosterone levels cannot confirm that the targeted levels are achieved. With an accurate model, these levels can now be predicted and achieved.

The lower the baseline level is, the more likely that adequate therapy will partially or completely suppress endogenous production. If the suppression level is below the targeted trough level, all endogenous testosterone production will be suppressed. Because of this, the practice of basing the initial dose on the baseline level is not logical. The initial implanted dose should depend more upon the patient's BMI than upon their baseline level.

Assuming an elimination half-life of 45 days, it would take 4 x 45 or 180 days (about 6 months) before the effects of prior implants are minimal. If new pellets are inserted with a greater than 6-month interval, there will be no accumulation effect and each cycle will yield values equal to the values of previous cycles, satisfying steady state conditions.

However, if pellets are inserted prior to 6 months, then it will take longer before a steady state is reached. If therapy is **n** pellets implanted every **m** months, it will take as long as 4 cycles or approximately 4**m** months for steady state conditions to prevail. Since current practice appears to repeat insertions every 13 to 26 weeks, it will take at least one year (and perhaps up to two years) before successive trough values will be equal signifying that a steady state condition is reached. To predict the serum testosterone levels, the

contribution from all implants performed within the prior 12-24 months must be taken into account if we want our calculations to be accurate. It is nearly impossible to perform these calculations without a computer and a good model, which may explain why many urologists have difficulty managing Testopel® therapy.

4.4. The Model as a Guide for Clinical Management

The best approach to reach steady state sooner than one year is to alter either the first implant dosage or the first cycle interval.

A steady state is rapidly reached with intravenous vancomycin by administering a loading dose. Similarly, a "loading dose" of pellets can be used to quickly elevate the patient's levels to steady state levels. The loading dose is approximately the maintenance dose divided by $1-e^{-T/\tau}$. Since the likelihood of this calculation equaling an integral number of pellets, this approach is not ideal. In addition, there is a good likelihood that the peak level obtained during the first cycle will be higher than desired and it may not be considered safe.

An alternate, and perhaps, safer approach shortens the first interval. The second set of pellets is implanted as soon as the serum testosterone level drops to the steady state trough level predicted by the model. An example of this approach is shown in Figure 7. Assume the baseline level is 233 ng/dL and the maintenance therapy is 8 pellets every 14 weeks (98 days). The steady state trough will be 384 ng/dL (307 ng/dL from the pellets and 77 ng/dL produced endogenously). According to the model's predictions, the serum level in cycle one will be 385 ng/dL on day 83. Implanting 8 new pellets on day 83 instead of waiting until day 98 will essentially give us steady state conditions at the start of the second cycle.

When we started Testopel® therapy, we did not have the luxury of knowing the model's parameters, so we did not know if the regimen chosen would be on target. Once we had preliminary estimates for the parameters, we produced a guide for initiation and maintenance therapy suitable for other patients. This is shown below, with our values placed in brackets.

1) Obtain baseline testosterone levels before starting therapy, or after previous testosterone supplementation has worn off [233ng/dL]. Use the same HoSt certified assay for all measurements (confirm current assay is HoSt certified).
2) Decide upon an average level to target [value close to 600ng/dL].
3) Decide upon a maximum acceptable peak level [value less than 900ng/dL].
4) Choose a maintenance Testopel® therapy schedule using the model's predictions and the levels targeted above.
   a) Choose the maintenance Testopel® dosage [8 pellets implanted at each procedure].
   b) Choose the interval between maintenance insertions [14 weeks].
   c) Take note of the expected steady state trough level for this regimen [384 ng/dL].
5) Change the initial Testopel® therapy to reduce the time to steady state.
   a) Shorten the interval between the first and second implants so that the second implant occurs when the serum level drops to the maintenance trough level.
   b) The first interval will likely be shorter than the maintenance interval.

The model's parameters (absorption constant $\boldsymbol{\alpha}$, elimination constant $\boldsymbol{\tau}$, and pellet constant $\boldsymbol{K}$) were calculated for one patient. Since this model accurately predicted one patient's serum testosterone with an accuracy equal to the assay used, we believe the model can be used to aid in the management of other patients. Data from numerous other patients would be needed to truly validate this model and the values computed. Although Testopel® is the only testosterone pellet approved by the FDA for use in the USA, similar pellets with different strengths have been compounded and are being used in patients. Data from these patients are needed to confirm applicability of our model to these other implants.

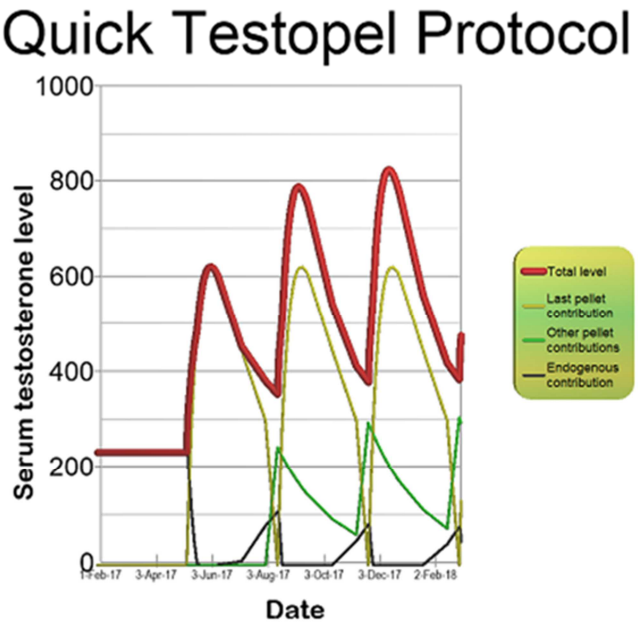

Figure 7. *Projected testosterone levels with targeted therapy.*

Red curve shows rapid attainment of steady state after an initial 8 pellet insertion repeated on day 83 before continuing with maintenance 8 pellets every 98 days.

Although the object of this study did not include the effects of adequate testosterone supplementation, we noted that, over time, the patient's bone density rose to the normal range; his hemoglobin rose from 10 mg% to 15mg%; hair growth returned to his pre-50 year old appearance; and his libido rose.

To our knowledge, this is the first time a multi-compartment model has been successfully used to predict serum testosterone levels and the first time a specific testosterone assay was shown to average closer than 5% of the values calculated from the model. To our knowledge, it is also the first time a pharmacokinetic model was used to determine testosterone therapy with target doses reached within three months.

5. Conclusions

Modern testosterone assays that are HoSt certified, such as the Esoterix assay and the current Labcorp assay, yield more consistent results than assays from prior years. Clinicians can rely on these results with more confidence than previously [21, 22]. Although this model relied on the Esoterix assay, there is no reason to assume that other, equally unbiased, assays would not also yield similar results. It is likely that other assays will require some tweaking of the current parameter values so that the model's predictions will yield the best-fit (i.e., lowest ***SSE)*** for each different assay.

Our modified two-compartment model accounts for most of the perturbations one expects with testosterone absorption, production, and elimination.

The exact influence of administration of exogenous testosterone on the endogenous production of testosterone is not well-defined and pharmacokinetic equations describing the interaction do not exist. However, it is clear that as the exogenous serum testosterone levels increase, the endogenous production becomes non-contributory. The model incorporates a very simple, linear relationship, in the hopes that the model's predictions would still be accurate. The data suggests that our assumptions are reasonable.

Our predictions and the values reported by the Esoterix assay are closer than typically seen in clinical medicine despite the assumptions made in our empiric model. There are three possible conclusions which can be drawn from this.

The assay and the model are both biased in the same direction from the "truth", which is why they report the same values,

Both the model and the Esoterix assay are remarkably accurate, which is why our model's predictions and the measurements are clinically equivalent.

The actual relationship between Testopel® implants and serum testosterone probably involves more pathways than accounted for in the model, but, for clinical purposes, we have accounted for the important relationships.

Because our confidence in the accuracy of our model and in the Esoterix assay is high, we propose using the model as a predictive tool to initiate and maintain Testopel® therapy. Our quantitative approach replaces the qualitative approach to therapy which has been the mainstay until now. Clinicians can choose average, peak, and trough levels, as well as implantation frequency before starting therapy. When the initial dosage or interval is properly personalized, steady state levels are possible by the beginning of the second cycle of Testopel® implants. Our model is clinically applicable and its use removes the need to wait more than 12 months (four times the implant interval) to reach targeted levels. Target values can be obtained as early as the beginning of the second cycle of therapy, allowing for more rapid correction of the symptoms of hypogonadism.

Although not a goal of this study, we believe that the approach used can be duplicated to target therapy with other moieties of testosterone pellets, thereby increasing the scope of useful outcomes from this study.

Acknowledgements

The authors would like to acknowledge the use of the Wolfram Cloud Integrated Access to Computational Intelligence (Wolfram Research, Inc., 100 Trade Center Drive, Champaign, IL 61820-7237, USA) as an aid to confirm the accuracy of the equation derivations.

The authors would also like to thank Ms. Judith G. Miller for her editorial assistance and her assistance with refining the algorithms.

Appendix

Appendix A. Algorithm to determine best parameters

This appendix describes how the best triad ($\boldsymbol{\alpha_0}$, $\boldsymbol{\tau_0}$, $\boldsymbol{K_0}$) was obtained. All triad values for $\boldsymbol{\alpha}$ and $\boldsymbol{\tau}$ were calculated as the half-lives, not the time-constants. The process of obtaining the triad corresponding to the lowest ***SSE*** was programmed as a macro to eliminate human calculation error and to hasten the process. To assure that the best three parameters were obtained, the algorithm evolved over time even as additional data was collected. Three of the major steps in the algorithm's development will be described.

A primary assumption was that each of the parameters needed to be accurate to only three digits; in real life, this would be considered exceptionally precise. Calculations were performed using four or more digits, and then the results were rounded to the appropriate accuracy or precision. The basic technique was to pick a triad in 3-D space ($\boldsymbol{\alpha_0}$, $\boldsymbol{\tau_0}$, $\boldsymbol{K_0}$), compute the ***SSE*** of nearby points, move towards the point with the lowest ***SSE***, and repeat the process.

Data was analyzed on an HP Pavilion x360 Convertible laptop with an Intel® Core ™ i5-8250U CPU @ 1.60 GHz running at 1.80 GHz and 8.00 GB RAM. The time needed to perform the processing is mentioned to show ballpark figures, as the computer processor typically spends part of the time multiprocessing other tasks.

In the early algorithms, the smallest increment in the calculations was 0.01 for $\boldsymbol{\alpha}$ and $\boldsymbol{\tau}$, and 1 for $\boldsymbol{K}$. The first algorithm started by picking eight points ($\boldsymbol{\alpha_0} \pm 0.01$, $\boldsymbol{\tau_0} \pm 0.01$, $\boldsymbol{K_0} \pm 1$) near the starting point, and computing the ***SSE***'s. The parameters corresponding to the minimal ***SSE*** was then set as the new trial point, and the process repeated. When no new minimum was identified, the process ended. Unfortunately, using different starting points did not always identify the same local minimum. Because only a few actual data points had been collected at this time, the multiple minima were deemed a consequence of the sparse data. Even though the parameters identified were further apart than the accuracy of the numbers noted above, the values predicted by the model, using each of the "minimum" triads, were clinically close. The algorithm took more than 24 hours of computation time, and, unfortunately, the number of local minima did not decrease when the number of data points analyzed was increased.

In an effort to streamline the analysis, the algorithm was modified. In this second version, each trial point ($\boldsymbol{\alpha_0}$, $\boldsymbol{\tau_0}$, $\boldsymbol{K_0}$)

was now associated with 26 co-spherical points such that $(\alpha-\alpha_0)^2 + (\tau-\tau_0)^2 + (K-K_0)^2 = r^2$. The ratio between the allowable increment for each of the parameters remained the same as before (0.1x, 0.1x, 1.0x). Performing this analysis using polar coordinates is equivalent to the more common method of computing in orthogonal coordinates described above, but the number of possible directions taken from a trial point is increased at each step.

The ***SSE***'s for all 27 points (center point plus 26 co-spherical points) were computed using a large starting radius (equivalent to a large value of "x" applied to the ratios above). The triad with the lowest ***SSE*** became the new trial point, and this process was repeated until the center point (α_0, τ_0, K_0) was associated with the lowest ***SSE***. Then, the radius ***r*** was decreased and the process repeated until the variation in the parameters approximated the precision of the measurements. Multiple trials differed by reducing the radius with factors between 2 and 5, but the results were essentially unchanged.

In order to assure that the best parameters were obtained, the algorithm was now run using 12 specific starting points. Eight points represented the "corners" of the rectangular prism encompassing the range of likely values for the parameters, and five points were more centrally located on the faces. Table A-1 shows the starting points used.

Table A1. *Starting triads used for analysis and verification.*

parameter run	Pellet weight K (ng/dL/pellet)	Absorption half-life α·ln(2) (days)	Terminal half-life τ·ln(2) (days)
A	2000	10	30
B	2000	10	80
C	2000	20	30
D	2000	20	80
J	3700	15	55
E	5500	10	30
F	5000	10	80
G	5500	20	30
H	5000	20	80
K	8000	10	30
M	8000	20	80
N	8000	10	80
P	8000	20	30

The process of reducing the radius from its starting value to its minimum value was called one "loop" and it produced one minimal ***SSE***. However, there was no way of knowing if this value was a global minimum as well as a local minimum. So, the entire algorithm was run again, using the previously obtained triad (end of the last loop) with the radius which started the last loop. This process was repeated until the same triad was identified at the end of two successive loops. The triad thus obtained was deemed the triad representing the best fit of the data.

To obtain all the best values using the 12 starting points, it typically took more than five loops (for each starting point) and more than 48 hours total to compute SSE's at more than 36,000 points. Although multiple local minima were again often identified, all the triads representing best-fit parameters yielded clinically similar values. The values obtained using the polar approach were consistently closer to each other than those using the orthogonal approach.

Analysis of the results now led us to believe that the various minima were artifacts related to the increments used for each of the parameters.

The third version of the algorithm changed the parameter increments to yield more precise results. In its current and final form, the increments were varied by a percentage of the value of each parameter instead of by an absolute amount. The basic increment for α is 0.0705%; the basic increment for τ is 0.025%; and the basic increment for K is 0.028%. These basic increments were chosen empirically as values which caused equal increases in the ***SSE***, when the ***SSE*** was near its minimal value. Co-spherical points were examined as before, except that the radius was now equivalent to a multiplier applied to each of the basic increments. In the current algorithm, the radius starts at a value of 512, and is halved with each iteration, until its value equals 0.5. The first loop starts with a multiplier (radius) of 512, and each subsequent loop reduces the multiplier by 25%. So, the next multipliers are 128, 32, 8, and finally, in the last loop, 0.5.

As an example, assume the current value of α_0 is 20, then the minimal increment along the α axis is ± 0.0141 (= 20 x 0.0705%). In the first iteration, α will vary by ±7.2192 (= 0.0141 x 512) along the α axis. The other parameters will vary by 512 times their corresponding minimal percentages when moving along their respective axes. Co-spherical points are identified as before. Also, as before, the radius is quartered after each iteration, until it finally equals 0.5. Assume the value of α is now 14.248, then α will next vary by 0.00502242 (= 14.248 x 0.0705% x 0.5) when moving along its axis. Suppose the best triad is found at the next higher point along the α axis, where α = 14.25302242 (= 14.248 + 0.00502242), and no further reductions in the ***SSE*** are possible. The loop is restarted with the current triad and the multiplier (radius) becomes 128. Assume that the same point is again identified at the end of the next loop, the algorithm will now terminate and return the value of α = 14.3 (rounded to three-digit accuracy).

Finding the best triad with this algorithm was way more satisfactory than the previous versions of the algorithm. The first data analyzed was the "training" set, which contained serum measurements taken between June 13, 2017, and August 3, 2018, and it included pellet insertions starting from November 8, 2016. Using the 13 starting points shown in Table A1, the best triad was found at the end of the 1st loop with a second loop confirming the triad. The total time needed for all the calculations was reduced to 13 hours. Thirteen minima were located, but, after rounding off the values, only four triads remained. Table A2 shows these triads, which are all close in value.

Table A2. *Local minima identified with training set.*

Pellet weight K (ng/dL/pellet)	Absorption half-life α·ln(2) (days)	Terminal half-life τ·ln(2) (days)	Sum of squares residual SSEs (exact parameters)	Starting points
5270	14.8	38.3	1599.70*	A, B, F, G, H, J, M, N
5300	14.9	38.2	1599.70	K, P
5310	14.9	38.2	1599.71	E, G
5260	14.8	38.4	1599.71	D

* absolute avg%=2.929 %. mean= -0.400 %. SD = 4.583 %.

Appendix B. Algorithm Validation

Appendix B describes the methods used to internally validate this algorithm.

The third and final version of the algorithm as described in Appendix A was used to provide validation of the model. This appendix describes how the algorithm itself was validated.

Five different tests were used to demonstrate that the algorithm predicts accurate values for the three parameters. For each test, data was generated by the algorithm using target values: $\alpha \cdot \ln(2) = 15.0$, $\tau \cdot \ln(2) = 40.0$, $K = 6000$. For each test, random perturbations were introduced to vary one or more values in a normal distribution. Fifteen mock pellet insertion dates were chosen to represent likely real-life scenarios. In addition, mock serum values were computed on 28 dates representative of those which might be used during intensive clinical monitoring.

Test 1 was used as a control; the actual values predicted by the algorithm were used. In Test 2, the predicted serum values were varied randomly with a mean of 0 and a standard deviation of 3.2% (chosen purposely since HoSt certification requires duplicate results to be within 6.4%). In Test 3, the time of the implantations was varied randomly with a mean of 0 hours and a standard deviation of ½ hour. In Test 4, both the predicted serum values and the implantation time were varied the same as in Test 2 and Test 3. The results are summarized in Figure B1 through Figure B4, respectively.

TEST 1.1 Exact serum levels generated (control)

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5980	15.0	40.1	0.64	C
5980	14.9	40.1	2.46	H, M
5990	15.0	40.0	1.95	A, F, J, G
6000	15.0	40.0	0.00	B
6010	15.0	40.0	1.95	E, N, P
6020	15.0	39.9	0.63	D, K
Target Parameter				
6000	15.0	40.0	0.00	

Figure B-1a. Control test. No randomization of the data. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 1.2 Exact serum levels generated (control)

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5990	15.0	40.0	1.95	A, C, F, G, H, J, M
6000	15.0	40.0	0.00	B
6010	15.0	40.0	1.95	D, E, K, N, P
Target Parameter				
6000	15.0	40.0	0.00	

Figure B-1b*. Control test. No randomization of the data. Multiplier varies between 512 and 0.25. See Table A1 for definitions of the parameter sets.*

TEST 1.3 Exact serum levels generated (control)

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
6000	15.0	40.0	0.00	All starting sets
			2 loops	M, N
			3 loops	B
			4 loops	A, C, D, E, F, G, J, K, P
			5 loops	H
Target Parameter				
6000	15.0	40.0	0.00	

Figure B-1c*. Control test. No randomization of the data. Multiplier varies between 512 and 0.5. At end of loop (multiplier=0.5), all parameters are rounded before starting next loop. See Table A1 for definitions of the parameter sets.*

Our control (Test 1) was run three times. We wished to show that slight changes to the algorithm caused small changes in the convergence speed, but did not change the actual results.

Test 1.1 (Test 1, run 1) yielded six sets of closely related parameters. This is the algorithm used for predicting the final, clinical parameters. The parameters (half-lives, not time-constants) obtained were:

$$(\alpha_0, \tau_0, K_0) = (14.9, 40.1, 5980),\ (15.0, 40.1, 5980),\ (15.0, 40.0, 5990),\ \mathbf{(15.0, 40.0, 6000)},\ (15.0, 40.0, 6010),\ (15.0, 39.9, 6020)$$

Note the symmetry around our target parameters (15, 40, 6000).

For Test 1, run 2, the algorithm was modified to terminate when the multiplier reached 0.25 instead 0.5. This allowed the processing to continue past the precision level before the values were rounded. In this trial, only three parameters were identified:

$$(\alpha_0, \tau_0, K_0) = (15.0, 40.0, 5990),\ (15.0, 40.0, 6000),\ (15.0, 40.0, 6010)$$

Note that the algorithm now identified one point on each side of our target parameters (15, 40, 6000).

In the final modification (Test 1, run 3), the interim parameters identified at the end of each loop (when the multiplier reaches 0.5), were rounded before starting the next loop. Although the target parameters (15, 40, 6000) were identified as the best parameters regardless of the starting parameter values, it now took between 2 and 5 loops to converge upon the final values. As a comparison, all the calculations in the other Tests (with only one exception) took only 2 loops.

TEST 2.1 - Random noise added to serum levels

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
6990	17.4	36.7	717.15	J
7000	17.4	36.7	716.00	C, E, F, G, M
7000	17.5	36.7	719.35	A, D, N
7010	17.5	36.7	716.23	B, H
7050	17.6	36.6	716.00	K, P
Target Parameter				
6000	15.0	40.0	778.28	

Serum levels altered by a random percentage	Mean	Standard Deviation
Expected distribution of the changes	0.00%	3.20%
Actual distribution of the changes	0.03%	3.25%

Figure B-2a. Serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 2.2 - Random noise added to serum levels

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5690	13.4	40.6	593.16	D, H
5700	13.4	40.6	592.72	A, B, F, G, J, M, N
5720	13.5	40.5	593.14	C, E, P
5730	13.5	40.5	592.80	K
Target Parameter				
6000	15.0	40.0	678.53	

Serum levels altered by a random percentage	Mean	Standard Deviation
Expected distribution of the changes	0.00%	3.20%
Actual distribution of the changes	12.54%	3.10%

Figure B-2b. Serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 2.3 - Random noise added to serum levels

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5490	14.3	42.4	472.36	A, C, J
5500	14.3	42.4	471.65	B, D, F, H
5510	14.3	42.4	475.56	M
5520	14.4	42.3	471.74	E, G, N, P
5530	14.4	42.3	472.20	K
Target Parameter				
6000	15.0	40.0	592.46	

Serum levels altered by a random percentage	Mean	Standard Deviation
Expected distribution of the changes	0.00%	5.44%
Actual distribution of the changes	3.20%	2.89%

Figure B-2c. Serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 3.1 - Random changes to insertion time

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5980	15.0	40.1	0.57	C
5980	14.9	40.1	2.63	F, G, M
5990	15.0	40.0	1.89	A, B, H, J
6010	15.0	40.0	2.10	D, K, P
6020	15.1	39.9	2.42	E, N
Target Parameter				
6000	15.0	40.0	0.05	

Randomized insertion time changes	Mean (min)	Standard Deviation (min)
Expected distribution of the changes	0.00	30.0
Actual distribution of the changes	5.65	26.9

Figure B-3a. Insertion times (n=15) varied by a normally distributed, random amount. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 3.2 - Random changes to insertion time

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5980	15.0	40.1	0.65	B
5980	14.9	40.1	2.55	M
5990	15.0	40.0	1.92	C, F, G
6000	15.0	40.0	0.02	A, H, J
6020	15.0	39.9	0.67	D, K, P
6020	15.1	39.9	2.45	E, K, N, P
Target Parameter				
6000	15.0	40.0	0.02	

Randomized insertion time changes	Mean (min)	Standard Deviation (min)
Expected distribution of the changes	0.00	-2.47
Actual distribution of the changes	30.0	26.8

Figure B-3b. Insertion times (n=15) varied by a normally distributed, random amount. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 3.3 - Random changes to insertion time

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5960	14.9	40.1	1.83	B, C, D, F, H, J
5970	14.9	40.1	0.15	A, G, M
5990	15.0	40.0	2.22	P
6000	15.0	40.0	0.15	E, N, K
Target Parameter				
6000	15.0	40.0	0.15	

Randomized insertion time changes	Mean	Standard Deviation (min)
Expected distribution of the changes	0.00	30.0
Actual distribution of the changes	0.86	29.7

Figure B-3c. Insertion times (n=15) varied by a normally distributed, random amount. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 4.1 - Insertion time and serum levels changed

Predicted Parameters			SSE	Starting parameter sets
Pellet constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
5480	13.4	42.0	999.40	D, F
5490	13.4	42.0	998.16	B, G
5500	13.4	41.9	997.88	H, M
5510	13.4	41.9	999.49	A, C, E, J, N, P
5520	13.5	41.9	998.74	K
Target Parameter				
6000	15.0	40.0	1022.24	

Randomized noise added	Mean	Standard Deviation
Expected percent serum level change	0.0%	3.20%
Actual percent serum level changes	10.84%	3.21%
Expected insertion time change	0.00 min	30.00 min
Actual insertion time changes	-1.378 min	27.97 min

Figure B-4a. Insertion times (n=15) varied by a normally distributed, random amount, and serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 4.2 - Insertion time and serum levels changed

Predicted Parameters			SSE	Starting parameter sets
Pellet Constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
7860	20.7	35.2	591.45	A
7880	20.7	35.1	591.78	D, F, J, K, N
7890	20.7	35.1	591.36	B, E
7900	20.8	35.1	591.40	M
7910	20.8	35.1	591.51	C, G, H
8050	21.2	34.8	591.51	P
Target Parameter				
6000	15.0	40.0	725.90	

Randomized noise added	Mean	Standard Deviation
Expected percent serum level change	0.0%	3.20%
Actual percent serum level changes	-0.83%	2.86%
Expected insertion time change	0.00 min	30.00 min
Actual insertion time changes	1.453 min	31.74 min

Figure B-4b. Insertion times (n=15) varied by a normally distributed, random amount, and serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

TEST 4.3 - Insertion time and serum levels changed

Predicted Parameters			SSE	Starting parameter sets
Pellet Constant (ng/dL/pellet)	Absorption half-life (hr)	Elimination half-life (hr)		
7520	19.2	35.8	799.40	B, J
7530	19.2	35.8	800.70	F, G, K, M
7540	19.2	35.7	799.94	A
7540	19.2	35.8	804.47	C, H
7540	19.3	35.7	804.98	D, N
7550	19.3	35.7	800.94	E
7630	19.5	35.6	800.40	P
Target Parameter				
6000	15.0	40.0	870.42	

Randomized noise added	Mean	Standard Deviation
Expected percent serum level change	0.0%	3.20%
Actual percent serum level changes	0.14%	3.51%
Expected insertion time change	0.00 min	30.00 min
Actual insertion time changes	1.058 min	30.52 min

Figure B-4c. Insertion times (n=15) varied by a normally distributed, random amount, and serum levels (n=28) varied by a normally distributed, random percentage. Multiplier varies between 512 and 0.5. See Table A1 for definitions of the parameter sets.

Tests 3, 4, and 5 only used a small number of random numbers: Test 2 used 28, Test 3 used 15, Test 4 used 43. Because of this, each test was repeated three times, using different random numbers. As can be seen from the tables, none of the randomly varied numbers actually had a mean difference of zero, although their standard deviations were close to the targeted 3.2%. Because of this, we might expect the algorithm to converge on parameters which were slightly different from the target parameters. The larger variation in the data seen in Test 4 caused the algorithm to converge on a few nearby parameters.

Our conclusion is that the algorithm, as it stands, is sufficient to predict the parameters. At the expense of a bit more computing time, we could reduce the number of triads identified, but the precision of the parameters is not improved. Clinically, the accuracy of serum laboratory testing is generally less than three digits [23]. Rounding off the values before the termination of the process is clearly disadvantageous.

The fact that the algorithm converged on one or more closely associated triads is a verification of the algorithm. An early assumption was that all parameters had three digits of precision, but examination of the triads identified above leads us to conjecture that the pellet weight might have a bit less than three digits of precision.

Since the double exponential terms in the model's equations preclude us from finding a single triad solution, the best hope is to identify a triad which predicts the serum testosterone levels within clinical significance. An exact solution is simply not possible, but our algorithm does produce acceptable solutions.

References

[1] Baillargeon J, Kuo YF, Westra JR, Urban R, Goodwin J (2018) Testosterone prescribing in the United States, 2002-2016, JAMA - Journal of the American Medical Association, vol. 320, no. 2, pp. 200-202. https://doi.org/10.1001/jama.2018.7999

[2] Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB (2007) Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab.; 92: 4241–4247.

[3] CDC Laboratory/Manufacturer Hormone Standardization (HoSt) Program: Total Testosterone - Participant Protocol (report created December 2012, updated January 2013) https://www.cdc.gov/labstandards/pdf/hs/Testosterone_Protocol.pdf

[4] CDC HoSt Certified Total Testosterone Procedures (updated November 2018) https://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Testosterone_Procedures-508.pdf

[5] CDC Improving Steroid Hormone Measurements in Patient Care and Research Translation (updated July 6, 2017) https://www.cdc.gov/labstandards/hs_workshop.html

[6] Vesper HW, and Botelho JC (2012) Testosterone. An Overview of CDC's Standardization Initiative, JUN. 1. 2012, Clinical Laboratory News

[7] McCullough, A. (2014) Curr Sex Health Rep 6: 265. https://doi.org/10.1007/s11930-014-0033-7

[8] Seitman D, Fallon J, Kimmel B (2019) Testosterone therapy with Testopel® and the Esoterix Laboratory assay: a CASE study. Urology case reports. https://doi.org/10.1016/j.eucr.2021.101714

[9] Greenblatt, DJ, Koch-Weser, J (1975) The New England Journal of Medicine, Oct 22, 293:7023-705.

[10] Kaminetsky JC, Moclair B, Hemani M, Sand M (2011) A Phase IV Prospective Evaluation of the Safety and Efficacy of Extended Release Testosterone Pellets for the Treatment of Male Hypogonadism. April Journal of Sexual Medicine 8 (4): 1186-96(ISSN: 1743-6109). DOI:10.1111/j.1743-6109.2010.02196.xs

[11] McCullough AR, Khera M, Goldstein I, Hellstrom WJ, Morgentaler A, Levine LA (2012) A multi-institutional observational study of testosterone levels after testosterone pellet (Testopel®) insertion. J Sex Med. 9 (2): 594-601 (ISSN: 1743-6109)DOI: https://doi.org/10.1111/j.1743-6109.2011.02570.x

[12] Pastuszak AW, Mittakanti H, Liu JS, Khera M (2012) Pharmacokinetic Evaluation and Dosing of Subcutaneous Testosterone Pellets. Journal of Andrology, March 33 (5): 927-37 (ISSN: 1939-4640), DOI: 10.2164/jandrol.111.016295

[13] McMahon CG, Shusterman N, Cohen B. (2017) Pharmacokinetics, Clinical Efficacy, Safety Profile, and Patient-Reported Outcomes in Patients Receiving Subcutaneous Testosterone Pellets 900 mg for Treatment of Symptoms Associated With Androgen Deficiency. J Sex Med 14:883e890 DOI: https://doi.org/10.1016/j.jsxm.2017.04.734

[14] Handelsman DJ, Conway AJ, Boylan LM. (1990) Pharmacokinetics and pharmacodynamics of testosterone pellets in man. J Clin Endocrinol Metab 71: 216–222.

[15] Jockenhövel F, Vogel E, Kreutzer M, Reinhardt W, Lederbogen S, Reinwein D. (1996) Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. Clin Endocrinol (Oxf) 45: 61–71.

[16] Kelleher S, Turner L, Howe C, Conway AJ, Handelsman DJ. (2004) Testosterone release rate and duration of action of testosterone pellet implants, Clinical Endocrinology, 27 February, https://doi.org/10.1111/j.1365-2265.2004.01994.x

[17] Seftel A. (2007) Testosterone Replacement Therapy for Male Hypogonadism: Part III. Pharmacologic and Clinical Profiles, Monitoring, Safety Issues, and Potential Future Agents. Int J Impot Res. 19 (1): 2-24.

[18] Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. (2018) Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 103, Issue 5, 1 May, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

[19] Jones H (ed) (2008) Testosterone Deficiency in Men, edited by Hugh Jones, Oxford University Press.. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/alliant/detail.action?docID=975596.

[20] Lehtihet M, Arver S, Bartuseviciene I, Pousette Å. (2012) S-testosterone decrease after a mixed meal in healthy men independent of SHBG and gonadotrophin levels. Andrologia. 23 April https://doi.org/10.1111/j.1439-0272.2012.01296.x

[21] Matsumoto AM, Bremner WJ (2004) Serum testosterone assays — accuracy matters, J Clin Endocrinol Metab (89): 520–524.

[22] Rosner W, Auchus R, Azziz R, Sluss P, Raff H (2007) Utility, Limitations, and Pitfalls in Measuring Testosterone: An Endocrine Society Position Statement J Clin Endocrinol Metab 92 (2): 405–413.

[23] Clinical Lab Navigator. (2021) www.clinlabnavigator.com/precision.html