Choosing an optimal input for an intravenous glucose tolerance test to aid parameter identification

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Keywords
Fisher information matrix; glucose; insulin; minimal model; parameter estimation

Abstract

Objective The minimal model is used to estimate insulin sensitivity in patients with diabetes, following an intravenous glucose tolerance test (IVGTT). Issues have been reported regarding parameter estimation, including correlation between insulin sensitivity and action parameters. The objective was to reduce these issues, by modifying the input of glucose in the test.

Methods Data were available for 24 volunteers following an IVGTT and glucose clamp test. Correlation between parameters was explored using likelihood heat-maps. An integrated glucose–insulin model was used to simulate glucose and insulin concentrations following new glucose inputs. The improved input for the test was selected by finding the minimum inverse of the determinant of the Fisher information matrix.

Key findings When the minimal model was fitted to the IVGTT data, there was clear correlation between the insulin parameters. With the glucose clamp, all parameters were correlated and badly estimated. The modified input, a bolus dose followed by constant infusion, resulted in improvement in parameter estimation and reduction in parameter correlation.

Conclusions It is possible to reduce the issues with parameter estimation in the minimal model by modifying the glucose input, leading to a simplified test design and a reduction in the total amount of glucose infused.

Introduction

Diabetes mellitus is a chronic disease, resulting in increased glucose concentration in the blood, due to reduced sensitivity to insulin. Being able to estimate a patient’s insulin sensitivity can therefore be important in diagnosis and treatment. Tests such as the intravenous glucose tolerance test (IVGTT) can be used to estimate insulin sensitivity, whereby a short infusion (60–90 s) of glucose is given and then glucose and insulin blood concentrations are measured over a period of time to assess the response. Alternative tests, such as the glucose clamp test, can also be used where the rate of glucose infusion required to maintain a given glucose concentration can be used to estimate insulin sensitivity. While IVGTT and glucose clamp tests are considered to be the most reliable methods for estimating insulin sensitivity, many others exist and have been summarised in a number of review articles.\(^1\)–\(^3\)

Many models have been developed based on data from IVGTT experiments, but one of the most widely used is the minimal model proposed by Bergman et al.,\(^4\) which describes glucose kinetics with one compartment, and the effect of insulin via a remote compartment. Despite its popularity, numerous issues have been reported with the minimal model. There are suggestions it may be ‘too minimal’, with a single compartment to model glucose thought to be inadequate.\(^5\)–\(^6\) Problems with parameter estimation have also been reported. One study found the estimate of glucose effectiveness was being overestimated, leading to underestimation of insulin sensitivity.\(^7\) Similarly, in another study, it was found that often insulin sensitivity was impossible to distinguish from zero.\(^8\) It was also reported that the estimate of glucose effectiveness was found to be reduced in patients with diabetes.\(^9\) Issues with identifiability have also been raised, with insulin sensitivity and insulin action found to be correlated and at risk of numerical non-identifiability.\(^10\) Poor agreement between the minimal model and glucose clamp estimates of insulin sensitivity has also been reported for patients with diabetes.\(^11\) A few solutions have been proposed, one being the use of Bayesian estimation.\(^10\)
In this study, we aimed to improve the design of these tests in order to overcome the issues discussed above. To compare new test designs, data had to be simulated following each design. However, the minimal model only describes the glucose concentration over time, given observed insulin concentrations. This means insulin concentrations could not be simulated by the minimal model, and as glucose and insulin levels are interdependent, glucose could not be simulated given a change in the study design. Therefore, a second more mechanistic model was used to simulate proposed study designs.

Methods

The data

Data were available from a double-blind, crossover study with 24 volunteers, comparing two different formulations of human insulin for similarity of performance. The same data have previously been used to develop a new model using a proportional–integral–derivative controller. Each volunteer first underwent an IVGTT, with a 0.3 g/kg dose of a 20% glucose solution being infused over 60–90 s. The following day each volunteer had a euglycaemic clamp, where a 0.2U/kg subcutaneous dose of the new insulin formulation was given, and their glucose concentration was clamped at their individual fasting blood glucose level on that day using an I.V. 20% glucose infusion. Data from the other insulin formulation were not included. More information on the study design and original data analysis can be found in Mills, 2006.

During the IVGTT, roughly 11 samples were taken per volunteer at recorded times, initially every 5 min and then in increasing intervals of 10, 20 and 40 min up to about 4 h after the dose was administered. In the glucose clamp test, the glucose concentration was sampled approximately 20 times per subject after the insulin dose, initially in intervals of 5 min, increasing to intervals of 60 min, for a total of 8 h. The exact sampling times varied between volunteers. The infusion rate was altered every 5 min, using a bedside HemoCue® to monitor glucose concentrations, starting 50 min from the start of the test. Blood samples were taken so that the insulin concentration could be measured. Plots of the available data are shown in Figure 1.

Modelling

The minimal model

The minimal model was first introduced by Bergman et al. in 1979 and was found to be capable of describing glucose disappearance following an IVGTT. Its main use is to estimate insulin sensitivity in patients, through the estimation of the insulin sensitivity parameter SI, and it is widely used to investigate glucose metabolism.

The model consists of one central compartment, in which glucose concentration is observed and a remote insulin compartment which effects glucose disappearance, and can inhibit glucose production, as seen in Figure 2. There are four parameters to be estimated, insulin sensitivity S_I, glucose effectiveness SG, insulin action p_2 and the volume of distribution of glucose V.

The equations used for the minimal model are given in equations 1 and 2, with parameterisation as in Pillonetto et al., 2003.

Figure 1 Individual glucose and insulin profiles from 24 healthy volunteers following intravenous glucose tolerance test (top) and glucose clamp experiments (bottom), with mean profiles (solid lines).
glucose and insulin profiles to be simulated. The model was developed by Silber et al.\cite{16} in both healthy volunteers and patients with type 2 diabetes, using data from IVGTT and glucose clamp experiments, and simultaneously modelled glucose, labelled glucose and insulin.

Glucose was modelled using a two-compartment model, with a central compartment $G_C$ and peripheral compartment $G_P$, whose volumes were $V_C$ and $V_P$, respectively. Both insulin-dependent ($CL_{Gd}$) elimination and insulin-independent ($CL_G$) elimination were included. Two effect compartments were included for glucose, one controlling glucose production ($G_{E2}$) and the other second-phase insulin secretion ($G_{E2}$), which were included to allow delays in effect. Glucose production ($GP_{ROD}$) was dependent on both the steady-state glucose concentration ($G_S$) and elimination rate of glucose at baseline. Insulin was described with a one-compartment model, with volume $V_I$. The glucose model is described by equations 5–11 in the Appendix. Insulin secretion was separated into two phases with the first phase described with a bolus dose ($FPS$) and second phase being dependent on glucose concentration. Baseline insulin secretion was assumed to be the product of steady-state insulin ($I_S$) and elimination rate, and insulin elimination was described by $CL_I$. Insulin had one effect compartment, for regulation of insulin-dependent glucose elimination $I_P$. The glucose model is described by equations 12–19 in the Appendix. More detailed explanation of the model and its development can be found in Silber et al., 2007.\cite{16}

The model had to be modified, as the clamp experiment included a subcutaneous dose of insulin before the beginning of the glucose clamp test. In order to add this to the existing model, an absorption model was adapted from Nucci et al., 2000.\cite{17} The model had two compartments, the depot where the insulin is initially added, and a soluble compartment that introduces a delay before insulin reaches the blood stream, with rate constant $k_{A}$. The whole adapted model structure is shown in Figure 3.

The integrated glucose–insulin model was fitted to the combined data in NONMEM using first-order conditional estimation (FOCE) as in.\cite{16} The model was fitted to log-transformed data, with an additive residual error model assumed for both glucose and insulin and interindividual variation following an exponential model. The glucose units were changed to be consistent with those used in the minimal model. Parameters specific to patients or labelled glucose were excluded as they did not apply to this population. For the clamp data, no first-phase insulin secretion was assumed, as glucose concentration is too low to trigger it.\cite{18}

**Heatmaps**

Heatmaps were created for each pair of the four parameters in the minimal model using the method outlined in

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\textbf{The integrated insulin–glucose model}

An integrated insulin–glucose model was also fitted to the data as it was more comprehensive and allowed both

\[ \frac{dQ(t)}{dt} = -(S_G + X(t))Q(t) + S_G G_B V, \quad Q(0) = G_B V \]  

\[ \frac{dX(t)}{dt} = -p_2(X(t) - S_1(1 - I(t) - I_0)), \quad X(0) = 0 \]

where $G(t) = Q(t)/V$ and $l(t)$ are glucose and insulin concentrations, $G_B$ and $I_0$ are the glucose and insulin baseline values for each individual, $V$ is the volume of distribution, and $X(t)$ denotes insulin action. $I(t)$ is assumed to be known. The $k$s in the Figure 2 are rate constants, the model was reparametrised to make it \textit{a priori} uniquely identifiable,\cite{14} with $S_G = k_1 + k_5$, $p_2 = k_3$, $S_1 = k_4(k_4 + k_6)$, and $X(t) = (K_4 + K_6) I(t)$, where $I(t)$ is the concentration of insulin in the remote insulin compartment.

While the minimal model is generally fitted to data generated during an IVGTT, here it was also fitted to the data generated during glucose clamp tests, with the aim being to reduce issues with the minimal model using additional data which is commonly available in practice. The minimal model was fitted to the IVGTT and clamp data separately, as well as to the combined data set in NONMEM 7.3\cite{15} using the first-order (FO) estimation method, interindividual variabilities were estimated on all four parameters using an exponential model, and the glucose residual variation was assumed to be additive, as in.\cite{13} Simulation of both glucose and insulin profiles was not possible using the minimal model as insulin was treated as a covariate, and not explicitly modelled, meaning no extrapolation of dose or sampling times could be carried out.
To create the heatmap, data were simulated in MATLAB with each pair of parameters being varied, and the remaining two parameters held at the population estimates from the minimal model fitted to the data. The likelihood function for each combination of the varying parameter values was then plotted as a heatmap.

The likelihood function for a given set of parameters $\theta$ is shown in Equation 3.

$$L(y, \theta) = \frac{1}{\det(2\pi \Sigma)^{1/2}} \exp \left( -\frac{1}{2} \sum_{i=1}^{N} \left( \frac{y_i - G(t_i, \theta)}{\sigma_i} \right)^2 \right)$$

(3)

where $\Sigma$ is the covariance matrix, which is diagonal with elements $\sigma_i^2$, the variance at each time point $i$, which in this case is constant due to the additive error model being used, $y_i$ is the observed glucose concentration at time point $i$ and $G(t_i, \theta)$ is the predicted glucose concentration at time point $i$ given the set of parameter values $\theta$. Heatmaps were created in MATLAB, using the colormap function, for IVGTT and glucose clamp data, as well as the data sets combined.

### Dose dependency of the information content in the model

In order to improve the ability to estimate the parameters of the minimal model, and reduce the correlation of parameters, different doses were simulated for the IVGTT experiment. Different constant infusion rates were also tested to be used as a simplified approximation of the glucose clamp test. As it was not possible to simulate data from the minimal model, data were instead simulated from the integrated model. Data were only simulated for one volunteer for each design, as the purpose of the minimal model is to assess each individual’s insulin sensitivity.

The minimal model was then fitted to each simulated individual, assuming fixed effects only. In order to then assess how well each test input allowed the parameters of the minimal model to be estimated, the determinant of the Fisher information matrix (FIM) was calculated. The higher the determinant of the FIM, the lower the standard errors on the parameter. This metric is often used in optimal design, which upon maximisation gives the D-optimal design, although other optimality criteria could also be used. The FIM for a fixed effects model is given in Equation 4. Details of how to calculate this matrix can be found in the literature.

$$F(t, \theta) = \int \sum_{i}^{-1} J^T$$

(4)

where $\Sigma$ is the diagonal variance matrix, and $J$ is the Jacobian matrix for a given set of parameter values.

The resulting determinant of the FIM was then plotted for different doses and infusion rates, to assess which input gave the best parameter estimates. The best bolus dose and constant infusion rate were then combined, and the resulting heatmaps from the fitting of the minimal model were created. These were then compared to the heatmaps from the combined observed data, to assess whether there had been any reduction in correlation.

### Results

#### Modelling

**The minimal model**

The parameter estimates from the minimal model for each of the data sets are given in Table 1.
may be due to the expected correlation of this parameter data alone, suggests that when the minimal model is fitted to the IVGTT were analysed together. This supports evidence that sug-
to have higher insulin sensitivity when data from both tests set separately, so in general the volunteers were estimated
estimate is higher for the combined data than in either data
errors calculated for
of
error in its estimate of interindividual variability. The value
cose in this test, which is reflected in the very high standard
clamp data, which may be due to difficulties in estimating
remains. In
the other pairs of parameters show less evidence of correla-
tion. However, there are occasions where the most likely parameter values fall outside of the valid parameter spaces by falling below zero (S_I vs S_I and p_2), which could be addressed by instead estimating the logarithm of the parameters.
When using the minimal model with the clamp data, there is generally more uncertainty around parameter esti-
mates, and the correlation between S_I and p_2 remains. In the case of S_I and V, the parameter values with the highest likelihood fall far away from those found using the other two data sets, which is reflected in the parameter estimates in Table 1.
When the minimal model is fitted to the combined data set, the uncertainty around the parameter estimates is much smaller. There is a suggestion of correlation between S_I and p_2, but it is reduced compared to either data set alone. The most likely value of S_I appears higher than in either data set on its own. Both V and S_I are estimated to be higher, which is reflected in the minimal model parameter estimates (Table 1). All parameters are now expected to be positive.

### Table 1 Parameter estimates from the minimal model, with relative standard errors (RSE %) from bootstrapping in parentheses

| Parameter estimates | IVGTT | Clamp | Combined |
|---------------------|--------|-------|----------|
| SI (min⁻¹)          | 0.00075 (1400) | 0.00044 (20) | 0.00134 (13) |
| SG (min⁻¹)          | 0.0340 (7) | 0.0568 (5) | 0.0181 (15) |
| V (l/kg)            | 0.139 (43) | 0.472 (76) | 0.165 (4) |
| p2 (min⁻¹)          | 0.0005 (74) | 0.0170 (18) | 0.0138 (13) |
| Interindividual variation CV% | 0.31 (50) | 31.5 (273) | 39.4 (36) |
| Additive residual error | 0.210 (25) | 0.165 (18) | 0.311 (19) |

The parameter estimates differ between the three data sets. In the case of insulin sensitivity (S_I), the population estimate is higher for the combined data than in either data set separately, so in general the volunteers were estimated to have higher insulin sensitivity when data from both tests were analysed together. This supports evidence that sug-
to have higher insulin sensitivity when data from both tests set separately, so in general the volunteers were estimated
estimate is higher for the combined data than in either data
errors calculated for
of
error in its estimate of interindividual variability. The value
cose in this test, which is reflected in the very high standard
clamp data, which may be due to difficulties in estimating
remains. In
the other pairs of parameters show less evidence of correla-
tion. However, there are occasions where the most likely parameter values fall outside of the valid parameter spaces by falling below zero (S_I vs S_I and p_2), which could be addressed by instead estimating the logarithm of the parameters.
When using the minimal model with the clamp data, there is generally more uncertainty around parameter esti-
mates, and the correlation between S_I and p_2 remains. In the case of S_I and V, the parameter values with the highest likelihood fall far away from those found using the other two data sets, which is reflected in the parameter estimates in Table 1.
When the minimal model is fitted to the combined data set, the uncertainty around the parameter estimates is much smaller. There is a suggestion of correlation between S_I and p_2, but it is reduced compared to either data set alone. The most likely value of S_I appears higher than in either data set on its own. Both V and S_I are estimated to be higher, which is reflected in the minimal model parameter estimates (Table 1). All parameters are now expected to be positive.

### Table 2 Parameter estimates for integrated glucose–insulin model, with relative standard errors (RSE %) from bootstrapping in parentheses

| Parameter                        | Estimated value | CV% |
|----------------------------------|----------------|-----|
| GSS – Glucose baseline (mmol/l)  | 5.12 (2)       | 5.78 (1) |
| BS – Insulin baseline (mU/l)     | 6.33 (32)      | 31.59 (123) |
| VG – Central glucose volume (l)  | 10.8 (5)       | 37.82 (71) |
| CLG – Glucose clearance (l/min)  | 0.104 (23)     | 37.42 (19) |
| CLI – Insulin clearance (l/min)  | 0.774 (10)     | 56.75 (413) |
| CLGI – Insulin-dependent glucose clearance (l/min/mU/l) | 0.000896 (16) | 46.37 (151) |
| KGE1 – Rate constant for effect compartment (1/min) | 0.00057 (361) | – |
| FPS – Magnitude of first-phase insulin secretion (mU/l) | 649 (9) | 449.44 (61) |
| Q – Intercompartmental clearance (l/min) | 0.0528 (178) | 308.54 (218) |
| VP – Peripheral glucose volume (l) | 33.8 (45) | 0.30 (819) |
| KGE2 – Rate constant for effect compartment (1/min) | 0.710 (0) | 243.72 (4940) |
| KIE – Rate constant for effect compartment (1/min) | 0.0177 (34) | 68.34 (284) |
| IPRG – Power function (–) | 1.78 (75) | 62.77 (4131) |
| V1 – Insulin volume (l) | 0.837 (536) | 175.21 (14) |
| GPRG – Power function (–) | –0.161 (117) | – |
| KIS – Rate constant for first-phase insulin secretion (1/min) | 0.0854 (129) | – |
| KA – Subcutaneous insulin absorption rate constant (1/min) | 0.0062 (45) | 25.14 (4) |
| Glucose residual error – (%) | 9.01 (5) | – |
| Insulin residual error – (%) | 15.4 (2) | – |

The integrated insulin–glucose model

The parameter estimates from the integrated glucose model are shown in Table 2, and model fits can be found in the supplementary material (Figure S3).

### Heatmaps

Heatmaps for every pair of parameters are shown for one individual below for IVGTT (Figure 4a), glucose clamp (Figure 4b) and combined data sets (Figure 4c).

The heatmaps show that when using the minimal model with the IVGTT data, the S_I and p_2 parameters are highly correlated, as has been previously reported in the literature.
Figure 4  Heatmaps showing the likelihood for each combination of parameters when fitting the minimal model to (a) the intravenous glucose tolerance test data, (b) the glucose clamp data and (c) the IVGGT and clamp data combined. [Colour figure can be viewed at wileyonlinelibrary.com]
**Dose dependency of the information content in the model**

The dose currently given during an IVGTT of 0.3 g/kg is close to optimal for the fitting of the minimal model. However, a constant infusion at a lower rate of 0.00075 g/kg.min for 4 h is better for the minimal model than the average infusion rate in the first 240 min of the clamp experiment, which was around 0.004 g/kg.min. It is noted that the best bolus dose with the best constant infusion rate is not necessarily the best combination of doses; however, numerical issues were encountered when attempting to simultaneously improve both. Plots of the determinant of the FIM for varying doses in both the IVGTT and constant infusion are shown in Figure 5.

The heatmaps created from the simulated data set using the improved design are shown in Figure 6. These heatmaps are not directly comparable to those shown in Figure 4 in terms of size and parameter estimates as they are dependent on the data set used. The previous plots were based on observed test data from one individual subject, whereas those in Figure 6 are based on simulated profiles for one individual with the improved test design. However, the general shape of the relationship between the pairs of parameters is comparable. The correlation between $S_I$ and $p_2$ has been reduced compared to the previous inputs. There is some evidence of correlation between $S_I$ and $S_G$ which has not been previously apparent but has been reported in the literature.[7,8]

**Discussion**

Through modifying the test input, by finding the best bolus dose and constant infusion rate, it has been possible to improve the glucose test input, so that when the resulting data are modelled using the minimal model, the correlation between the important insulin sensitivity parameters $S_I$ and $p_2$ has been greatly reduced. This shows how study designs can be improved with respect to a model, through simulations, even though it is not possible to simulate from the model itself. Here, a number of different doses have been simulated, and the best chosen based on the FIM, but the method could be further extended to formally optimise designs.

In general, improving study designs using this method could lead to more information being gained from the same number of subjects, or may allow fewer subjects to be used overall. In this case, the new test design could allow improved estimation of a patient’s insulin sensitivity, which is the primary aim of this model. Additionally, the chosen test design of a bolus dose, followed by a constant infusion, means a reduction in the total amount of glucose being infused and the length of the test, which would be beneficial for future patients undergoing such a test.

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**Figure 5** Determinant of the Fisher information matrix for varying doses in the intravenous glucose tolerance test (left) and constant infusion (right). Vertical line in left-hand plot shows the dose given in the intravenous glucose tolerance test experiment, and vertical line in the right-hand plot shows the average infusion rate in the first 240 mins of the glucose clamp experiments. [Colour figure can be viewed at wileyonlinelibrary.com]

**Figure 6** Heatmaps showing the likelihood for each combination of parameters when fitting the minimal model to the modified input data. [Colour figure can be viewed at wileyonlinelibrary.com]
The limitation of this method is the dependence on the model that is used for the simulations. In this case, the results depend upon the integrated glucose–insulin model; any model misspecification may lead to the wrong study design being chosen. Using this method in other settings relies on having a good, comprehensive model on which the simulations can be based. However, the results show that if such a model is available or can be developed, it is possible to improve the study design.

Conclusions
The minimal model fitted to IVGTT data has established issues with parameter estimation, in particular correlation between $S_I$ and $p_2$. The aim was to improve the parameter estimation by improving the IVGTT design. Data could not be simulated using the minimal model itself, so the more mechanistic integrated glucose–insulin model was used to simulate from new glucose inputs. The new glucose input reduces correlation between parameter estimates. Using this new glucose input, rather than conducting an IVGTT alone can improve the estimation of insulin sensitivity in patients with diabetes. It also reduces the length of the time of the test for patients and reduces the total amount of glucose infused compared to a glucose clamp test.

Declarations

Conflicts of interest
The authors declare they have no conflicts of interest.

Funding
This work was supported by the Biotechnology and Biological Sciences Research Council (BBSRC) [BB/L502583/1].

Acknowledgement
The authors would like to acknowledge Dr Richard Mills, ICON, and Dr Steen Hvass Ingwersen, Novo Nordisk, for the clinical data set. This study was approved by an independent ethics committee. Volunteers gave informed consent.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Individual predictions vs. observed glucose concentrations for the minimal model in the IVGTT, glucose clamp and combined data sets

Figure S2 Individual fits from the minimal model (red) against observed profiles (black) for the same three individuals for IVGTT (top), glucose clamp (middle) and combined data (bottom)

Figure S3 Population fit (blue) of integrated glucose insulin model to IVGTT data (top), and individual predictions vs. observed values for glucose clamp (bottom) for glucose (left) and insulin (right)

Appendix

Equations describing the two-compartment glucose model, glucose effect compartments and baseline glucose production.

\[
\frac{dG_C(t)}{dt} = G_{PROD}(t) + \frac{Q}{V_P} \cdot G_P(t) - \left( \frac{CL_G}{V_G} + \frac{CL_{GI}}{V_G} \cdot I_E(t) + \frac{Q}{V_G} \right) \cdot G_C(t), \quad G_C(0) = G_{SS} \cdot V_G
\]  

(5)

\[
\frac{dG_p(t)}{dt} = \frac{Q}{V_G} \cdot G_C(t) - \frac{Q}{V_P} \cdot G_P(t), \quad G_P(0) = G_{SS} \cdot V_P
\]  

(6)

\[
\frac{dG_{E1}(t)}{dt} = k_{GE1} \cdot \frac{G_C(t)}{V_G} - k_{GE1} \cdot G_{E1}(t), \quad G_{E1}(0) = G_{SS}
\]  

(7)

\[
\frac{dG_{E2}(t)}{dt} = k_{GE2} \cdot \frac{G_C(t)}{V_G} - k_{GE2} \cdot G_{E2}(t), \quad G_{E2}(0) = G_{SS}
\]  

(8)

\[
G_{PROD,0} = G_{SS} \cdot (CL_G + CL_{GI} \cdot ISS)
\]  

(9)

\[
G_{CM1}(t) = \left( \frac{G_{E1}(t)}{G_{SS}} \right)^{GPRG}
\]  

(10)

\[
G_{PROD}(t) = G_{PROD,0} \cdot G_{CM1}(t)
\]  

(11)

Equations describing the one-compartment insulin model, baseline insulin production and first- and second-phase insulin secretion.

\[
\frac{dI(t)}{dt} = I_{SEC}(t) - \frac{CL_I}{V_I} \cdot I(t) + K_A \cdot SC_i(t), I(0) = I_{SS} \cdot V_I
\]  

(12)

\[
\frac{dI_E}{dt} = K_{IE} \cdot I(t) - K_{IE} \cdot I_E(t), I_E(0) = I_{SS}
\]  

(13)

\[
\frac{dSC_D(t)}{dt} = -K_A \cdot SC_D(t)
\]  

(14)

\[
\frac{dSC_i(t)}{dt} = K_A \cdot SC_D(t) - K_A \cdot SC_i(t)
\]  

(15)

\[
\frac{dIFPS(t)}{dt} = -K_{IS} \cdot IFPS(t), IFPS(0) = FPS
\]  

(16)

\[
I_{SEC,0} = I_{SS} \cdot CL_I
\]  

(17)

\[
G_{CM2}(t) = \left( \frac{G_{E2}(t)}{G_{SS}} \right)^{IPRG}
\]  

(18)

\[
I_{SEC}(t) = I_{SEC,0} \cdot G_{CM2}(t) + K_{IS} \cdot IFPS(t)
\]  

(19)

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