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Optimal villi density for maximal oxygen uptake in the human placenta

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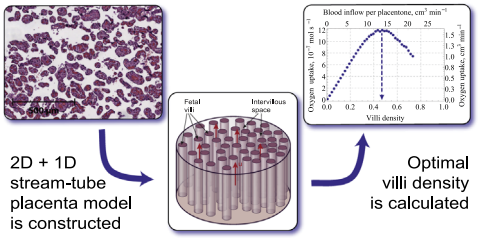
HIGHLIGHTS

- A 2D+1D stream-tube model of the human placenta is proposed.
- An optimal villi density providing the maximal oxygen uptake is calculated.
- The optimality is due to a trade-off between the inflow and the absorbing surface.
- The optimality predictions correspond to experimental observations.
- The model can be used as a tool for placenta-derived risks diagnostics in newborns.

GRAPHICAL ABSTRACT



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ABSTRACT

We present a stream-tube model of oxygen exchange inside a human placenta functional unit (a placentone). The effect of villi density on oxygen transfer efficiency is assessed by numerically solving the diffusion–convection equation in a 2D+1D geometry for a wide range of villi densities. For each set of physiological parameters, we observe the existence of an optimal villi density providing a maximal oxygen uptake as a trade-off between the incoming oxygen flow and the absorbing villus surface. The predicted optimal villi density 0.47 ± 0.06 is compatible to previous experimental measurements. Several other ways to experimentally validate the model are also proposed. The proposed stream-tube model can serve as a basis for analyzing the efficiency of human placentas, detecting possible pathologies and diagnosing placental health risks for newborns by using routine histology sections collected after birth.

1. Introduction

The human placenta is the sole organ of exchange between the mother and the growing fetus. It consists of two principal components: (i) fetal chorionic villi, and (ii) the intervillous blood basin in which maternal blood flows (Fig. 1). The placental fetal villi have a tree-like structure and are immersed in the maternal blood basin anchoring to the basal plate and supporting the placenta shape (Benirschke et al., 2006). Fetal arterial blood goes from the umbilical arteries to the capillaries inside the villi and returns to the umbilical vein, while maternal blood percolates outside this arboreous structure. The exchange of oxygen and nutrients takes place at the surface of the villous tree. We aim to understand how the geometry of the villous tree affects the placenta exchange function.

The normal development of the baby largely depends on the ability of the placenta to efficiently transfer oxygen, nutrients and other substances. Both placenta weight and placenta-fetus weight ratio are associated with the newborns health (Hutcheon et al., 2012; Teng et al., 2012). Moreover, "fetal origins of adult health"

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research has identified links between placenta size and risk of heart disease in adults (Barker, 1995).

Routinely stained 2D histology sections of the placenta collected after birth (Fig. 2) may provide valuable insights into its function during pregnancy. Fig. 2 illustrates our basic idea: random sampling of a normal placenta (Fig. 2B) contains intervillous space (IVS) and villous tree sections in "normal" proportions (which allow efficient function), whereas pre-eclamptic (Fig. 2A, disproportionally large IVS, rare villi) and diabetic (Fig. 2C, denser and larger villi) cases exhibit a very different geometry.

Assessing the relation between the placenta structure and its function is problematic because (i) it is unethical to manipulate the human placenta *in vivo*; (ii) histological and physiological features commonly co-vary (e.g. changes in villi distribution alter the blood flow); and (iii) quantitative histological analysis of the placenta structure can only be performed post-partum when maternal blood flow (MBF) and fetal blood flow have ceased. Mathematical modeling and numerical simulations are in this case valuable tools to gain deeper insights into the *in vivo* functioning of the placenta.

Mathematical models of the human and animal placenta function have been proposed for at least 60 years (see discussions in Battaglia and Meschia, 1986; Aifantis, 1978; Gill et al., 2011; Chernyavsky et al., 2010). Previous models mainly focused either on a single villus scale or on the whole placenta scale (different kinds of the flat wall exchanger model: Bartles et al., 1962; Shapiro et al., 1967; Kirschbaum and Shapiro, 1969; Hill et al., 1973; Longo et al., 1972; Lardner, 1975; Groome, 1991; Wilbur et al., 1978; Gill et al., 2011); several studies dealt with flow patterns (coorientation of maternal and fetal flows: Battaglia and Meschia, 1986; Bartles et al., 1962; Metcalfe et al., 1964; Shapiro et al., 1967; Faber, 1969; Kirschbaum and Shapiro, 1969; Guilbeau et al., 1970; Moll, 1972; Schröder, 1982); other works represented the placenta as a porous medium (Erian et al., 1977; Schmid-Schönbein, 1988; Chernyavsky et al., 2010), restricted, with one exception (Chernyavsky et al., 2010), to one or two dimensions. Some efforts have been devoted to understanding the relation between morphometric data and gas transfer in 1D in terms of diffusing capacity (see Mayhew et al., 1986, 1986 and references therein).

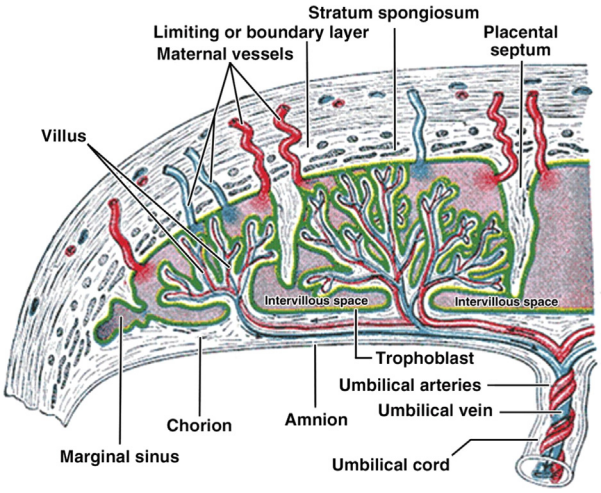

Fig. 1. Structure of the human placenta (reproduced from Gray, 1918).

Better understanding of the transfer function of the placenta requires a model of the 3D geometry of the organ on a larger scale than a few villi, predictions of which could be compared to experimental data. We use a simplified engineering representation of the complex system in order to reveal the most relevant transport mechanisms.

The driving questions of our placenta modeling are:

- What are the relevant parameters (geometrical and physiological) that govern oxygen transfer efficiency?
- For a given set of physiological parameters (such as MBF velocity or oxygen content of blood), is there an "optimal" villous tree geometry which maximizes the oxygen uptake?

In the following, we present a simplified stream-tube placenta model (STPM) of oxygen exchange. The mathematical equations governing oxygen transfer in the placentone are then numerically solved for different values of geometrical and physiological parameters. The results are compared to published histomorphometric measurements near term (Mayhew and Jairam, 2000; Aherne and Dunnill, 1966; Nelson et al., 2009; Lee and Mayhew, 1995; Mayhew et al., 1993).

2. Mathematical model

2.1. Outline

Our 3D STPM is inspired by the observation that the human placenta resembles "a closed cubical room supported by cylindrical pillars running from floor to ceiling" (Lee and Mayhew, 1995). The model consists of a large cylinder (Fig. 3A) representing a stream tube along which maternal blood flows (Fig. 3C). This cylinder contains multiple smaller parallel cylinders which represent fetal villi (terminal and mature intermediate), filled with fetal blood. In this paper, we consider these small cylinders to be

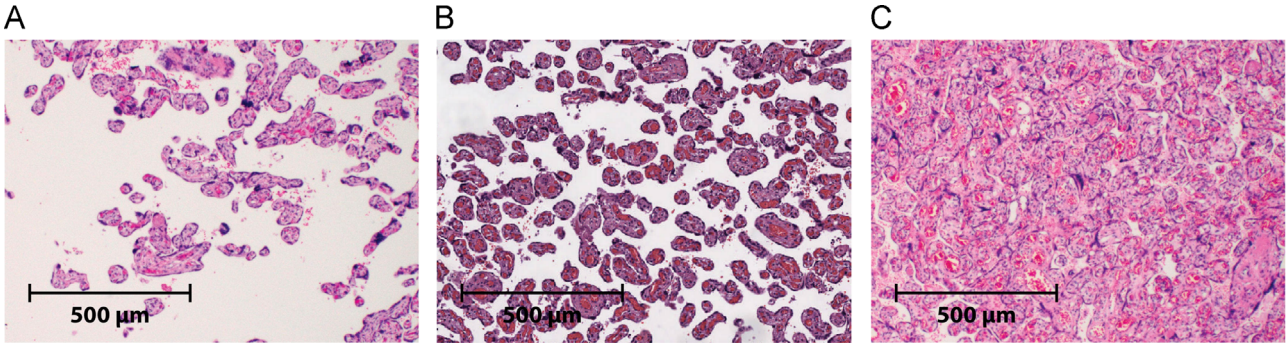

Fig. 2. Typical 2D placenta cross-sections: (A) pre-eclamptic placenta (rarefied villi, reduced exchange surface); (B) normal placenta; (C) diabetic placenta (dense villi, reduced surface accessibility). White space is intervillous space (IVS), normally filled with maternal blood, which has been washed away during the preparation of the slides (some residual red blood cells are still present). The dark shapes are cross-sections of fetal villi. The sections are H&E stained and have been taken in the direction from the basal (maternal) to the chorionic (fetal) plate.