Homotopy perturbation approximate solutions for Bergman’s minimal blood glucose-insulin model

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Abstract

In this paper, we use the Homotopy Decomposition Method (HDM), to solve fractional nonlinear differential equations systems that arise in Bergman's minimal model, used to describe blood glucose and insulin metabolism, after intravenous tolerance testing. Consequently, numerical simulations representing Bergman approximate solutions demonstrate they are indeed continuous functions of derivatives. Not only is the HDM extremely versatile throughout in solving nonlinear fractional partial differential equations systems, but also, despite its direct simplicity, does turn out to be highly efficient, as thoroughly shown below.

Introduction and Motivation

During the nineties, when faced with blood or blood constituent’s dynamical transport phenomena, researchers almost always tried their hand at applying classical theory tools to describe related processes, (see refs in [1-4]). Certainly successful as those efforts were, attempts to see biological and fluid physiological flavor phenomena related to transport processes may be looked from stochastic points of views, emphasizing the pursuit of individual particles, balanced with the particle ensemble approach [5,6], in light of convective diffusion equations. A decade later, such efforts were further enriched with serious and rather successful attempts at connecting state of the art approaches at the time with Naviers-Stokes and Burgers equations with intentions to study turbulence, via the Hopf-Cole transformation setup [7-10]. Now, nearly a quarter of a century on since the Biophysical Journal article [1], having to some extent manipulated tools from the classical Eulerean Continuum Calculus, and the Lagrangian Stochastic Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other Calculus, and expanded techniques that we propose to term: the Hopf-Cole Calculus, here in a total change of gear, the stage is set for no other

In this paper, we consider the Fractional setup of Bergman minimal model for blood glucose-insulin interactions. For a practical purpose we solve the consequent system of fractional partial differential equations moderate the glucose-insulin metabolism, after intravenous tolerance testing. Worthy is it to note here, that typically, to describe physiological and biological processes, standard mathematical models of integer-order derivatives, including nonlinear models, do not always work adequately in many such cases, and the Bergman minimal model turns out to be of no exception. That is why, we found it necessary to implement the non-classical tools, which proved very useful and pragmatic in various fields such as modeling physical and engineering processes [7,19,20]. In the foreword, we propose to make use of the HDM [21-23], a relatively new analytical technique. The technique is described and illustrated in a computationally numerical set up.

Bergman’s minimal model [24-28] is a one compartment model, meaning that the body is described as a compartment with a basal concentration of glucose and insulin. The minimal model has two variations. The first describe glucose kinetics, how blood glucose concentration reacts with blood insulin concentration. Reciprocally, the alternative variation itemizes the insulin kinetics, which describes the blood insulin concentration reactions with glucose concentration in the blood. Both models alternatives take insulin and glucose data as an input, respectively. Both models have been used mostly to interpret the blood glucose insulin interactions during the Glucose Tolerance Test [25,26].

Below the Bergman minimal model is presented in light of the following in view of the nomenclature of parameters.

Nomenclature of Parameters for Bergman’s Minimal Model

| Parameter | Unit     | Description                                      |
|-----------|----------|--------------------------------------------------|
| X(t)      | [mg/dL]  | Blood glucose concentration                      |
| I(t)      | [mU/L]   | Blood insulin concentration                      |
| G(t)      | [1/min]  | The effect of active insulin                     |
| l        | [mU/L]   | Basal blood insulin concentration                |
| G b      | [mg/dL]  | Basal blood glucose concentration                |
| I b      | [mU/L]   | Basal blood insulin concentration                |
| p 1      | [1/min]  | Insulin independent glucose clearance rate       |
| p 2      | [1/min]  | Active insulin clearance rate (upt. decrease)    |
| p 3      | [L/min/mU] | Increase in uptake ability caused by insulin    |
| p 4      | [1/min]  | Decay rate of blood insulin                      |
| p 5      | [mg/dL]  | The target glucose level                         |
| p 6      | [mUdL/Lmgmin] | Pancreatic release rate after glucose bolus    |

In order to describe the time course of these concentrations, the

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minimal model of the glucose insulin kinetics has been proposed. We will use the standard formulation of the minimal model represented by the following system of differential equations,

\[
\begin{align*}
\frac{d^\alpha G(t)}{dt^\alpha} &= -(p_i + \chi(t))G(t) + p_i G_i, \quad 0 < \alpha \leq 1 \\
\frac{d^\beta X(t)}{dt^\beta} &= -p_x X(t) + p_x (l(t) - I_s), \quad 0 < \beta \leq 1 \\
\frac{d^\gamma I(t)}{dt^\gamma} &= p_x [G(t) - p_i ] - p_x (l(t) - I_s), \quad 0 < \gamma \leq 1 \\
\end{align*}
\]

subject to the initial conditions,

\[
G(0) = G_o, \quad X(0) = X_o, \quad I(0) = I_0
\]

This model can be used to describe the pancreas as the source of insulin. In a healthy individual a small amount of insulin is always created and cleared [24]. This helps to keep the basal concentration \(I_b\). The glucose independent production and clearance of insulin is proportional to the blood insulin concentration. If the insulin level is above the base level concentration, clearance is increased. On the other hand, if the insulin level is below basal concentration, production increases. When the glucose level gets high, the pancreas reacts by releasing more insulin, at a given rate. To explain this mathematically one has to derive a function describing the reaction of the pancreas. This function was derived by Bergman et al., [27], and adjusted by Gaetano et al. [25] to become,

\[
\text{Pancreas}(t)=\left[G(t)-p_i\right]^+ t, \quad \text{where } [G(t)-p_i]^+ = \text{Maximum} \left(\{G(t)-p_i\}, 0\right) \tag{1.1}
\]

The layout of this paper is as follows: a brief history and properties of fractional derivatives are given in section 2, followed by the HDM a description of the application mechanism to non-homogenous nonlinear fractional partial differential equations for both Caputo and Riemann-Liouville types derivatives in section 3. Implementation of the HDM to the Bergman model is presented in section 4. In section 5, we present the numerical simulation results, and the treatment and resolution of the Bergman model special case is and discussed.

Some Background on Fractional Order Derivatives

For longer than five decades, fractional calculus proved to be a major player in modeling and analyzing linear and complex phenomena in engineering and the applied sciences. Extending the tools of its classical counterpart, non-integer type model equations and systems, most often describing nonlinear processes, are frequently treated and solved with the advent of what came to be known as fractional calculus. In recent years, fractional calculus started playing an even more essential role in various fields such as biology, biomedical engineering, geophysics, electricity, fluid dynamics, and mechanics [12,13,18,22]. Among its major contexts are Brownian motion, random walks and stochastic processes, control dynamics, fractional power law, Riesz potentials, fractals, nonlocal phenomena and porous media. Methods concentration span fractional type of computational derivative equations and systems, variational principles, boundary value problems, transform theory applications. Related studies scopes include, but are certainly not limited to, acoustic dissipation, chaos dynamics, control theory, image and signal processing, materials relaxation and creep, heat conduction, special functions, singularities analysis and integral representations, as well as viscoelasticity [23,29-36,37-42].

A vast literature exists presenting and discussing on various definitions advantages and disadvantages (see [33,43,44]). The most commonly fractional derivatives invoked in the literature to date are the Riemann-Liouville, and the Caputo derivatives.

While, the Caputo derivative is given by,

\[
\frac{D^\alpha f(x)}{dx^\alpha} = \frac{1}{\Gamma(m-\alpha)} \int_0^x (x-t)^{m-\alpha-1} f^{(m)}(t) \, dt
\]

the Riemann-Liouville, is given by,

\[
D^\alpha f(x) = \frac{1}{\Gamma(m-\alpha)} \frac{d^m}{dx^m} \int_0^x (x-t)^{m-\alpha-1} f(t) \, dt
\]

Although, the Caputo derivative of a constant is zero, it demands higher conditions of regularity for differentiability than the Riemann-Liouville derivative, for which, and in contrast, the fractional derivative of a constant is not zero. We need to calculate a function first derivative a priori to determine the fractional derivative in the Caputo sense. Consequently, the Caputo derivatives can be defined only for differentiable functions. On the other hand, functions with no first-order derivative may have fractional derivatives of all orders less than one, in the Riemann-Liouville sense. In 2006, Guy Jumarie proposed an alternative definition to the Riemann-Liouville, [43], (see also 44) and refs therein,

\[
D^\alpha f(x) = \frac{1}{\Gamma(m-\alpha)} \frac{d^m}{dx^m} \int_0^x (x-t)^{m-\alpha-1} [f(t)-f(0)] \, dt
\]

The modified Riemann-Liouville derivative contains advantages over both the Riemann-Liouville, and the Caputo fractional derivatives. Being defined for arbitrary continuous, even non-differentiable ones, the Jumarie fractional derivative of a constant turns out to be zero.

Definition 1. A real function \(f(x), x>0\), is said to be in the space \(C_{\alpha,\mu} \in P_{\alpha,\mu}\), if there exists a real number \(\mu > p\), such that \(f(x) = x^\mu b(x)\), where \(b(x) \in C_{0,n}\), and it is said to be in the space \(C_{\alpha,\mu}\) if \(f(x) \in C_{\alpha,\mu,\nu} \in N\).

Definition 2. The Riemann–Liouville fractional integral operator of order, \(\alpha \geq 0\), of a function, \(f(t) \in C_{\alpha,\mu} \in N\), is defined through implementation of the integration operator, \(J^\alpha\), in the following manner:

\[
J^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) \, d\tau, \quad t > 0
\]

\[
J^\alpha f(t) = f(t)
\]

For, \(f \in C_{\alpha,\mu} \in N\), \(\alpha \beta \geq 0\) and \(\gamma > -1\), we have,

\[
J^\alpha J^\beta f(t) = J^{\alpha+\beta} f(t)
\]

\[
J^\alpha J^\beta f(t) = J^\beta J^\alpha f(t)
\]

\[
J^\alpha (f(\nu)) = \frac{\Gamma(\nu+1)}{\Gamma(\alpha+\nu+1)} J^\alpha f(t)
\]

More relevant detailed properties of the operator \(J\) can be found in [43].

Lemma 1. If, \(n-1 < \alpha < n, n \in N\), and \(f \in C_{\alpha,\mu} \in N\), then,

\[
D^\alpha J^\alpha f(t) = f(t)
\]

\[
D^\alpha f(t) = f(t) - \frac{1}{\Gamma(n)} \int_0^t \frac{f^{(n)}(t)}{t^n} \, dt, \quad t > 0
\]

Definition3. Consider then-variables, \(x_i, i \in 1, \ldots, n\), function \(f(x)\), of class \(C_{\alpha,\mu} \in P_{\alpha,\mu}\). We define the partial derivative of fractional order \(\alpha\), for \(f\) with respect to \(x_i\) by,
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\[
a^a \frac{d^n f}{dx^n} = \frac{1}{\Gamma(m - a)} \int_0^x (x - \tau)^{m-1} \frac{d^n f(\tau)}{d\tau^n} d\tau, 
\]

(2.11)

where, \( \frac{d^n f}{dx^n} \) is the usual partial derivative of integer-order \( m \).

**HDM Applications to Nonlinear Fractional Differential Equations**

To illustrate the basic idea of HDM by considering a general fractional nonlinear, non-homogeneous partial differential equation, with the initial condition,

\[
\frac{\partial^n u(x, t)}{\partial t^n} = Lu(x, t) + Nu(x, t) + f(x, t), \quad m > 0
\]

(3.1)

with respect to the initial conditions,

\[
D_t^{\alpha} u(x, 0) = f(x), \quad (k = 0, 1, ..., n - 1), \quad D^{\alpha} u(x, 0) = 0 \quad \text{and} \quad n = [m]
\]

(3.2)

where, \( \frac{\partial^n f}{\partial t^n} \) denotes the Caputo or Riemann-Liouville fractional derivative operator, \( L \) is the linear fractional differential operator, \( N \) represents the general nonlinear fractional differential operator and \( f(x, t) \) is a known function.

On taking the inverse operator, \( \frac{\partial^n f}{\partial t^n} \), on both sides of eqn. (3.1), in the case of the Riemann-Liouville fractional derivative,

\[
U(x, t) = - \frac{1}{\Gamma(m - n + 1)} \int_0^t (t - \tau)^{m-1} \left[ L(U(x, \tau)) + N(U(x, \tau)) + f(x, \tau) \right] d\tau. 
\]

(3.3)

In the case of Caputo fractional derivative,

\[
U(x, t) = \frac{1}{\Gamma(m - n + 1)} \int_0^t (t - \tau)^{m-1} \left[ L(U(x, \tau)) + N(U(x, \tau)) + f(x, \tau) \right] d\tau. 
\]

(3.4)

By setting,

\[
\sum_{k=0}^n \frac{f(x)}{\Gamma(m - k + 1)} = G(x, t), \quad \text{or} \quad \sum_{k=0}^n \frac{g(x)}{\Gamma(m - k + 1)} = G(x, t)
\]

(3.5)

we get,

\[
U(x, t) = G(x, t), \quad \text{or} \quad \sum_{k=0}^n \frac{g(x)}{\Gamma(m - k + 1)} = G(x, t)
\]

(3.6)

Now, by implementing the HDM, we get,

\[
U(x, t, p) = \sum_{n=0}^\infty p^n U_n(x, t),
\]

(3.7)

and the nonlinear term can be decomposed as,

\[
NU(x, t) = \sum_{n=0}^\infty p^n H_n(U_n), \quad p \in (0, 1]. 
\]

(3.8)

Now, using He’s polynomials, \( H_n(U) \), (see for instance, [37, 38]), given by,

\[
H_n(U_1, U_2, ..., U_n) = \frac{1}{n! \partial^n \partial U^n} \left[ n! \sum_{i=0}^n \partial_i U_i \right], \quad n = 0, 1, 2, ..., 
\]

(3.9)

The HDM is obtained by combining the method with the Abel integral, and is given by,

\[
\sum_{n=0}^\infty p^n U_n(x, t) = G(x, t) + \frac{1}{\Gamma(m - n + 1)} \int_0^t (t - \tau)^{m-1} \left[ \sum_{n=0}^\infty p^n H_n(U_n(x, t)) + f(x, \tau) \right] d\tau. 
\]

(3.10)

Relating the terms of same powers of \( p \), this gives solutions of various orders. The initial guess of the approximation is, \( G(x, t) \), actually the Taylor series of the exact solution of order \( m \). Uniqueness of the series decompositions is insured by this initial guess [23,40,45].

**Approximate Solutions for Bergman’s Minimal Model Fractional Module**

In this section we apply the steps of the HDM developed above to solving the system of fractional differential equations defined by,

\[
\frac{d^\alpha G(t)}{dt^\alpha} = -(p_1 + X(t)) G(t) + p_1 G_\infty, \quad 0 < \alpha \leq 1
\]

\[
\frac{d^\beta X(t)}{dt^\beta} = -p_2 X(t) + p_3 \left( I(t) - I_\infty \right), \quad 0 < \beta \leq 1
\]

\[
\frac{d^\gamma I(t)}{dt^\gamma} = p_4 \left[ G(t) - p_5 \right] t - p_4 \left( I(t) - I_\infty \right), \quad 0 < \gamma \leq 1.
\]

On using the HDM steps, we arrive at the following equations,

\[
\sum_{n=0}^\infty \frac{t \alpha G_n(t)}{\Gamma(\alpha)} = G(0) + \frac{p_1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} \left[ -(p_1 + X(t)) G(t) + p_1 G_\infty \right] d\tau
\]

(4.1)

\[
\sum_{n=0}^\infty \frac{t \beta X_n(t)}{\Gamma(\beta)} = X(0) + \frac{p_2}{\Gamma(\beta)} \int_0^t (t - \tau)^{\beta-1} \left[ -p_2 X(t) + p_3 \left( I(t) - I_\infty \right) \right] d\tau
\]

(4.2)

\[
\sum_{n=0}^\infty \frac{t \gamma I_n(t)}{\Gamma(\gamma)} = I(0) + \frac{p_4}{\Gamma(\gamma)} \int_0^t (t - \tau)^{\gamma-1} \left[ p_4 \left[ G(t) - p_5 \right] \tau - p_4 \left( I(t) - I_\infty \right) \right] d\tau
\]

(4.3)

Comparing the coefficients of the same power of \( p \), we get the following integral equations,

\[
p^0 : G_n(t) = G(0), \quad G(0) = G_0
\]

(4.4)

\[
p^0 : X_n(t) = X(0), \quad X(0) = X_0
\]

(4.5)

\[
p^0 : I_n(t) = I(0), \quad I(0) = I_0
\]

(4.6)

\[
p^1 : G_1(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} \left[ -(p_1 + X(\tau)) G(\tau) + p_1 G_\infty \right] d\tau, \quad G_1(0) = 0
\]

(4.7)

\[
p^1 : X_1(t) = \frac{1}{\Gamma(\beta)} \int_0^t (t - \tau)^{\beta-1} \left[ -p_2 X(\tau) + p_3 \left( I(\tau) - I_\infty \right) \right] d\tau, \quad X_1(0) = 0
\]

(4.8)

\[
p^1 : I_1(t) = \frac{1}{\Gamma(\gamma)} \int_0^t (t - \tau)^{\gamma-1} \left[ p_4 \left[ G(\tau) - p_5 \right] \tau - p_4 \left( I(\tau) - I_\infty \right) \right] d\tau, \quad I_1(0) = 0
\]

(4.9)

\[
p^2 : G_2(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} \left[ -(p_1 + X(\tau)) G(\tau) + p_1 G_\infty \right] d\tau, \quad G_2(0) = 0
\]

(4.10)

\[
p^2 : X_2(t) = \frac{1}{\Gamma(\beta)} \int_0^t (t - \tau)^{\beta-1} \left[ -p_2 X(\tau) + p_3 \left( I(\tau) - I_\infty \right) \right] d\tau, \quad X_2(0) = 0
\]

(4.11)

\[
p^2 : I_2(t) = \frac{1}{\Gamma(\gamma)} \int_0^t (t - \tau)^{\gamma-1} \left[ p_4 \left[ G(\tau) - p_5 \right] \tau - p_4 \left( I(\tau) - I_\infty \right) \right] d\tau, \quad I_2(0) = 0
\]
The components of the series solution are obtained directly

\[ G(0) = G_0 = 287 \text{ unit}, \quad X(0) = X_0 = 0, \quad I(0) = I_0 = 403.4 \text{ unit}, \quad G_t = \frac{6.0999a^e}{\Gamma(a+1)} \text{ unit}, \]

\[ X_t = \frac{0.00421}{\Gamma(b+1)} e^{\frac{t^n}{(a+1)}} + \frac{1.0612}{\Gamma(a+1)} e^{\frac{t}{(a+1)}} \text{ unit}, \]

\[ G_t = \frac{0.18523}{\Gamma(2(a+1))} + \frac{1.207283}{\Gamma(a+1)} \text{ unit}, \]

\[ X_t = -0.0000884376126 \frac{e^{\frac{t^n}{(a+1)}}}{\Gamma(a+2+1)} + 0.00007 \frac{e^{\frac{t^n}{(a+2+1)}}}{\Gamma(a+2+1)} \text{ unit}, \]

\[ I_t = -0.020127155 \frac{e^{\frac{t^n}{(a+1)}}}{\Gamma(a+2+1)} - 0.19842825 \frac{e^{\frac{t^n}{(a+2+1)}}}{\Gamma(2+1)} + 35.649 \frac{e^{\frac{t^n}{(a+2+1)}}}{\Gamma(2+2)} \text{ unit}. \]

The remaining terms can be obtained in the similar manner.

Here we consider, only few terms of the series solutions, and the asymptotic solution is,

\[ G(t) = G_0(t) + G_1(t) + G_2(t) + ..., \quad (4.14) \]

\[ X(t) = X_0(t) + X_1(t) + X_2(t) + ..., \quad (4.15) \]

\[ I(t) = I_0(t) + I_1(t) + I_2(t) + ... . \quad (4.16) \]
Conclusion and future directions

Numerical solutions in our study cases investigated seem to represent the biological behavior of real life situations. The approximate solutions of the fractional order are increasing continuous functions of the fractional order derivatives. Both systems of nonlinear equations were solved via an iteratively direct technique, namely, the HDM. The basic characters of the relatively highly versatile technique were presented in detail. As a means for solving the illustrated problems above, and various other problems of engineering and physical sciences processes, the HDM turns out to be straightforward, economic in time consumption, on top of being user-friendly [19,20,23,37-42,44,46,47]. We propose to use it in future works with classical or fractionally modeled diabetic retino-graphy stages, or mast cells growth based multiple sclerosis cure [48,49]. Furthermore, while standard Tuberculosis models development can be for instance found in [50,51], the models presented above, cover both integer and non-integer-order derivatives. A follow-up study shall focus on comparisons such works and ramifications, as non-factional orders tend to integer ones in the limit, and possibly vice versa. We call on interested readers and researchers to join this planned task.

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