Analytical theory of oxygen transfer in the human placenta

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Abstract

We propose an analytical approach to solving the diffusion-convection equations governing oxygen transfer in the human placenta. We show that in a placental cross-section only two geometrical characteristics, villi density and the effective villi radius, are needed to predict fetal oxygen uptake. We also identify two combinations of physiological parameters that determine oxygen uptake in a given placenta: (i) the maximal possible oxygen inflow of one placentone, and (ii) the dimensionless ratio of the transit time of the maternal blood through the placenta over the oxygen extraction time. We derive analytical formulas for a fast and simple calculation of oxygen uptake and provide two diagrams of the efficiency of oxygen transfer in a given placental cross-section. We finally show that artificial perfusion experiments with no hemoglobin tend to give a two-orders-of-magnitude underestimation of the in vivo oxygen uptake and that the optimal geometry for such setup alters significantly. The theory allows one to adjust the results of artificial placenta perfusion to account for oxygen-hemoglobin dissociation. Combined with image analysis techniques, the presented model can give an easy-to-use tool for prediction of the human placenta efficiency.

Keywords: human placenta model; oxygen transfer; diffusion-convection; optimal villi density; placenta efficiency.

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Fig. 1 (a): Schematic representation of the human placenta (reproduced from Gray, 1918). Basal plate (maternal side) is at the top, chorionic plate (fetal side) — at the bottom. (b): A typical 2D slide of the human placenta. White space is intervillous space, normally filled with maternal blood, which has been washed away during the preparation of the slides (some residual red blood cells are still present). Red shapes are cross-sections of fetal villi. Redder regions inside correspond to fetal capillaries and the dark, violet dots at the perimeter are syncytiotrophoblast boundary layers. The sections have been taken in the direction from the basal plate to the chorionic plate, and are H&E stained.

1 Introduction

The human placenta consists of maternal and fetal parts (Fig. 1a). The maternal part is a blood basin which is supplied by spiral arteries and drained by maternal veins (Benirschke et al., 2006). The fetal part is a villous tree, inside which fetal blood goes from umbilical arteries to the umbilical vein. The maternal blood percolates through the same arboreous structure on the outside. The maternal and fetal blood do not mix, so the gas and nutrient exchange takes place at the surface of the villous tree, sections of which can be observed in a typical histological 2D placenta slide (Fig. 1b). The relation between the geometrical structure of the exchange surface of the villous tree and the efficiency of the transfer function of the placenta constitutes the central object of our study.

Placenta models have been proposed previously (see discussions in Aifantis, 1978, Battaglia and Meschia, 1986, Chernyavsky et al., 2010, Gill et al., 2011). 1D models dealt with oxygen transfer at the scale of either one single villus or the whole placenta, in both cases imposing a flat exchange surface between maternal and fetal blood (Bartels et al., 1962, Groome, 1991, Hill et al., 1972, 1973, Kirschbaum and Shapiro, 1969, Lardner, 1975, Longo et al., 1972a,b, Power et al., 1972a,b, Shapiro et al., 1967, Wilbur et al., 1978); some 2D models were used to study the co-orientation of maternal and fetal flows (Bartels et al., 1962, Battaglia and Meschia,
1986, Faber, 1969, Guilbeau et al., 1970, Kirschbaum and Shapiro, 1969, Metcalfe et al., 1964, Moll, 1972, Schröder, 1982, Shapiro et al., 1967); others represented the placenta as a porous medium (Bartels et al., 1962, Battaglia and Meschia, 1986, Faber, 1969, Guilbeau et al., 1970, Kirschbaum and Shapiro, 1969, Metcalfe et al., 1964, Moll, 1972, Schröder, 1982, Shapiro et al., 1967). To our knowledge, the only 3D placenta model was introduced by Chernyavsky et al. (2010) to study the influence of the position of venous outlets and of the existence of a central cavity on oxygen transfer in a hemispherical placentone filled with porous medium. A method of calculation of 1D diffusing capacity through a lumped element model has been proposed as well to relate morphometric data and the efficiency of gas transfer (see Mayhew et al., 1984, Mayhew et al., 1986 and references inside). However, none of these models uses fine geometrical structure of experimentally obtained placenta slides (Fig. 1b) as direct input.

We have previously introduced a Stream-Tube Placenta Model (STPM), which can be related to experimental placental slide geometry (Fig. 1b), thus using new information as compared to previous placenta models. For this model, the existence of an optimal villi density was shown by numerical calculations (Serov et al., 2014). Here we present an analytical theory which extends these numerical results to an arbitrary geometry of the stream tube and fetal villi and analyzes how the results depend on the parameters of the model. Additionally, the importance of taking oxygen-hemoglobin reaction into account is demonstrated. To our knowledge, the influence of the presence of hemoglobin on oxygen transfer in the placenta has not yet been studied in the relation to the placental geometry, although such setup is common in artificial perfusion experiments.

2 The model

Here we outline the STPM, which has been introduced and discussed in details in Serov et al. (2014). The model describes oxygen uptake by fetal villi, while maternal blood flows from the central cavity to a decidual vein. To simplify the physical analysis, the complex flow pattern of maternal blood can be subdivided into smaller regions (stream tubes, see Fig.2a). Each stream tube is oriented along the maternal blood flow (MBF). The cross-section of each stream-tube is small enough, so that the flow of blood can be considered parallel in each cross-section, but is much larger than the radius of an individual villus.

We model one such stream tube unfolded as a cylinder of an arbitrary cross-section containing multiple parallel cylinders of arbitrary cross-sections, which represent fetal villi (Fig. 2b). The shapes and locations of the villi can be taken from a histological slide. Since we aim to base the STPM on histological slides (Fig. 1b), which provide only one section of a stream tube without any information about the change of this section along the tube, we further postulate that the same shapes and locations of the villi are conserved along the stream-tube. This is obviously an oversimplification of the irregular 3D structure of the placenta, but it is the most straightforward assumption given the lack of complete 3D geometrical data spatially resolving all terminal and mature intermediate villi.
The model relies on several other assumptions:

1. **Fetal blood is considered as a perfect oxygen sink.** This assumption means that we study the effects of the maternal circulation and IVS geometry, while assuming that fetal villi can efficiently transfer to the fetus all oxygen received from the maternal blood. Since we do not consider oxygen transport inside villi, there is no correlation in villi structure along the model axis, and villi act independently in each cross-section. Instead, we concentrate our attention on the distribution of villi in the cross-section;

2. **MBF is considered to be laminar with slip conditions at all boundaries (no liquid-wall friction), so that the velocity profile in any cross-section is flat.** This strong assumption is supported by calculations obtained for capillary-tissue cylinders modeled in brain (Reneau et al., 1967). The brain model has been used to compare the effect of non-slip boundary conditions (and thus a non-flat velocity profile) versus slip boundary conditions (and thus a flat velocity profile) on the distribution of $pO_2$ in a Krogh’s type cylindrical tissue layer. The difference between the two cases in $pO_2$ distribution was less than 10%. This assumption of non-slip boundary conditions is further discussed in Serov et al. (2014);

3. The oxygen-hemoglobin dissociation curve is linearized in the physiological range of partial
Table 1 Parameters of the human placenta used in our calculations. See Serov et al. (2014) for the explanation of the values.

| Parameter                                                      | Value                        |
|----------------------------------------------------------------|------------------------------|
| Maximal Hb-bound oxygen concentration at 100% Hb saturation \(c_{\text{max}}\), mol/m³ | 7.82                         |
| Oxygen-hemoglobin dissociation constant \(B\)                  | 101                          |
| Oxygen concentration in blood at the entrance to the IVS \(c_0\), mol/m³ | \(6.7 \cdot 10^{-2}\)       |
| Oxygen diffusivity in blood \(D\), m²/s                       | \(2 \cdot 10^{-9}\)         |
| Stream tube length \(L_0\), m                                 | \(1.6 \cdot 10^{-2}\)       |
| Effective villi radius \(r_e\), m                            | \(4.1 \cdot 10^{-5}\)       |
| Placentone radius \(R\), m                                   | \(1.7 \cdot 10^{-2}\)       |
| Radius of stream tube used in numerical calculations \(R_{\text{num}}\), m | \(6 \cdot 10^{-4}\)         |
| Velocity of the maternal blood flow \(u\), m/s                | \([5-7] \cdot 10^{-4}\)     |
| Permeability of the effective materno-fetal interface \(w\), m/s | \(2.4 \cdot 10^{-4}\)       |

Pressure of oxygen 0–60 mmHg observed in the human placenta (see Fig. 3 and discussion in Sect. 4.4);

4. Oxygen uptake occurs at the feto-maternal interface, i.e. at the boundaries of the small cylinders, and is directly proportional to the interface permeability and to oxygen concentration on the maternal side of the interface;

5. In a cross-section perpendicular to the MBF, oxygen is only redistributed by diffusion;

6. Erythrocytes are uniformly distributed in the maternal blood;

7. Oxygen bound to hemoglobin does not diffuse, so that only oxygen dissolved in the blood plasma does;

8. Oxygen uptake is stationary.

3 Parameters values

Our model is based on the following geometrical and physiological parameters: oxygen-hemoglobin dissociation constant \(B\), oxygen concentration at the entrance to the IVS \(c_0\), maximal bound oxygen concentration \(c_{\text{max}}\), oxygen diffusivity in blood \(D\), average stream-tube length \(L_0\), radii of the placentone \(R\) and of fetal villi \(r\), velocity of the MBF \(u\), and permeability of
the feto-maternal interface \((u)\). These parameters are described in Sect. 4 and their values are summarized in Table 1, while an explanation of their calculation can be found in Serov et al. (2014).

4 Mathematical formulation

4.1 Time scales of the system

Our model encompasses three different transport processes: convective flow of maternal blood through the inter villous space (IVS) with velocity \(u\); diffusion of oxygen; and equilibration between oxygen bound to hemoglobin and oxygen dissolved in blood plasma. We have previously demonstrated that oxygen-hemoglobin dissociation can be considered instantaneous as compared to diffusion and convection; the two latter, on the contrary, have to be studied simultaneously (Serov et al., 2014).

4.2 Equilibrium between bound and dissolved oxygen

The very fast oxygen-hemoglobin reaction can be accounted for by assuming that the concentration of oxygen dissolved in blood plasma \((c_{pl})\) and that of oxygen bound to hemoglobin \((c_{bnd})\) instantaneously mirror each other’s changes. Mathematically both concentrations can be related by equating oxygen partial pressures in these two forms.

**Oxygen dissolved in plasma.** Because of low solubility of oxygen in blood, partial pressure of dissolved oxygen \((p_{O_2})\) can be related to its concentration \((c_{pl})\) using Henry’s law:

\[
p_{O_2} = \frac{k_{hn}}{\rho_{hl}} \cdot c_{pl},
\]

where \(\rho_{hl} \approx 1000 \text{ kg/m}^3\) is the density of blood and the coefficient \(k_{hn}\) can be estimated from the fact that a concentration \(c_{pl} \approx 0.13 \text{ mol/m}^3\) of dissolved oxygen corresponds to oxygen content of 3 ml \(O_2/l\) blood or partial pressure of 13 kPa at normal conditions (Law and Bukwirwa, 1999), yielding \(k_{hn} \sim 7.5 \times 10^5 \text{ mmHg} \cdot \text{kg/mol}\) for oxygen dissolved in blood.

**Hemoglobin-bound oxygen.** The partial pressure of hemoglobin-bound oxygen depends on its concentration through Hill equation:

\[
c_{bnd} = c_{max} \cdot S(p_{O_2}), \quad S(p_{O_2}) \equiv \frac{(k_{hl}p_{O_2})^\alpha}{1 + (k_{hl}p_{O_2})^\alpha},
\]

where \(c_{max}\) is oxygen content of maternal blood at full saturation; \(k_{hl} \approx 0.04 \text{ mmHg}^{-1}\) and \(\alpha \approx 2.65\) are coefficients of Hill equation, obtained by fitting the experimental curve of Severinghaus (1979) (Fig. 3).
Equilibrium relation between $c_{pl}$ and $c_{bnd}$ can then be obtained by substituting Eq. (1) into Eq. (2):

$$c_{bnd} = c_{max} S \left( \frac{k_{hn}}{\rho_{bl}} c_{pl} \right).$$

(3)

### 4.3 Diffusive-convective transport of oxygen

Diffusive-convective transport of oxygen is governed by the mass conservation law for the total concentration of oxygen in a volume of blood:

$$\frac{\partial (c_{pl} + c_{bnd})}{\partial t} + \text{div} \vec{j}_{tot} = 0,$$

(4)

where $\vec{j}_{tot}$ is the total flux of oxygen, transported both by diffusion and convection for the dissolved form and only by convection (RBCs being too large objects) for the bound form:

$$\vec{j}_{tot} = -D \vec{\nabla} c_{pl} + \vec{u} (c_{pl} + c_{bnd}),$$

(5)

where $\vec{u}$ denotes the velocity of the MBF, $D$ is the diffusivity of oxygen in blood and $\Delta \equiv \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$ is the Laplace operator. Omitting the time derivatives in the stationary regime, substituting Eq. (5) into Eq. (4) and choosing $z$ as the direction of the MBF, we obtain

$$\Delta c_{pl} = \frac{u}{D} \frac{\partial (c_{pl} + c_{bnd})}{\partial z}.$$
Using the relation (3) between the dissolved and bound oxygen concentrations we then derive an equation for the unknown $c_{pl}$ only:

$$
\Delta c_{pl} = \frac{u}{D} \frac{\partial}{\partial z} \left( c_{pl} + c_{\text{max}} S \left( \frac{k_{hn}}{\rho_{bl}} c_{pl} \right) \right) = \frac{u}{D} \left( 1 + \frac{c_{\text{max}} k_{hn}}{\rho_{bl}} S' \left( \frac{k_{hn}}{\rho_{bl}} c_{pl} \right) \right) \frac{\partial c_{pl}}{\partial z}.
$$

(6)

This equation is non-linear as $c_{pl}$ appears also in the argument of the derivative of Hill saturation function $S'$. In a first approximation, we can linearize it, assuming $S'$ to be constant in the range of partial pressures of oxygen encountered in the human placenta.

### 4.4 Linearization of Hill equation

The idea of linearization is simple: to replace the sigmoid saturation function (2) with a linear function of $p_{O_2}$. Although it is natural to make the line pass through the origin, the slope of the line may be chosen differently depending on the range of partial pressures in which we approximate the curve (Fig. 3). Data found in the literature indicate that maternal blood in the IVS of the human placenta has $p_{O_2}$ of about 60 mmHg (Challier and Uzan, 2003, Jauniaux et al., 2000, Rodesch et al., 1992). We further suppose that this pressure is the maximal value in the whole placenta and hence delimits the range of the needed linear approximation. Fitting then the experimental curve of Severinghaus (1979) in the region 0–60 mmHg with a straight line passing through zero we obtain a linear approximation

$$
S(p_{O_2}) \approx \beta_{60} p_{O_2}, \quad S'(p_{O_2}) = \beta_{60} \approx 0.017 \text{ mmHg}^{-1},
$$

displayed in Fig. 3.

This approximation leads to the following relation between $c_{\text{tot}}$, $c_{pl}$ and $c_{\text{bnd}}$: $c_{\text{tot}} \equiv c_{pl} + c_{\text{bnd}} = c_{pl}B$, or

$$
c_{pl} = \frac{c_{\text{bnd}}}{B - 1} = \frac{c_{\text{max}}}{B - 1} S(p_{O_2}), \quad \text{where} \quad B \equiv \left( 1 + \frac{c_{\text{max}} \beta_{60} k_{hn}}{\rho_{bl}} \right).
$$

We emphasize here that ignoring oxygen-hemoglobin interaction would be equivalent to setting $B = 1$, which would lead to a hundred-fold underestimation of this constant (Table 1).

From Eq. (5), a linearized version of the corresponding total oxygen flux is then:

$$
\vec{j}_{\text{tot}} = -D \nabla c_{pl} + \vec{u} c_{pl} B.
$$

(7)

Finally the partial differential equation (6) becomes

$$
\Delta c_{pl} = \frac{uB \partial c_{pl}}{D} \frac{\partial c_{pl}}{\partial z}.
$$

(8)
4.5 Boundary conditions

Boundary conditions should be imposed on Eq. (8):

- the boundary of the large cylinder represents the boundary of a stream tube. Assuming there is no exchange of oxygen between different stream tubes, we consider zero flux on its wall:
  \[
  \frac{\partial c_{pl}}{\partial n} = 0,
  \]
  where \(\partial/\partial n\) is the normal derivative directed outside the IVS;
- uptake at the effective feto-maternal interface is proportional to the concentration of oxygen dissolved in the maternal blood plasma:
  \[
  D \frac{\partial c_{pl}}{\partial n} = w c_{pl},
  \]
  where \(w\) is the permeability of the interface which accounts for the resistance of IVS-villus and villus-capillary membranes as well as for diffusion in the connective tissue separating the two membranes;
- the total concentration of oxygen in blood is uniform and constant at the entrance of the stream tube \((z = 0)\):
  \[
  c_{pl}(x, y, z = 0) = c_0, \quad \forall (x, y) \in S_{IVS},
  \]
  where \(c_0\) is oxygen concentration in the incoming blood plasma.

4.6 Conversion to a 2D eigenvalue equation

To solve Eq. (8), we separate the coordinate \(z\) along the stream-tube axis from the coordinates \(x\) and \(y\) in the transverse cross-section. The general solution of Eq. (8) then takes the following form:

\[
  c_{pl}(x, y, z) = c_0 \sum_{j=1}^{\infty} a_j v_j(x, y) e^{-\mu_j z},
\]

where \(\{\mu_j\}\) are decay rates in the \(z\)-direction and \(\{a_j\}\) are weights of \(c_{pl}\) in the orthonormal eigenbasis \(\{v_j(x, y)\}\) of the Laplace operator \(\Delta_{xy}\) in the transverse cross-section. \(\{v_j(x, y)\}\) satisfy the following equations:
\[
\begin{aligned}
(\Delta_{xy} + \Lambda_j) v_j &= 0, \\
\frac{\partial v_j}{\partial n} &= 0 \quad \text{on large cylinder boundary,} \\
\left( \frac{\partial}{\partial n} + \frac{w}{D} \right) v_j &= 0 \quad \text{on small cylinders boundaries,} \\
\sum_j a_j v_j &= 1 \quad \text{in } z = 0 \text{ plane,}
\end{aligned}
\]  

(10)\hspace{1cm} (11)\hspace{1cm} (12)\hspace{1cm} (13)

where \( \Delta_{xy} \equiv \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \), \( \Lambda_j \equiv \mu_j^2 + \mu_j \frac{uB}{D} \).  

(14)

Eigenvalues \( \{\mu_j\} \), eigenfunctions \( \{v_j(x,y)\} \) and weights \( \{a_j\} \) are determined by Eqs (10)–(14) for a given cross-section. In particular, from Eq. (13) it follows that \( a_j \equiv \int_{S_{IVS}} v_j dS \).

### 4.7 General expression for oxygen uptake

According to the mass conservation law, oxygen uptake up to length \( L \) is equal to the difference between oxygen flow coming into the system at \( z = 0 \) and oxygen flow leaving the system at \( z = L \). Using Eqs (7) and (9) one can derive an explicit dependence of oxygen uptake on stream-tube length:

\[
F(L) = \int_{S_{IVS}} \left( \vec{j}_{\text{tot}} \cdot \vec{n} \right) \bigg|_{z=0} dS - \int_{S_{IVS}} \left( \vec{j}_{\text{tot}} \cdot \vec{n} \right) \bigg|_{z=L} dS = c_0 \sum_{j=1}^{\infty} a_j^2 (D\mu_j + uB) \left( 1 - e^{-\mu_j L} \right),
\]

(15)

where the definition of \( \{a_j\} \) has been used. This is an exact expression for oxygen uptake, into which the geometrical structure of the placental cross-section enters through the spectral characteristics \( \{\mu_j\} \) and \( \{a_j\} \). Our goal now is to simplify this expression and to identify the most relevant geometrical and physiological parameters that determine oxygen uptake.

### 5 Approximate analytical solution

#### 5.1 Form of the approximation

From Eq. (15), one can see that \( F(L) \) is a smooth monotonous curve which is linear at small lengths and exponentially saturates at large lengths (Serov et al., 2014). In a first approximation, Eq. (15) can then be replaced by an expression which has the same behavior at these limit
cases:

\[ F^{sp}(L) = A(1 - e^{-\alpha L}), \]  

(16)

where \( A \) and \( \alpha \) are some parameters. The physical meaning of \( A \) is oxygen uptake at \( L \to \infty \) (equal to the total incoming oxygen flow), whereas \( \alpha \) is the mean decay rate of oxygen concentration with stream-tube length. We now relate \( A \) and \( \alpha \) to the parameters of the model.

5.2 Uptake at the infinite length

Large lengths are characterized by saturation when all incoming oxygen is transferred to the fetal blood.

An exact expression for the saturation limit can be obtained from Eq. (15) as \( L \to \infty \):

\[ F_{\infty} = c_0 u B S_{IVS} + c_0 D \sum_{j=1}^{\infty} a_j^2 \mu_j, \]  

(17)

where the identity \( \sum_{j=1}^{\infty} a_j^2 = S_{IVS} \), following from Eq. (13), was used.

Note that the flow in Eq. (17) includes two contributions: convective flow (the first term) and diffusive flow along the \( z \)-axis (the second term). It turns out that the second term is much smaller than the first one, so that Eq. (17) can be simplified by omitting the diffusive term:

\[ F_{\infty} \approx A = c_0 u B S_{IVS}. \]  

(18)

This approximation is justified by the following arguments:

1. Relative roles of diffusion and convection in a hydrodynamic problem are described by the Péclet number, which is the ratio of characteristic times of diffusive and convective transfer to the same distance \( \delta \): \( \text{Pe} = u \delta / D \). Large Péclet numbers (\( \text{Pe} \gg 1 \)) indicate predominant convective transport, whilst small values signify prevalence of the diffusive transport.

For the human placenta, the ratio \( u / D \) is of the order of \( 10^5 \) m\(^{-1} \) (Table 1), which means that \( \text{Pe} \gg 1 \) for lengths \( \delta \gg 10 \) \( \mu m \). As the characteristic length of the stream tube is \( L_0 \sim 1.6 \) cm \( \gg 10 \) \( \mu m \), we conclude that diffusion in the vertical direction can be omitted as compared to convection. At the same time, diffusion in the cross-section cannot be ignored as it is the only in-plane mechanism of oxygen transport;

2. Since 99\% of oxygen is bound to hemoglobin in red blood cells (RBC), and RBCs are too large to diffuse, the error from ignoring the diffusive transfer term in \( F_{\infty} \) does not exceed 1\% in terms of oxygen content.
Mathematically, the simplification we have used can be written as
\[ \mu_j \ll uB/D, \quad (19) \]
so that Eq. (14) becomes \[ \mu_j \approx \Lambda_j D/(uB). \] It should be noted that statement (19) does not contradict with the fact that \( \{\mu_j\} \) grow to infinity with eigenvalue number \( j \). In fact, each \( \mu_j \) contributes to the final expression with a weight \( a_j \), which diminishes with \( j \). Eq. (19) should be then understood as valid for all eigenvalues, which have significant contributions \( a_j \) to formulas.

Oxygen uptake (15) can then be approximated as
\[ F(L) \approx c_0 uBS_{IVS} \left( 1 - \sum_{j=1}^{\infty} \frac{a_j^2}{S_{IVS}} \exp \left( -\frac{D}{uB} \Lambda_j L \right) \right). \quad (20) \]

### 5.3 Average concentration decay rate

Using Eq. (18) and comparing Eq. (20) with the approximate form of oxygen uptake (16), one obtains the following definition of the average concentration decay rate \( \alpha \):
\[ \alpha(L) \equiv -\frac{1}{L} \ln \left( \sum_{j=1}^{\infty} \frac{a_j^2}{S_{IVS}} \exp \left( -\frac{D}{uB} \Lambda_j L \right) \right). \quad (21) \]
In this formula, \( \alpha \) depends explicitly on \( L \) and implicitly on the cross-section geometry. Our goal now is to extract the main part of this implicit dependence. For this purpose, we integrate Eq. (10) over the area of the IVS in the cross-section (\( S_{IVS} \)). We further apply the divergence theorem (Arfken et al., 2005) to transform the integral over the IVS to an integral over its boundary (\( P_{tot} \), which includes the perimeter \( P \) of the absorbing boundary of the villi and that of the outer boundary of the stream tube in a cross-section):
\[ \Lambda_j = -\frac{\int_{P_{tot}} \partial v_j/\partial n \ dP}{\int_{S_{IVS}} v_j \ dS} = \frac{w}{D} \frac{\int_P v_j \ dP}{\int_{S_{IVS}} v_j \ dS} = \left( \frac{wP}{DS_{IVS}} \right) q_j^2, \quad (22) \]
where boundary conditions (11) and (12) were used to remove the contribution from the non-absorbing boundary and
\[ q_j^2 \equiv \frac{1}{S_{IVS}} \frac{\int_P v_j \ dP}{\int_{S_{IVS}} v_j \ dS}. \]
is the dimensionless ratio of the mean value of \( v_j \) over the villi boundary over its mean value in the IVS.

In the first approximation, the coefficient \( wP/(DS_{IVS}) \) in Eq. (22) describes the dependence of \( \Lambda_j \) on the cross-section geometry. Introducing \( q_j \) and the dimensionless length \( \ell(L) \equiv \frac{wP}{uBS_{IVS}}L \) in Eq. (21), we transform Eq. (21) into
\[ \alpha = \frac{wP}{uBS_{IVS}} \kappa(L), \quad \text{where} \quad \kappa(L) \equiv -\frac{1}{\ell(L)} \ln \left( \sum_{j=1}^{\infty} \frac{a_j^2}{S_{IVS}} e^{-\ell(L)q_j^2} \right). \quad (23) \]
is a dimensionless coefficient depending on \( L \) and cross-section geometry and containing fine details of a given villi distribution and shapes, which are ignored by the integral parameters \( P \) and \( S_{IVS} \). Figure 4a shows the dependence of \( \kappa(L) \) on villi density \( \phi \equiv S_{vil}/S_{tot} \) in a large range of stream-tube lengths. Here \( S_{vil} \) is the area of the cross-section occupied by fetal villi, \( S_{tot} \) is the total area of a cross-section and \( L_0 \) is the average stream-tube length (see Table 1). One can see that in the first approximation, \( \kappa(L) \) is independent of villi configuration. (b): Dependence of \( \kappa(L) \) on the stream-tube length \( L \). Dashed vertical line denotes the average stream-tube length \( L_0 \)

\[ \kappa(L) = \left( 1 - \exp \left( -\frac{wP}{uBS_{IVS}} \kappa(L)L \right) \right) \]  

5.4 Dimensionless geometrical parameters

In Eq. (24), both geometrical cross-section parameters \( P \) and \( S_{IVS} \) depend on the size of the analyzed region. To facilitate physical analysis of the approximate solution and its comparison to experimental data, we identify two geometrical characteristics of a placental cross-section, that are independent of the size of the region:

- the fraction of the cross-section occupied by fetal villi, which we define as the ratio of the total area of villi in a cross-section to the total area of the cross-section: \( \phi \equiv S_{vil}/S_{tot} \);
- the effective villi radius, which we define as \( r_e \equiv \frac{2S_{vil}}{P} = \frac{2\phi S_{IVS}}{P(1-\phi)} \). In morphometric studies, the inverse parameter \( 2/r_e = P/S_{vil} \) is known as “villi surface density”. For

\( L_0 = 1.6 \) cm, Table 1, \( \kappa \approx 0.42 \). Using Eqs (18) and (23), the approximate oxygen uptake (16) can then be rewritten as
Fig. 5 (a): Oxygen extraction efficiency \( \zeta(\gamma, \phi) \equiv F^{ap}/F_0 \). Contours indicate the fraction of the maximal possible oxygen inflow \( F_0 \) that can be absorbed by a geometry characterized by \((\gamma, \phi)\). The plus symbol marks the parameters \( \gamma \approx 1.3 \) (Sect. 7.1.1) and \( \phi \approx 0.46 \) (Serov et al., 2014) expected on average in a healthy human placenta (with \( \kappa = \kappa(L_0) \approx 0.4 \)).

Circular villi of radius \( r \), \( r_e \equiv r \). The mean value of \( r_e \) for the human placenta can be found in Table 1.

Substitution of these definitions into Eq. (24) gives

\[
\zeta(\gamma, \phi) \equiv \frac{F^{ap}(\gamma, \phi)}{F_0} = (1 - \phi) \left( 1 - \exp \left( -\gamma(r_e, L) \frac{\phi}{1 - \phi} \right) \right),
\]

where

\[
\gamma(r_e, L) \equiv \frac{2w\kappa}{uBr_e} L, \quad F_0 \equiv c_0uBS_{tot}.
\]

The physical meaning of \( F_0 \) follows from its definition: it is the maximal oxygen flow of entering a stream tube, the value achieved if no villi were present in the IVS of this stream-tube. The incoming flow in the presence of villi is \( F_{in} \equiv F_0(1 - \phi) \). The physical meaning of \( \gamma \) is discussed later.

Note that \( \gamma \) includes information on the average villus shape through the parameter \( r_e \), and that \( F_0 \) is independent of the geometry of the cross-section. Normalized oxygen uptake \( \zeta(\gamma, \phi) \equiv F^{ap}/F_0 \) (which we will further call oxygen extraction efficiency) is plotted in Fig. 5a.
5.5 Optimal cross-sectional geometry

Looking at Fig. 5a and expression (25) for oxygen uptake, it is natural to ask what are the “optimal” values of the parameters $\phi$ and $\gamma$ that maximize oxygen uptake at a given stream-tube length. Figure 5a clearly shows two trends:

- for any fixed value of $\phi$, larger $\gamma$ provides larger uptake;
- for any fixed value of $\gamma$, there exists some intermediate value of $\phi$: $0 < \phi_{\text{opt}}(\gamma) < 1$ that maximizes oxygen uptake. This optimal value $\phi_{\text{opt}}(\gamma)$ tends to diminish with $\gamma$.

Note that from the definition (26) it follows that in terms of cross-sectional geometrical parameters, growth of $\gamma$ corresponds to the decrease of the effective radius $r_e$. Smaller values of $r_e$ for the same villi density mean that for oxygen exchange, it is more efficient to have many small villi than fewer big villi occupying the same area. This prediction can be understood if one considers the fact that small villi have more absorbing surface per unit of cross-sectional area.

However, in the human placenta, $r_e$ cannot be infinitely small (and hence $\gamma$ infinitely large). Indeed, villi possess an internal structure (e.g., fetal blood vessels) to transfer the absorbed oxygen to the fetus. The decrease of $r_e$ below some value risks making the villi less efficient in transporting the already absorbed oxygen. This argument is supported by experimental observation that in the terminal and mature intermediate villi of the human placenta (the smallest villi), blood vessels normally occupy the main part of the internal volume. The mean radius of these smallest villi is $r \approx 25–30 \mu m$ (see Table 28.7 in Benirschke et al., 2006). At the same time, villi density changes significantly in different regions of the same placenta as well as between different placentas (Serov et al., 2014).

It is then reasonable to reformulate the initial question as which villi density provides the highest oxygen uptake for a given effective villi radius $r_e$. Mathematically, it is the question of finding the maximum of $F$ against $\phi$ for a fixed $\gamma(r_e)$.

5.6 Optimal villi density

Under the constraint of fixed $\gamma$, Eq. (25) implies the existence of the maximal uptake at a certain villi density. The reasoning is the following:

- $F(\phi = 0) = 0$, because the condition $\phi = 0$ means no feto-maternal interface and hence no uptake;
- $F(\phi = 1) = 0$, because fetal vessels occupy the entire cross-section of the stream tube and the incoming MBF is zero as it does not have space to flow;
- $F > 0$ for $0 < \phi < 1$, this corresponds to the fact that the placenta transfers oxygen from mother to fetus for intermediate villi densities. Hence, maximal oxygen uptake $F_{\text{max}}(L)$ always exists at a certain villi density $0 < \phi_{\text{opt}}(L) < 1$ for any $\gamma(r_e)$. 

15
Fig. 6 Analytical predictions of the optimal villi density (a) and of the normalized maximal uptake (b) as functions of $\gamma$. Small $\gamma$ asymptotics are shown by blue circles; large $\gamma$ asymptotics are shown by red triangles. Dashed lines mark values observed in a healthy human placenta.

Here we have used $F$ and not $F_{ap}$ symbol for oxygen uptake to underline that these arguments are general and are valid not only for the approximate flow, but for the exact flow as well.

The optimal villi density can then be obtained by solving the equation
$$\left.\frac{\partial F_{ap}(\phi,L)}{\partial \phi}\right|_{\phi=\phi_{opt}} = 0,$$

or
$$\exp\left(\gamma \frac{\phi_{opt}}{1 - \phi_{opt}}\right) = 1 + \frac{\gamma}{1 - \phi_{opt}}. \quad (27)$$

One can note that Eq. (27) is an explicit equation on $\phi_{opt}$ as a function of $\gamma$ only. As a consequence, it does not require any eigenvalue calculation.

The substitution $\phi \equiv \gamma\phi_{opt}/(1 - \phi_{opt})$ reduces Eq. (27) to the form $\gamma = g(\phi)$, where $g(\phi) \equiv e^x - x - 1$, and its solution can be represented as $x = g^{-1}(\gamma)$. Although the inverse function $g^{-1}(\gamma)$ does not have an explicit representation, its form can be easily calculated once and then the tabulated values can be used in practice. Returning to the definition of $x$, one obtains $\phi_{opt}$ as a function of $\gamma$:
$$\phi_{opt}(\gamma) = \frac{1}{1 + \frac{\gamma}{g^{-1}(\gamma)}}. \quad (28)$$

The function $\phi_{opt}(\gamma)$ (Fig. 6a) can be used to calculate the optimal villi density for a placenta region from a known value of $\gamma$ for this region. Substitution of the last result into Eq. (25) gives the corresponding maximal uptake:
$$\frac{F_{ap}^{\text{max}}(\gamma)}{F_0} = \gamma \frac{1 - \exp(-g^{-1}(\gamma))}{\gamma + g^{-1}(\gamma)}. \quad (29)$$
From the asymptotic behavior of $g(x)$ at small and large $x$, we obtain the following asymptotic formulas for $\phi_{opt}$ and $F_{\text{max}}^{\text{ap}}/F_0$:

\[
\phi_{\text{opt}}(\gamma) \sim \begin{cases} 
\frac{1}{1 + \sqrt{\gamma/2}}, & \gamma \ll 1 \\
\ln(\gamma)/\gamma, & \gamma \gg 1 
\end{cases}
\]

\[
F_{\text{max}}^{\text{ap}}(\gamma)/F_0 \sim \begin{cases} 
\frac{1 - e^{-\sqrt{2\gamma}}}{1 + \sqrt{2/\gamma}}, & \gamma \ll 1 \\
1 - 1/\gamma, & \gamma \gg 1 
\end{cases}
\]

(30)

Figure 6 shows that these asymptotics accurately approximate $\phi_{\text{opt}}(\gamma)$ and $F_{\text{max}}^{\text{ap}}(\gamma)/F_0$ not only in the limits of $\gamma \ll 1$ and $\gamma \gg 1$, but for all $\gamma$. For instance, it can be calculated that if small-$\gamma$ asymptotic is used for $\log_{10} \gamma \leq 0.5$ and large-$\gamma$ asymptotic is used for $\log_{10} \gamma > 0.5$, the maximal relative error of the second formula of Eq. (30) is less than 4%.

5.7 Villi density efficiency

Basing on the optimal villi density and maximal uptake introduced in the previous section for fixed $\gamma$, one can define a quantitative measure of the optimality of villi density in a given (not optimal) geometry.

If the given geometry is characterized by the parameters $(\gamma, \phi)$, its villi density efficiency can be defined as the ratio of oxygen uptake in this particular geometry over the maximal value, which can be obtained with the same $\gamma$ (Fig. 6b):

\[
\eta(\gamma, \phi) \equiv \frac{F_{\text{max}}^{\text{ap}}(\gamma, \phi)}{F_{\text{max}}^{\text{ap}}(\gamma)} = \frac{(1 - \phi) \left(1 - \exp \left(-\gamma \frac{\phi}{1 - \phi} \right)\right)}{(1 - \phi_{\text{opt}}(\gamma)) \left(1 - \exp \left(-\gamma \frac{\phi_{\text{opt}}(\gamma)}{1 - \phi_{\text{opt}}(\gamma)} \right)\right)}. 
\]

(31)

Figure 5b presents the villi density efficiency $\eta(\gamma, \phi)$ in a physiological range of $(\gamma, \phi)$ and at $L = L_0$.

Following the comment given to Eq. (30), Eq. (31) can be rewritten as

\[
\eta(\gamma, \phi) \approx \begin{cases} 
\frac{(1 - \phi) \left(1 - \exp \left(-\gamma \frac{\phi}{1 - \phi} \right)\right) \left(1 + \sqrt{2/\gamma}\right)}{1 - e^{-\sqrt{2\gamma}}}, & \log_{10} \gamma \leq 0.5 \\
\frac{(1 - \phi) \left(1 - \exp \left(-\gamma \frac{\phi}{1 - \phi} \right)\right) \left(1 + \ln(\gamma)/\gamma\right)}{1 - 1/\gamma}, & \log_{10} \gamma > 0.5
\end{cases}
\]

with a maximal relative error of 4%. Note that the last equation does not require the calculation of $\phi_{\text{opt}}$ and is an explicit function of $\gamma$ and $\phi$.

Note finally that the optimality characteristics $\zeta$ and $\eta$ play different roles. Oxygen extraction efficiency $\zeta$ (Fig. 5a) indicates the fraction of the maximal possible incoming oxygen flow $F_0$ that is absorbed by the given cross-sectional geometry. The higher is the value of $\zeta$, the more
Fig. 7 Oxygen uptake for a single placentone as a function of geometrical parameters. Solid lines correspond to the analytical approximation; symbols reproduce the results of numerical simulations of Serov et al. (2014). (a) Oxygen uptake as a function of villi density $\phi$ for three lengths $L$: $L_0/3$, $2L_0/3$, and $L_0$. For each of these lengths, the corresponding value of $\kappa$ was determined from Fig. 4b: $\kappa \approx \{0.53, 0.46, 0.42\}$ for $L = \{L_0/3, 2L_0/3, L_0\}$ respectively. Peak uptake moves to smaller villi densities for larger stream-tube lengths $L$. A MBF velocity $u = 0.6\,\text{mm/s}$ has been used. In the analytical theory oxygen uptake has been calculated directly for the radius $R$, whereas in the numerical simulation oxygen uptake has been calculated for $R_{\text{num}}$ and rescaled to the placentone radius $R$ by multiplying by $R^2/R_{\text{num}}^2$. (b) Oxygen uptake as a function of stream-tube length $L$ for a fixed villi density $\phi$. The small deviations of the theory from the numerical results are explained by the fixed $\kappa = \kappa(L_0) \approx 0.42$ used for all lengths. Various symbols represent villi densities of Fig. 8.

Oxygen is received by the fetus. At the same time, villi density efficiency $\eta$ (Fig. 5b) shows how far the villi density of a given cross-section is from the maximal value for the given $\gamma(r_e)$. The higher is the value of $\eta$, the more oxygen is received by the fetus if the effective villi radius $r_e$ is fixed.

6 Results

Figure 7 shows that fetal oxygen uptake predicted by the analytical Eq. (25) agrees well with the numerically calculated results (Serov et al., 2014) in all ranges of stream-tube lengths ($L$) and villi densities ($\phi$). Figure 7a demonstrates the existence of the maximal uptake corresponding to an optimal villi density for each stream-tube length. The value of $\kappa(L)$ has been determined from Fig. 4b for each considered length $L$. These results have been calculated for the same geometries as in our earlier numerical simulation (Fig. 8). Note that the analytical theory uses only villi density and the effective villi radius ($r_e$) as geometrical information, and not the exact spatial distribution of villi. The agreement of analytical curves with numerical points shows
Fig. 8 Villi distributions for which oxygen uptake has been calculated in Serov et al. (2014). Number of villi ($N$) and the corresponding villi density ($\phi$) are displayed above each case. The analytical theory was applied to the corresponding $\phi$ with $r_e$ shown in Table 1. Maternal blood flows in the white space in the direction perpendicular to the cross-sections.

It can be seen that the numerical curves do not go beyond the villi density $\phi \approx 0.75$ in contrast to analytical curves. The explanation is quite simple: there exists a maximal packing density of circles in a large circle, so that numerical results cannot be calculated beyond a certain density (see Specht, 2009). The analytical theory, on the contrary, does not rely on particular shapes or distributions of villi, but operates only with villi density and the effective villi radius, thus allowing the results to be calculated for villi densities beyond this limit. Although in the region of $\phi > 0.75$ villi cannot be circular, the same $r_e$ is maintained.

Change of the parameter $\gamma$ in the analytical predictions of optimal villi density and maximal uptake (Eqs (28), (29)) can be interpreted in terms of changes of individual parameters of the model, the other parameters being fixed. For example, optimal villi density and maximal uptake can be plotted as functions of MBF velocity (Figs 9a, 9c) or stream-tube length (Figs 9b and 9d). An agreement between the plotted curves and the numerical results of Serov et al. (2014) can be observed.

All four plots in Fig. 9 feature a dashed black curve representing a fictitious case of blood having no hemoglobin but transporting only oxygen dissolved in blood plasma. Mathematically, this case is described by oxygen-hemoglobin dissociation parameter $B = 1$, which is about 100 times smaller than that for blood with Hb. As predicted by Eq. (28), the no-Hb curves for optimal villi density have the same shape but are shifted by two orders of magnitude as compared to those for blood with Hb.
Fig. 9 (a), (c): Dependence of the optimal villi density (a) and the maximal oxygen uptake (c) on MBF velocity at a fixed length $L_0 = 1.6\,\text{cm}$ for a single placentone. Dashed curves show the same results in blood with no hemoglobin (as in artificial perfusion experiments). (b), (d): Dependence of optimal villi density (b) and maximal oxygen uptake (d) on stream-tube length at a fixed MBF velocity $u = 0.6\,\text{mm/s}$ for a single placentone. Straight dashed lines indicate the expected average stream-tube length $L_0$. Shaded region shows the average MBF velocity expected in a healthy human placenta: $[0.5-0.7]\,\text{mm/s}$ (Table 1) and the corresponding optimal villi density and maximal oxygen uptake.

7 Discussion

7.1 Parameters $\gamma$ and $F_0$

7.1.1 Values

Taking $\pi R^2$ as the total area of the cross-section, parameters from Table 1 and $\kappa(L_0) \approx 0.4$ for the average length $L_0 \approx 1.6\,\text{cm}$ of a stream tube (Fig. 4b), from Eq. (26) one can estimate the values of $\gamma$ and $F_0$, which characterize a “healthy” regime of our placenta model: $\gamma \approx 1.3$, $F_0 \approx 4 \cdot 10^{-6}\,\text{mol/s}$. The obtained average value of $\gamma$ together with the average villi density $\phi \approx 0.46$ (Serov et al., 2014) are marked by crosses in the diagrams in Fig. 5. One can then
see that the theory predicts that the average placenta extracts around 35% of the maximal possible incoming oxygen flow $F_0$ (Fig. 5a), and that this value is close to the maximal one for the given effective villi radius (Figs 5b). However, to have real predictive power, $\gamma$ and $\phi$ need to be measured for different healthy as well as pathological placentas over the whole exchange region. Such measurements require the development of image analysis techniques, which could for instance automatically determine these characteristics for typical histological placenta slides. Such measurements have not yet been performed and present an important perspective to this study. At the same time, because of the lack of experimental information about several other parameters (namely, $u$, $w$, $L$) in each studied placenta, correlations of changes of ($\gamma$, $\phi$) with changes of fetal development characteristics (such as birth-weight, placenta weight or their ratio) are expected to be of more practical use than absolute values of ($\gamma$, $\phi$). Note finally that the optimal geometry and maximal uptake may change for non-slip boundary conditions; further studies are required to clarify this point (for discussion see Serov et al., 2014).

7.1.2 Roles

The two parameters $\gamma$ and $F_0$ play different roles in our model. According to Eq. (27), $\gamma$ alone determines the optimal villi density, while $F_0$ together with $\gamma$ determines the maximal oxygen uptake.

A clear physical interpretation of $\gamma$ can be obtained by rewriting (26) as

$$\gamma = \frac{L/u}{Br_e/(2w\kappa)} = \frac{\tau_{tr}}{\tau_e},$$

where $\tau_{tr} = L/u$ is the transit time of maternal blood through the placenta (while it flows along a stream tube of length $L$ with a velocity $u$) and $\tau_e = Br_e/(2w\kappa)$ is the oxygen extraction time of a placental cross-section. As a consequence, $\gamma$ can be understood as a quantitative measure of balance between two transport mechanisms of oxygen: the longitudinal convective flow and the transverse diffusion. In other words, $\gamma$ quantitatively describes the level of adaptation of the geometry of the cross-section and uptake parameters to the incoming MBF. Large values of $\gamma$ ($\gamma \gg 1$) mean that oxygen is quickly transferred to the fetal circulation at the beginning of the stream-tube and is rapidly depleted, so that poor in oxygen maternal blood flows through the remaining part. Thus, this large remaining part is not efficient. Small values of $\gamma$ ($\gamma \ll 1$) mean that maternal blood passes too quickly through the placenta as compared to the oxygen extraction time, and that a considerable part of the incoming oxygen flow may not be transferred. One can then speculate that the transfer of oxygen is the most efficient in the placentas, for which $\gamma$ is of the order of 1. The value around 1 calculated from the model parameters suggests that a healthy placenta may indeed function optimally.
7.2 The analytical theory

The advantages of the analytical solution over the numerical one are numerous. In fact, the analytical theory allows one:

1. To estimate the efficiency of oxygen transfer in a given placental cross-section by means of oxygen extraction efficiency $\zeta$ and villi density efficiency $\eta$ plotted in Fig. 5. These two quantities allow for comparison of different placentas or placental regions once the parameters $\phi$ and $\gamma$ are calculated for them;

2. To suggest that oxygen uptake in the human placenta is rather robust to changes of villi density. Indeed, the diagram in Fig. 5a shows that placental villi density can vary by about 10% around the optimal value with the villi density efficiency $\eta$ staying in the 90–100% interval. Far from the optimal villi density, $\eta$ tends to decrease faster.

3. To demonstrate that the villi density $\phi$ and the effective villi radius $r_e$ are the only geometrical parameters necessary to predict oxygen uptake of a more or less uniform villi distribution in a placenta cross-section (see Figs 7, 9). These two parameters allow for a simple application of the theory to distributions of villi of an arbitrary shape. The validity of the theory in the case of strongly non-uniform villi distributions remains to be investigated.

Finer details of villi distributions, which produce differences between numerical and analytical results in Figs 7 and 9, are stored in the coefficient $\kappa$. This coefficient encompasses not only the details of villi distributions, but also their influence on oxygen uptake at a given length $L$. In other words, it quantitatively describes the fact that in each geometry, different regions of the IVS are not equivalent due to random distribution of villi, and that with length $L$, oxygen in some regions is exhausted faster than in the others. This effect makes the parameter $\alpha$ in Eq. (23) change with $L$, which is accounted for by the dependence $\kappa(L)$. However, the effect of this change on oxygen uptake is rather weak. This observation can be made from Fig. 7b, in which $F_{\text{in}}^\text{opt}(L)$ was plotted for all lengths with the same $\kappa = \kappa(L_0) \approx 0.42$. In the first approximation, $\kappa$ can hence be considered constant.

4. To analyze the consequences of neglecting oxygen-hemoglobin reaction on oxygen uptake as well as on the optimal villi density of a placenta region. Moreover, the theory gives a method of recalculation of the results obtained for no-Hb blood in artificial placenta perfusion experiments into those for blood with Hb. Imagine that at the end of an artificial perfusion experiment with no-Hb blood, one obtains the total oxygen inflow $\bar{F}_{\text{in}}$ into the placenta, fetal oxygen uptake $\bar{F}$ and the average villi density $\bar{\phi}$ from histomorphometry of the same placenta (note that $\bar{F}_{\text{in}}$ and $\bar{F}$ differ from $F_{\text{in}}$ and $F$ which would have been obtained for blood with Hb). From these data one can then calculate $\bar{F}_0 = \bar{F}_{\text{in}}/(1 - \bar{\phi})$ (see the discussion of Eq. (26)) and then $\bar{\gamma}$ as a root of Eq. (25). These values can be
recalculated for blood containing Hb: $\gamma = \tilde{\gamma}/B$ and $F_0 = \tilde{F}_0 B$, where $B \approx 101$ (Table 1), and can be substituted into Eq. (25) to give oxygen uptake $F$ in the same placenta for blood containing Hb. One can see that oxygen uptake in a no-Hb perfusion experiment gives on the average a hundred-times underestimation of the real uptake. Finally, the values of $\gamma$ and $\phi$ for the given placenta can be compared with the diagram in Fig. 5b to determine how far the geometry of the region is from the optimal one. Note that this recalculation introduces a small error as in no-Hb case the diffusive part of the total flow omitted in Eq. (17) becomes important;

5. To reduce the computation time as calculations of eigenfunctions and eigenvalues of the diffusion equation are not required. Note that due to long computation time, numerical simulations of Serov et al. (2014) had to be performed on a smaller placentone radius $R_{\text{num}}$ and then rescaled to the radius $R$ by multiplying oxygen uptake by $R^2/R_{\text{num}}^2$. This constraint does not apply to the analytical theory. In particular, good agreement between both approaches justifies the rescaling of results performed in the numerical calculations.

Note finally that the derivation of Eq. (26) implies that, strictly speaking, $P$ is not the total perimeter of the villi, but the effective absorbing perimeter of the villi (i.e. only its part that is directly in contact with the IVS). In the case of well-separated villi, there is no difference between the two definitions. However, it is not always the case in the placental cross-sections. For instance, in Fig. 10b one can see several isolated groups of villi, inside which villi lie so close to each other, that there is virtually no IVS left between them. The parts of the villous boundary which are not in contact with large parts of the IVS are then screened from participating in oxygen uptake and, hence, should not be accounted for in the effective absorbing perimeter of the villi. A schematic description of this situation is shown in Fig. 10a. This remark can be understood by considering the fact that oxygen diffuses in the IVS, and only the parts of the villous boundary that are in contact with the IVS will participate in the uptake. In the case of well separated singular villi, the entire perimeter is absorbing.

8 Conclusions

In the present work, an analytical solution to the diffusion-convection equation governing oxygen transfer in the human placenta has been developed. It has been shown that for a more or less uniform spatial distribution of villi in a placental cross-section, only two geometrical characteristics, villi density $\phi$ and the effective villi radius $r_e$, are needed to predict fetal oxygen uptake.

It has been also demonstrated that all the parameters of the model do not influence oxygen uptake independently, but instead form two combinations of physiological parameters: (i) the maximal oxygen inflow of one placentone $F_0$, and (ii) the ratio $\gamma$ of the transit time of maternal blood over the oxygen extraction time. These parameters together with villi density determine oxygen uptake. Analytical formulas and diagrams have been obtained to allow for a quantitative
Fig. 10 Illustration of the difference between the total villous perimeter and the effective absorbing villous perimeter. (a) Example of an isolated group of villi. In the shaded villi group, some parts of absorbing villi boundaries are inefficient as they are screened by other villi from the outside of the isolated group, where the main reservoir of oxygen is supposed to be. The effective absorbing perimeter of the group is close to the perimeter outlined by the dashed line. This perimeter (the perimeter of the IVS surrounding the villi) can be several times smaller than the total perimeter of the villi in the shaded group. Note also that adding a new villus into such group (the villus outside the shaded group) does not increase the effective absorbing perimeter proportionally to the increase of the total villi perimeter. In the example above, the new perimeter (the dotted contour) is approximately the same as the old one. (b) Illustration of the same concept in a histological slide of the human placenta. Two dashed contours show the effective absorbing perimeters of two groups of villi, which are considerably smaller than the total perimeters of the villi in the groups. Discussion of similar screening concepts can be found in Felici et al. (2005), Gill et al. (2011), Sapoval et al. (2002)

estimation of the efficiency of oxygen transfer by a given placenta region based on measurements of $\phi$ and $r_e$.

Finally, a fictitious case of blood containing no hemoglobin was analyzed to study oxygen transfer in artificial placenta perfusion experiments as well as in some early placenta exchange models that did not take oxygen-hemoglobin interaction into account. It has been demonstrated that artificial perfusion experiments with no hemoglobin tend to give a two-orders-of-magnitude underestimation of the in vivo oxygen uptake. A method of recalculation of the results of artificial placenta perfusion to account for oxygen-hemoglobin dissociation has been proposed.

In combination with image analysis techniques, this analytical theory can be the base of a future tool for fast diagnostics of placenta efficiency based on its histological slides.
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27
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