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Mathematical Model for Nutrient Exchange across the Placenta

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Abstract

This study presents a new mathematical model for nutrient exchange across the placenta which include nutrient exchange from foetus to mother to provide a system of equations in the form, $\dot{Y} = AY + \vec{r}(t)$ and whose solution was analyzed for equilibrium and stability. This model introduces another parameter that takes care of waste elimination from foetus to mother. It was established that the final model is stable compared to the existing models, that is, the eigenvalues of the coefficient matrix are negative real number and complex numbers with negative real parts. This shows that the new model provides one straight line of solutions tending to the origin and a plane of solutions which spiral towards the origin. This gives a more accurate mathematical model for nutrient exchange in the placenta. This model would create a lot of insight into nutrient exchange in the placenta, the elimination of waste from the foetus and open room for further research from the mathematical concept developed.

Mathematics Subject Classification: Primary 93A30; Secondary 91B74, 93C15, 92C50, 92C42, 91B50, 03C45, 45M10

Keywords: Mathematical model; Linear system; Equilibrium; Stability

Introduction

The placenta forms on the uterus wall during pregnancy and, via the umbilical cord, links the baby to its mother. The word placenta means 'cake' in latin and, appropriately enough, its job is to nourish the developing baby by transferring nutrients from the mother's bloodstream into the foetal circulation and removing waste products. The placenta is also responsible for gaseous exchange, including delivering oxygen to the baby and picking up Carbon (IV) Oxide, controlling waste balance and pH, and producing hormones, such as progesterone, which are involved in maintaining pregnancy. By the time the baby is born it resembles a large disk, 20*cm* across and 3*cm* thick weighing about 500*g*, [11]. The problems encountered in biology are frequently complex and often not totally understood. Mathematical modeling provides a means to better understand the processes and unravel some of these complexities, [3]. The mathematical tool provides ways of delivering a better qualitative and quantitative understanding to some biological problems, while the biological problems often stretch the techniques that the mathematician must use to find solutions, [10]. Recent evidence has emerged with extensive literature on mathematical models on nutritive relationship between a mother and a foetus throughout pregnancy. Sam Zimmerman [14] modeled the mother and foetus in a twocompartment system but did not explain what happens to the waste products from the foetus. The transfer of substances occurs both ways across the placenta. The bulk of the substances transferred from mother to foetus consists of oxygen and nutrients. The placenta represents the means for the final elimination of Carbon (IV) Oxide and other foetal waste materials into the maternal circulation. Under some circumstances, other substances, some of them harmful, can be transferred across the placenta. From mother to foetus, we have, Oxygen, Water, Electrolytes, Nutrients, Carbohydrates, Amino acids, Lipids, Hormones, Antibodies, Vitamins, Iron, trace elements, drugs, Toxic substances, Alcohol and Some viruses. From foetus to mother, we have, Carbon(IV) oxide, Water, Electrolytes, Urea, uric acid, Creatinine, Bilirubin, Hormones, Red blood cell and antigens.

Small quantities of foetal blood cells often escape into the maternal circulation, either through small defects in the placental vasculature or through hemorrhage at birth. If the foetal erythrocytes are positive for the Rh anti-gen, and the mother is Rh negative, the presence of foetal erythrocytes in the maternal circulation can stimulate the formation of anti-Rh antibody by the immune system of the mother. The foetus in the first pregnancy is usually spared the effects of the maternal antibody (often because it has not formed in sufficient quantities), but in subsequent pregnancies, Rh-positive foetuses are attacked by the maternal anti-Rh antibodies, which make their way into the foetal bloodstream. This antibody causes hemolysis of the Rh-positive foetal erythrocytes, and the foetus develops erythroblastosisfetalis, sometimes known as hemolytic disease. In severe cases, the bilirubin released from the hemolysed red blood cells causes jaundice and brain damage in addition to Anemia. When recognized, this condition is treated by exchange transfusions of Rh-negative donor blood into either the foetus or the newborn. An indication of the severity of this condition can be gained by examining the amniotic fluid.

As for the gases, water and electrolytes are readily transferred across the placenta. The rates of transfer are modified by colloid osmotic pressure in the case of water and the function of ion channels in the case of electrolytes. Foetal wastes, that is, urea, creatinine, and bilirubin, are rapidly transferred across the placenta from the foetal circulation to the maternal blood bathing the villi. Foetus undertakes metabolic reactions which produces waste which must be eliminated to avoid harming the foetus, [1]. With this in mind we intend to develop and solve a model showing the movement of waste from the foetus to the mother.

Preliminaries

In mid 2011's Zimmerman [14] with the guidance from Nijihout [14] of the Mayo Clinic discovered a fairly reliable criterion for interpreting the results of nutrient exchange across the placenta. Their discovery was based on a simple model they developed for the nutrient exchange. The aim of Zimmerman's [14] study was to construct a model which accurately describe the movement of nurients from the mother to the foetus across the placenta. His model however did not include the movement of waste products from foetus to mother, that is, Carbon (IV) Oxide, Bilirubin, drugs, alcohol, nicotine, deoxygenated blood, urea etc and the interface(placenta) through which substances move from mother to foetus before entering the foetus and vice versa. The model treated nutrient exchange as a unidirectional flow from mother to foetus only, yet the foetus also undertakes metabolic reactions that produce waste products which must be eliminated to avoid harming the foetus. With this in mind we intend to construct a model that takes care of waste products from the foetus to the mother. So far the existing models of nutrient exchange places modeling of the placental transport function into one broad group, that is, homogeneous trans-membrane exchange and diffusion of oxygen, Carbon (IV) Oxide, water, amino acids, and other species at constant maternal and fetal flow rates. In 1969, Kirschbaum and Shapiro [8] modeled an equilibrium mass transfer in the lamb placenta. The aim of the model was to investigate the influence of the placental shunt.

In 1969, Faber [5] modeled the steady transfer of inert solutes for concurrent, counter current, crosscurrent and pool flow arrangement of placental circulation based on one dimensional mass transfer model. The model aimed at identifying a three dimensional parameters representing placental permeability, maternal foetal blood flow and solute transport rates. Hill *et al* [7] modeled gas transfer in human placenta. Their study obtained the time course of oxygen and Carbon(IV)Oxide partial pressure in the maternal and foetal erythrocytes in the placenta. Lardner [9], later modeled one dimensional oxygen transfer in the human placenta. The model was described by a system of nonlinear ordinary differential equation and proposed a set of dimensional parameters characterizing diffusion, uptake and flow rates. The model established the dependence of oxygen uptake and partial pressure on these parameters. Wilbur *et al* [15] modeled water and solute exchange in the human placenta. They outlined the steady distribution of water and solute transfer rates between mother and foetus along the placental membrane. They also performed a sensitivity analysis to the model parameters. In 1992, Costa *et al* [4] modeled steady oxygen exchange in the human placenta, based on one dimensional diffusion and uptake in an individual foetal capillary. Their study focused on the dependence of oxygen partial pressure in foetus blood on gestational age and on thickness of the materno-foetal barrier, Reneaur *et al* [13]. Groome [6] modeled steady one dimensional oxygen transport in the human placenta, described by a system of nonlinear ordinary differential equations with a Hill-type law [7] for haemoglobin dissociation. The study investigated the effect of placental oxygen consumption, due to metabolism, on the foetal oxygenation in a microscopic uteroplacental unit.

In all the above literature none incorporated waste product in the nutrient exchange from foetus to mother. This is the gap to be filled by this study. From the existing models in the literature only nutrient exchange from mother to foetus have been considered. Medically, it is known that waste products are also transported from foetus to mother. This fact has so far not been modeled by many researchers. Zimmerman in his model did not include the interface(placenta) between the mother and the foetus. It was therefore necessary to model nutrient exchange from foetus to mother with the interface included.

Model Development

Sam Zimmermans model had two compartmental diagrams namely that of the mother and the foetus, but it is known that there is always a cord connecting the mother and the foetus. In his model he did not include the interphase that lies between the mother and the foetus. In this study we have developed a three compartmental diagram with placenta as an interphase.

The New Model

In this study we have developed a three compartmental diagram, figure (1) which is different from the Compartmental model developed by Sam Zimmerman, which did not include Placenta as an interface. The placenta represents the means for the final elimination of Carbon(IV)Oxide, other foetal waste materials and other substances, some of them harmful.

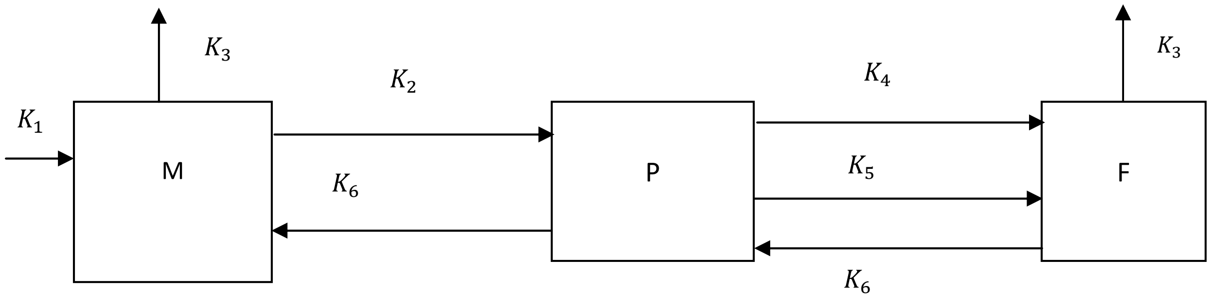

Figure 1: Mother, Placenta and Foetus in a Three-Compartment Diagram

Model formulation

From the compartmental diagram we can generate the following systems of equations;

$$\frac{dM}{dt} = K_1 + K_6P - (K_3 + K_2)M$$
$$\frac{dP}{dt} = K_2M + K_6F - (K_4 + K_5 + K_6)P \quad (1)$$
$$\frac{dF}{dt} = (K_4 + K_5)P - (K_3 + K_6)F$$

Where:

M = the total calories the mother has (calories)

F = the total calories the foetus has (calories)

P = the placenta(the interface)

K_1 = the number of calories the pregnant woman will intake in a given day (calories/day)

K_2 = the rate of calorie transfer between mother and foetus (1/day)

K_3 = the rate of calorie burn-of and waste (1/day)

K_4 = the rate of calorie transfer between mother and foetus partially consumed (1/day)

K_5 = the rate of calorie transfer between mother and foetus metabolized (1/day)

K_6 = the amount of waste product transferred from foetus to the mother through the placenta

Model Solution

The given equations of the system equation (1) are,

$$\frac{dM}{dt} = K_1 + K_6P - (K_3 + K_2)M \quad (2)$$
$$\frac{dP}{dt} = K_2M + K_6F - (K_4 + K_5 + K_6)P \quad (3)$$

$$\frac{dF}{dt} = (K_4 + K_5)P - (K_3 + K_6)F \quad (4)$$

At equilibrium point we equate equation (2), equation (3) and equation (4) to zero and solve for M, Pand F.

Using Mathematica, the nontrivial equilibrium values are given by,

$$M = -\frac{bK_1K_4}{K_2K_6 - ab}$$

$$P = \frac{1}{K_6}\left(\frac{abK_1K_6}{K_2K_6 - ab} - K_1\right)$$

$$F = \frac{1}{K_6}\left(-\frac{abK_1K_6}{K_2K_6 - ab} - K_1\right)\left(\frac{K_4 + K_5}{K_6 + K_3}\right)$$

Equating equation (2), equation (3) and equation (4) to A, B and C, we get,

$$\frac{dM}{dt} = K_1 + K_6P - (K_3 + K_2)M = A \quad (5)$$

$$\frac{dP}{dt} = K_2M + K_6F - (K_4 + K_5 + K_6)P = B \quad (6)$$

$$\frac{dF}{dt} = (K_4 + K_5)P - (K_3 + K_6)F = C \quad (7)$$

We find the the Jacobian J.

$$J = \begin{bmatrix} \frac{\partial A}{\partial M} & \frac{\partial A}{\partial P} & \frac{\partial A}{\partial F} \\ \frac{\partial B}{\partial M} & \frac{\partial B}{\partial P} & \frac{\partial B}{\partial F} \\ \frac{\partial C}{\partial M} & \frac{\partial C}{\partial P} & \frac{\partial C}{\partial F} \end{bmatrix} \quad (8)$$

giving;

$$J = \begin{bmatrix} -K_2 - K_3 & K_6 & 0 \\ K_2 & -K_4 - K_5 - K_6 & K_6 \\ 0 & K_4 + K_5 & -K_3 - K_6 \end{bmatrix} \quad (9)$$

After getting the Jacobian matrix, we obtain the eigenvalues,

$$\begin{bmatrix} -K_2 - K_3 - \lambda & K_6 & 0 \\ K_2 & -K_4 - K_5 - K_6 - \lambda & K_6 \\ 0 & K_4 + K_5 & -K_3 - K_6 - \lambda \end{bmatrix} = 0 \quad (10)$$

giving;

$$\begin{bmatrix} -a - \lambda & K_6 & 0 \\ K_2 & b - \lambda & K_6 \\ 0 & c & -d - \lambda \end{bmatrix} = 0 \quad (11)$$

Where

$a = K_2 + K_3$, $b = K_4 + K_5 + K_6$, $c = K_4 + K_5$, $d = K_3 + K_6$

Using Mathematica we get real negative eigenvalue and two complex eigenvalues with negative real parts

Results and Discussion

Eigen values can be used to determine whether a fixed point (also known as an equilibrium point) is stable or unstable. A stable fixed point is such that a system can be initially disturbed around its fixed point yet eventually return to its original location and remain there. A fixed point is unstable if it is not stable.

The Eigen values of a system linearized around a fixed point can determine the stability behavior of a system around the fixed point. The particular stability behavior depends upon the existence of real and imaginary components of the Eigen values, along with the signs of the real components and the distinctness of their values.

While there are more possible types of phase space pictures for three dimensional linear systems than for two dimensions, the list is still finite, Blanchard et al [2]. Just as for two dimensions, the nature of the system is determined by the Eigen values. Real Eigen values correspond to straight-line solutions that tend to towards the origin if the Eigen values is negative and away from the origin if the Eigen values is positive.

Complex Eigen values correspond to spiraling. Negative real parts indicate spiraling towards the origin while positive real parts indicate spiraling away from the origin.

Since the characteristic polynomial is a cubic, there are three Eigen values (which might not all be distinct if there are repeated roots). It is always the case that at least one of the Eigen values is real. The other two may be real or a complex conjugate pair. The most important types of three-dimensional linear systems can be divided into three categories; Sink, Source and Saddle.

Sinks: We call the equilibrium point at the origin a sink if all the solutions tend towards it as time increases. If all the three Eigen values are real and negative, then there are three straight lines of solutions, all of which tend to towards the origin. Since every other solution is a linear combination of these solutions, all solutions tend to the origin as time increases.

The other possibility of a sink is to have one real negative Eigen values and two complex Eigen values with negative real parts. This means that there is one straight line of solutions tending to the origin and a plane of solutions which spiral towards the origin.

Sources: There are two possibilities for sources as well. We can either have three real and positive Eigen values or one real positive Eigen values and a complex conjugate pair with positive real parts indicating that the solution move away from the origin as time increases.

Saddles: The equilibrium point at the origin is a saddle if, as time increases to infinity,some solutions tend towards it while other solutions move away from it. This can occur in four different ways. If all the Eigen values are real then we could have one positive and two negative or two positive and one negative. In the first case, one positive and two negative, there is one straight line of solutions which tend away from the origin as time increases and a plane of solutions which tend towards the origin as time increases. In the other case, two positive and on negative, there is a plane of solutions which tend towards the origin as time increases. In both cases, all other solutions will eventually move away from the origin as time increases or decrease.

The other two cases occur if there is only one real eigenvalue and the other two are complex conjugate pair. If the real eigenvalue is negative and the real parts of the eigenvalues are positive, then as time increases, there is a straight line of solutions that tend towards the origin and a plane of solutions that tend away from it.

All other solutions are a combination of these behaviors, so as time in- creases they spiral around the straight line of solutions in ever widening loops. The other possibility is that the real eigenvalue is positive and the complex eigenvalues have negative real part. In this case there is a straight line of solutions that tend away from the origin as time increases and a plane of solutions that spiral toward the origin as time increases. Every other solution spirals around the straight line of solutions while moving away from the origin.

The eigenvalues generated from Mathematica clearly indicates that the new model which incorporated waste product in the nutrient exchange from foetus to mother with placenta as the interface have real negative eigenvalue and two complex eigenvalues with negative real parts. This shows that the new model provides a more stable solution than the existing one since there is one straight line of solutions tending to the origin and a plane of solutions which spiral towards the origin. This gives a more accurate mathematical model of nutrient exchange in the placenta.

Conclusion and recommendation

This paper presents a new Mathematical model for nutrient exchange in the placenta described by equation (1). The model includes the interface(placenta) between the mother and the foetus and in which waste products are also trans- ported from foetus to mother. The model is expressed as a system of linear nonhomogeneous equations in the form $\dot{Y} = AY + \vec{r}(t)$ and whose solution was analyzed for equilibrium and stability. It was established that the final model is stable compared to the existing models, that is, the eigenvalues of the coefficient matrix are negative real number and complex numbers with negative real parts. This shows that the new model provides one straight line of solutions tending to the origin and a plane of solutions which spiral towards the origin. This is an important contribution to research in modeling and more particularly to research in the field of nutrient exchange in the placenta.

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