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A bio-mathematical approach: Speculations to construct virtual placenta

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ABSTRACT

The placenta is a transient organ responsible for invariable and unique biological functions including maternal fetus nutrient and oxygen transportation, hormonal regulation and immunological interaction during the gestation. The placental structure varies widely between species both in terms of barriers between maternal and fetal circulations and the shape of the interchange region. When studying both normal and pathological placental developments, mice models are often used. In some occasions, this is a less than perfect model for comparison with human placental physiology as murine placenta is somewhat different. At this juncture, one of the applications of computational biology is taken into consideration, i.e., constructing virtual placenta for understanding the placental interactions between mother and fetus by in-silico. As a stepping stone in this direction, the present study is designed with a bio-mathematical approach to formulate some speculations to construct virtual placenta.

1. Introduction

Evolution is a conservative process in which the expansion of sexual reproduction promoted the genetic variation and accelerated the speed of evolution. The transition from external to internal fertilization protected reproduction from a harmful outer environment such as predator, toxic chemicals, adverse temperature and pH. This resulted in reduction of number of gametes required per successful conception. Internal fertilization has been accomplished by the enfolding of excretory and reproductive function. Generation of innumerable eggs for external fertilization has been replaced by the cyclic modification of reproductive organs, sexual activity, placentation, gestation, parturition and lactation [1]. During pregnancy, the growing embryo is nourished by the mother, usually through a placenta or similar structure [2].

The placenta is a transient and unique organ that is present only during the pregnancy [3], and alterations in placental development and function have significant effects on fetus and its interaction with the intra-uterine environment. The placenta has also been used as a model for various aspects of biology, including cell biology, development, endocrinology, immunology and angiogenesis [4]. The placental structure varies significantly among different animal species and mice models are often used to study both normal as well as pathological placental developments. The murine placenta does not exactly match human placenta and is somewhat different, therefore one of the applications of computational biology is used to construct the virtual placenta for better understanding of placental interactions between the mother and fetus by *in-silico*.

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Successful completion of virtual placenta construction could lead to different models of placenta for different animal species. Our present study is designed with an overview of bio-mathematical approach to formulate some speculations to construct virtual placenta with respect to haemochorial placenta (mainly focused to human placenta). Placenta organogenesis and main functions of matured placenta such as transport and metabolism, protection and endocrine functions have been considered while constructing the mathematical model for the virtual placenta.

2. Biological background and model equations

2.1. Placenta organogenesis (placenta development)

At the early stage of mammalian development, the conceptus differentiates into inner cell mass (ultimately develops into embryo) and the superficial layer of cells called trophoblast, which exclusively contributes for the formation of extra embryonic membranes [5]. Trophoblasts have morphological, functional and molecular diversity within and across the species [2]. In human, immediately after fertilization, the ovum rapidly grows within the fallopian tube into a 16-cell morula and then a 32-cell blastocyst, reaching the endometrial cavity by day 3. The blastocyst is covered by zona pellucid that protects during the transportation from fallopian tube to uterine cavity. The blastocyst then uncovers its zona pellucid and implants into the receptive gestational endometrium by day 7 [6]. At the time of implantation, the outer cell layer of blastocyst differentiates into trophoblastic shell and the inner cell mass develops into the embryo [8,9].

The trophoblasts closer to endometrium proliferate and differentiate into two layers i.e., the inner cytotrophoblastic layer and outer overlying syncytiotrophoblastic layer. Cytotrophoblast likely possesses the stem cell properties in placenta. Syncytiotrophoblastic layer contributes to the barrier function of placenta. Even though the placenta exists only during pregnancy (gestation), there are constant morphological and biological fluctuations within it (proper placenta) and at the interface between placenta and the maternal system [7].

In human, the placenta has a disc shape with an average size of 22 cm in diameter with the thickness of 2–2.5 cm at the centre. At this point, the placenta typically weighs approximately 550 g. It is linked to the fetus by an umbilical cord of approximately 55–60 cm in length and containing two arteries and one vein. In the mature placenta, the fetal portion is known as chorionic plate, which carries the fetal chorionic blood vessels. The maternal part of placenta is called basal plate. In between these two regions, there is intervillous space, which possesses the main functional units of the placenta. This region is comprehensively branched and tightly packed villous structures containing fetal blood vessels. It is located at the terminal regions of fetal portion where the vast majority of maternal–fetal exchange occurs [10].

The system of placental development is certainly very complex and firmly integrated with many subsystems, in which some are yet unidentified and others are partially known. Hence, at present it is virtually complicated to put them all together. As a part of the present study, an attempt was made to formulate some mathematical models on spherical placenta. Let the spherical placenta has an internal radius, r_0, a thickness $\delta << r_0$ and be characterized by the following non-uniformity. Within a single-connected region 1, occupying a fraction α of the surface of shell, the diffusion coefficient will be assumed to be D_1, the rate of reaction q_1. In the remaining part of the shell, the diffusion coefficient has the value D_2, the rate of reaction – the value q_2. The external concentration of metabolized substance is denoted by c_0. Due to the infinite permeability, c_0 is also the inside concentration of substance at the outer surface of shell. If the shell is uniform in all respects, then the concentration inside the shell at the inner surface will also be the same at all points of the surface and within the cavity. Due to the non-uniformities assumed above, we shall have in general different concentrations c_1 and c_2 in two regions. Again, due to the assumption of infinite permeability, c_1 and c_2 also represent the concentrations of substance inside the cavity in immediate neighborhood of the shell. The corresponding system of equations reduces to

$$c_1 = c_0 + \frac{\delta^2 q_1}{D_1}; \quad c_2 = c_0 + \frac{\delta^2 q_2}{D_2}.$$

Fontelus and Friedman proved: for a given real number R (radius), there exists information derived from $\mu = \mu_n(R)$ symmetry breaking branches, including [11–13]

$$0 < \mu_2 < \mu_3 < \ldots < \mu_n < \ldots,$$
$$\mu = \mu_n + \varepsilon\mu_{n,1} + O(\varepsilon^2),$$
$$r = R + \varepsilon Y_{n,0}(\theta) + O(\varepsilon^2)$$

and where $Y_{n,0}(\theta)$ is the spherical harmonic of order $(n, 0)$. Hence it has been proved that: if $\mu < \mu_*(R)$, the spherical solution (when $t \to \infty$) is asymptotically stable, if $\mu > \mu_{ast}(R)$, then the ball's harmonic solution (when $t \to \infty$) is a linear stability [14]. If there is $R > \bar{R}$, then $\mu_*(R) = \mu_2(R)$. If it is $R < \bar{R}$, then $\mu_*(R) < \mu_2(R)$, hereinto $\bar{R} = 0.82459\ldots$ is a solution of a transcendental equation. In the case of $R > \bar{R}$, the first bifurcation point $\mu 2$ is supercritical, one of its branch is of linear stability, and another branch is not stable [15]. Such different results are then extended to the situation that Darcy's law replaced by Stokes equations; that established a model for example of situation that the fetus develops in liquid organization in the placenta tissue [17]:

$$r = R + \Sigma Y_{n^*(R),0}(\theta) + O(\varepsilon^2), \text{ here into, } n^*(R) \to \infty (\text{if } R \to \infty).$$