A mathematical model of intervillous blood flow in the human placentone

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Supplementary Material

A. The method of images for Darcy's flow in a hemispherical domain

We use cylindrical coordinates (z, r, θ) with a local maternal blood velocity $\mathbf{u}(r, z) = (u_z(r, z),\ u_r(r, z),\ 0)$ to describe the axisymmetric flow, where z is the axis of symmetry (on which the source and sinks lie), r is the radial distance normal to the axis and θ is the azimuthal angle (so that the placentone occupies $|z| \leq L,\ 0 \leq r \leq L,\ 0 \leq \theta \leq \pi,\ r^2 + z^2 \leq L^2$, see Fig. 2$a$).

Neglecting fluid inertia due to the low Reynolds number (see Table 2 and averaging mass and momentum conservation laws over lengthscales large compared to the scale of villous microstructure, but small compared to the placentone radius L, we can describe the steady flow of maternal blood by Darcy's law [23, 24]

$$\nabla \cdot \mathbf{u} = 0\,, \tag{A.1}$$

$$\mathbf{u} = -\frac{k}{\mu}\,\nabla P\,, \tag{A.2}$$

where $\mathbf{u}$ and P are the velocity and pressure of blood in the intervillous space; k is the hydraulic conductivity coefficient (inverse flow resistance) and μ is blood viscosity, which are both assumed constant.

Because Darcy flow (A.2) is by definition irrotational ($\nabla \times \mathbf{u} = 0$), we introduce a Stokes stream function and velocity potential with appropriate boundary conditions and apply the method of images to obtain the exact solution to the flow problem. In doing so we find analytical expressions for the pressure and velocity fields in closed form.

Equations (A.1)–(A.2) are solved subject to boundary conditions $\lim_{r\to 0} r\, u_r = \frac{q}{\pi}\big(\delta(z) - \frac{1}{2}\,[\,\delta(z - z_v) + \delta(z + z_v)\,]\big)$ on $S_1 = \{r^2 + z^2 \leq L^2,\ \theta = 0,\ \theta = \pi\}$ and $\mathbf{u} \cdot \mathbf{n} = 0$ on $S_2 = \{r^2 + z^2 = L^2,\ 0 \leq \theta \leq \pi\}$; here the Dirac δ-function is used to approximate the flow rate distribution of a singular source and sinks, q is the flow rate at the source (which is split equally between the sinks), and $\mathbf{n}$ is the outward unit normal vector to the hemispherical surface S_2. We explain how the finite sizes of the source and sink vessels influence the flow solution below.

The incompressibility condition (A.1) is identically satisfied if we introduce the Stokes stream function $\psi(r,z)$ in a cylindrical coordinate system, defined as $u_r = -\frac{1}{r}\frac{\partial\psi}{\partial z},\ u_z = \frac{1}{r}\frac{\partial\psi}{\partial r}$, where u_r and u_z are radial and axial velocity components. We also introduce a velocity potential $\varphi = -\frac{k}{\mu}P$, such that $\mathbf{u} = \nabla\varphi$. Thus, from (A.1)–(A.2) we obtain

$$\nabla^2\psi - \frac{2}{r}\frac{\partial\psi}{\partial r} = 0\,, \quad \nabla^2 P = 0\,, \tag{A.3}$$

where $\nabla^2 \equiv (\nabla\cdot\nabla) = \partial^2/\partial r^2 + r^{-1}\partial/\partial r + \partial^2/\partial z^2$ is the Laplace operator.

Since a single source emits in the half-space a flux q, the boundary condition for the Stokes stream function on S_1, describing a system of one source and two sinks with zero net flux, is $-\frac{\partial\psi}{\partial z}\Big|_{r=0} = \frac{q}{\pi}\left(\delta(z) - \frac{1}{2}\left[\,\delta(z-z_v)+\delta(z+z_v)\,\right]\right)$. In order to satisfy $\mathbf{u}\cdot\mathbf{n}=0$ on S_2, we take $\psi =$ constant and $\mathbf{n}\cdot\nabla P = 0$ on S_2. Without loss of generality, we set $\psi=0$ on S_2.

We rewrite (A.3), subject to boundary conditions, in dimensionless form. We choose the following non-dimensional variables: $r = L\,r'$, $z = L\,z'$, $\mathbf{u} = U\,\mathbf{u}'$ and $\psi = q\,\psi'$, $P = P_{\mathrm{ref}} + P_0\,P'$, where $U = q/L^2$ is typical flow velocity scale of maternal blood, $P_0 = \mu q/kL$ is a pressure scale characteristic of the viscous pressure drop across a porous medium, and P_{ref} is a reference pressure intermediate between the arterial and venous pressures (see Table 2). Then the dimensionless problem for blood flow in the hemispherical domain reads:

$$\begin{aligned}
&\nabla^2\psi' - \frac{2}{r'}\frac{\partial\psi'}{\partial r'} = 0\,, \quad \nabla^2 P' = 0 \qquad \text{in } V',\\
&\left.\begin{aligned}
&-\frac{\partial\psi'}{\partial z'}\bigg|_{r'=0} = \frac{1}{\pi}\left(\delta(z') - \frac{1}{2}\left[\,\delta(z'-h)+\delta(z'+h)\,\right]\right),\\
&-\lim_{r'\to 0} r'\,\frac{\partial P'}{\partial r'} = \frac{1}{\pi}\left(\delta(z') - \frac{1}{2}\left[\,\delta(z'-h)+\delta(z'+h)\,\right]\right),
\end{aligned}\right\}\quad \text{on } S_1'\,,\\
&\psi' = 0, \quad \frac{\partial P'}{\partial n} = 0 \qquad \text{on } S_2'\,,
\end{aligned} \tag{A.4}$$

where $V' = \{|z'|<1,\ 0<r'<1,\ 0<\theta<\pi,\ r'^2+z'^2\le 1\}$, $S_1' = \partial V' \cap \{\theta = 0\,, \theta = \pi\}$, $S_2' = \partial V' \cap \{r'^2 + z'^2 = 1\}$. The dimensionless source-sink distance is $h = z_v/L$. In the subsequent analysis, the primes over dimensionless variables are dropped.

The fundamental solutions (Green's functions) to the stream function and pressure equations with a singular uniform source at $z=1$ on the axis of symmetry in an unbounded domain ($z \in \mathbb{R},\ r > 0,\ 0 \le \theta < 2\pi$) are as follows [42]:

$$G_\psi = -\frac{1}{4\pi}\frac{z-1}{\sqrt{(z-1)^2+r^2}}, \quad G_P = \frac{1}{4\pi}\frac{1}{\sqrt{(z-1)^2+r^2}}. \tag{A.5}$$

The flow and pressure solutions of problem (A.4) in the unbounded half-space $|z| > 0,\ r > 0,$ $0 < \theta < \pi$ are given by superposition of the fundamental solutions (A.5) as

$$\begin{aligned} \psi_\infty(r,z) &= -\frac{1}{2\pi}\left(\frac{z}{\sqrt{z^2+r^2}} - \frac{1}{2}\left[\frac{z-h}{\sqrt{(z-h)^2+r^2}} + \frac{z+h}{\sqrt{(z+h)^2+r^2}}\right]\right), \\ P_\infty(r,z) &= \frac{1}{2\pi}\left(\frac{1}{\sqrt{z^2+r^2}} - \frac{1}{2}\left[\frac{1}{\sqrt{(z-h)^2+r^2}} + \frac{1}{\sqrt{(z+h)^2+r^2}}\right]\right). \end{aligned} \tag{A.6}$$

Thus along the z-axis, ψ_∞ takes the values $0, +\frac{1}{2\pi}, -\frac{1}{2\pi}, 0$ as z increases from -1 to $+1$.

The method of images allows us to satisfy the boundary conditions on S_2 by adding a correction to the flow and pressure fields (A.6). In order to do so, we apply Butler's and Weiss's Sphere theorems for axisymmetric fluid motions [42].

Given the unperturbed flow and pressure fields $\psi_\infty(r,z)$, $P_\infty(r,z)$ from (A.6), according to Butler's Sphere theorem [42] the stream function satisfying $\psi = 0$ on S_2 is

$$\psi(r,z) = \psi_\infty(r,z) + \frac{\sqrt{K}}{2\pi}\left(\frac{z}{\sqrt{r^2+z^2}} - \frac{1}{2}\left[\frac{z-Kh}{\sqrt{r^2+(z-Kh)^2}} + \frac{z+Kh}{\sqrt{r^2+(z+Kh)^2}}\right]\right), \tag{A.7}$$

where $K = r^2 + z^2$, $r, z \in V$. The image system consists of two point sinks at inverse points with respect to the sphere $\big((r,z) = (0, \pm 1/h)$ for $(0, \pm h)\big)$ and two line sinks, stretched from the inverse points to infinity ($r = 0,\ |z| \ge 1/h$).

By setting $K = 1$ in (A.7) we can readily see that $\psi = 0$ on S_2 as required. One can also check, by direct calculation using (A.7), that the normal component of fluid velocity at the boundary vanishes: $(\mathbf{u}\cdot\mathbf{n}) = \frac{z}{r}\frac{\partial \psi}{\partial r} - \frac{\partial \psi}{\partial z} = 0$ on S_2.

Application of Weiss's Sphere theorem [42] gives the pressure perturbation in the presence of a hemisphere:

$$P(r,z) = P_\infty(r,z) + \frac{1}{2\pi}\left(\ln r - \frac{1}{2}\left[\frac{{z_v}^*}{\sqrt{(z-{z_v}^*)^2+r^2}} + \ln\left(\frac{\sqrt{z^2+r^2}-z}{\sqrt{(z-{z_v}^*)^2+r^2}-(z-{z_v}^*)}\right)\right.\right.$$
$$\left.\left. + \frac{{z_v}^*}{\sqrt{(z+{z_v}^*)^2+r^2}} + \ln\left(\frac{\sqrt{z^2+r^2}+z}{\sqrt{(z+{z_v}^*)^2+r^2}+(z+{z_v}^*)}\right)\right]\right), \tag{A.8}$$

where ${z_v}^* = 1/h$ and $r, z \in V$.

In doing so we obtain exact solutions (A.7), (A.8) to the flow and pressure distributions of boundary-value problem (A.4), as shown in Fig. 3.

We can also find a relation between the (dimensional) source-sink pressure drop $\Delta P = P|_{r=a,z=0} - P|_{r=a,z=z_v}$ (evaluated in the vicinity of the vessel's junctions on the basal plate) and the flow rate q, based on (A.6) for an unbounded domain (in dimensional variables):

$$q = \frac{2\pi k}{\mu}\,\Delta P\left[\frac{3}{2a} - \frac{2}{\sqrt{a^2+{z_v}^2}} + \frac{1}{2\sqrt{a^2+4{z_v}^2}}\right]^{-1} = \frac{4\pi k a}{3\mu}\,\Delta P\left(1 + O\left(\frac{a}{z_v}\right)\right). \tag{A.9}$$

Here $a \ll z_v$ is the width of a small neighbourhood of a source or sink, of scale comparable with the maternal vessels' radius. We are here exploiting the singular pressure distributions in (A.6) near $z = 0, \pm h,$ and are matching the arterial pressure P_a to $P_\mathrm{ref} + \mu q/(2\pi k a)$ and venous pressure P_v to $P_\mathrm{ref} - \mu q/(4\pi k a)$. Thus we define $P_\mathrm{ref} = (P_\mathrm{a} + 2P_\mathrm{v})/3$, with $\Delta P = P_\mathrm{a} - P_\mathrm{v}$ (e.g. in dimensional variables, for $P_a = 9$ mmHg, $P_v = 3$ mmHg, we have $P_\mathrm{ref} = 5$ mmHg and $\Delta P = 6$ mmHg). The relation (A.9) also gives a good approximation in the case of the bounded hemispherical domain: one can show, via expansion in a power series in a, that for $L = 10a,\ z_v = 0.9L,$ the relative difference between expression (A.9) and relation based on the precise formula (A.8) is of order 10 %. Therefore, the intervillous maternal blood pressure in Fig. 3(*c,d*) is defined within levels set by the respective radii a of the basal vessels and the fluxes they carry, determining the overall pressure drop ΔP across the placentone.

One can generalise relation (A.9) to the case of the spiral artery (source) and decidual veins (sinks) of different radii a_s and a_v respectively, providing that they are sufficiently small and far apart ($a_s,\ a_v \ll z_v$). The leading order terms in (A.6) give $\Delta P = P|_{r=a_s,z=0} - P|_{r=a_v,z=z_v} \approx \frac{\mu q}{2\pi k}\left(\frac{1}{a_s} + \frac{1}{2\,a_v}\right)$. Comparing with (A.9), we find the effective vessel's lengthscale a to be a weighted harmonic mean of the source and sinks' lengthscales:

$$a = \frac{3}{2}\left(\frac{1}{a_s} + \frac{1}{2\,a_v}\right)^{-1} . \tag{A.10}$$

A direct corollary of (A.10) is the dominant influence of the vessels of smaller calibre on the placentone's overall conductance. Indeed, $a \sim 3a_v$ for $a_s \gg a_v$; $a \sim 3a_s/2$ for $a_s \ll a_v$, and $a = a_s$ for $a_s = a_v$.

B. Computation of the solute distribution and net uptake rate

The steady advection-dominated transport of a passive solute in a homogeneous porous medium is described by

$$(\mathbf{u} \cdot \nabla)\, C = -\alpha\, C\,, \quad C|_{r,z=0} = C_0\,, \tag{B.1}$$

where C is the concentration of a solute (gas or nutrient) in the maternal blood, C_0 is the solute concentration at the source (the spiral artery entering the placentone), α is a solute consumption rate averaged over the pore length scale. According to (B.1), the solute is convected along streamlines (due to relatively large Péclet number, see Table 2).

The concentration distribution of solute $C(r, z)$ in Fig. 5 and 6 is computed by numerical integration of the velocity field along streamlines, which are the trajectories of fluid "particles" in the intervillous space. The absolute and relative net uptake rates (shown in Fig. S1 and S2) are estimated as a weighted sum of uptakes per unit time over individual streamlines, as explained below.

The steady advective transport of a solute (B.1) is described in dimensionless form (scaling C on C_0; primes over dimensionless variables are dropped) by

$$(\mathbf{u} \cdot \nabla)\, C = -Da\, C\,, \quad C|_{r,z=0} = 1\,, \tag{B.2}$$

where $Da = \alpha L^3/q$ is the Damköhler number.

The concentration distribution of solute is computed by integration of the velocity field along streamlines. We use a Lagrangian formulation to rewrite equation (B.2) as

$$\frac{\mathrm{d}\,C}{\mathrm{d}\,t} = -Da\, C, \quad C(0) = 1\,, \tag{B.3}$$

where $C = C(t)$, $\mathbf{x} = (r(t), z(t))$ belongs to a particular streamline, defined as $\mathrm{d}\mathbf{x}/\mathrm{d}t = \mathbf{u}$, and $t = 0$ at the source ($r = z = 0$). Here t represents time evolution following a material particle along a streamline. Thus $C(t) = e^{-Da\,t}$.

The relative net uptake rate of a solute is

$$N_r = 1 - \int_{S_{\rm sink}} C\,\mathbf{u}\cdot\mathbf{n}\,\mathrm{d}S\,, \tag{B.4}$$

where $S_{\rm sink}$ is a surface in a small vicinity of the sink and $\mathbf{n}$ is the outward unit normal vector to this surface. The dimensional absolute net uptake rate is $N_a = q\,C_0\,N_r$.

The absolute and relative net uptake rates are estimated using a trapezium quadrature. The time t elapsed since a fluid particle has travelled along a streamline is calculated numerically from $t = \int \frac{\mathrm{d}s}{|\mathbf{u}|}$, where s is a distance along the streamline:

$$t = \sum_{i=1}^{n_i} \sqrt{\frac{(\Delta r_i)^2 + (\Delta z_i)^2}{u_r^2(r_i, z_i) + u_z^2(r_i, z_i)}},$$

where $\Delta r_i = r_{i+1} - r_i,\ \Delta z_i = z_{i+1} - z_i,\ n_i$ is the number of points at discretisation of a streamline, velocities u_r and u_z are computed in accord with the definition of the stream function and by use of the exact formula (A.7). The relative computational inaccuracy is of order $1/N$, where N is the number of points of a uniform mesh taken at discretisation in both the z and r directions. Typically 200 streamlines and $N = 800$ uniform grid points are used in the calculations. Linear interpolation between streamlines is used to get a continuous concentration field. Predicted values of N_a and N_r as functions of model parameters are shown in Fig. S1; for discussion see the main text.

An important characteristic of the placentone is the volume fraction of villous tissue ϕ. A qualitative analysis can be performed using the Kozeny–Carman formula for hydraulic conductivity [23]

$$k = \frac{d^2}{180}\,\frac{(1-\phi)^3}{\phi^2}\,, \tag{B.5}$$

where d is an average diameter of villi in the intraplacentone space. Expression (B.5) is most precise for a medium formed by a uniform distribution of solid spheres of constant diameter d.

Using (A.9) and (B.5), we can express the flow rate at the source q in terms of volume fraction, for a constant pressure drop $\Delta P = P|_{r=a,z=0} - P|_{r=a,z=z_v}$ in dimensional variables (evaluated a distance $a = 0.8$ mm from the vessels, where a is comparable to the radius of each vessel; see Table 2), as follows:

$$q(\phi) \simeq \frac{\pi a\, d^2 \Delta P}{135\mu}\,\frac{(1-\phi)^3}{\phi^2}. \tag{B.6}$$

If we assume that the pressure drop ΔP is constant, and the solute consumption rate per unit volume α is proportional to the surface area of villous tissue, then $q \approx 2q_0\,(1-\phi)^3/\phi^2$ and $\alpha \approx 1.6\,\alpha_0\,\phi^{2/3}$, where the coefficients of proportionality are chosen in such a way that $\alpha = \alpha_0$, $q = q_0$ at $\phi = 0.5$ (see Table 2). Fig. S2(a) shows the dependence of the absolute net uptake rate N_a (scaled to a reference inlet concentration flux $q_0 C_0$) on ϕ and demonstrates the existence of an optimal volume fraction near $\phi \approx 0.3$.

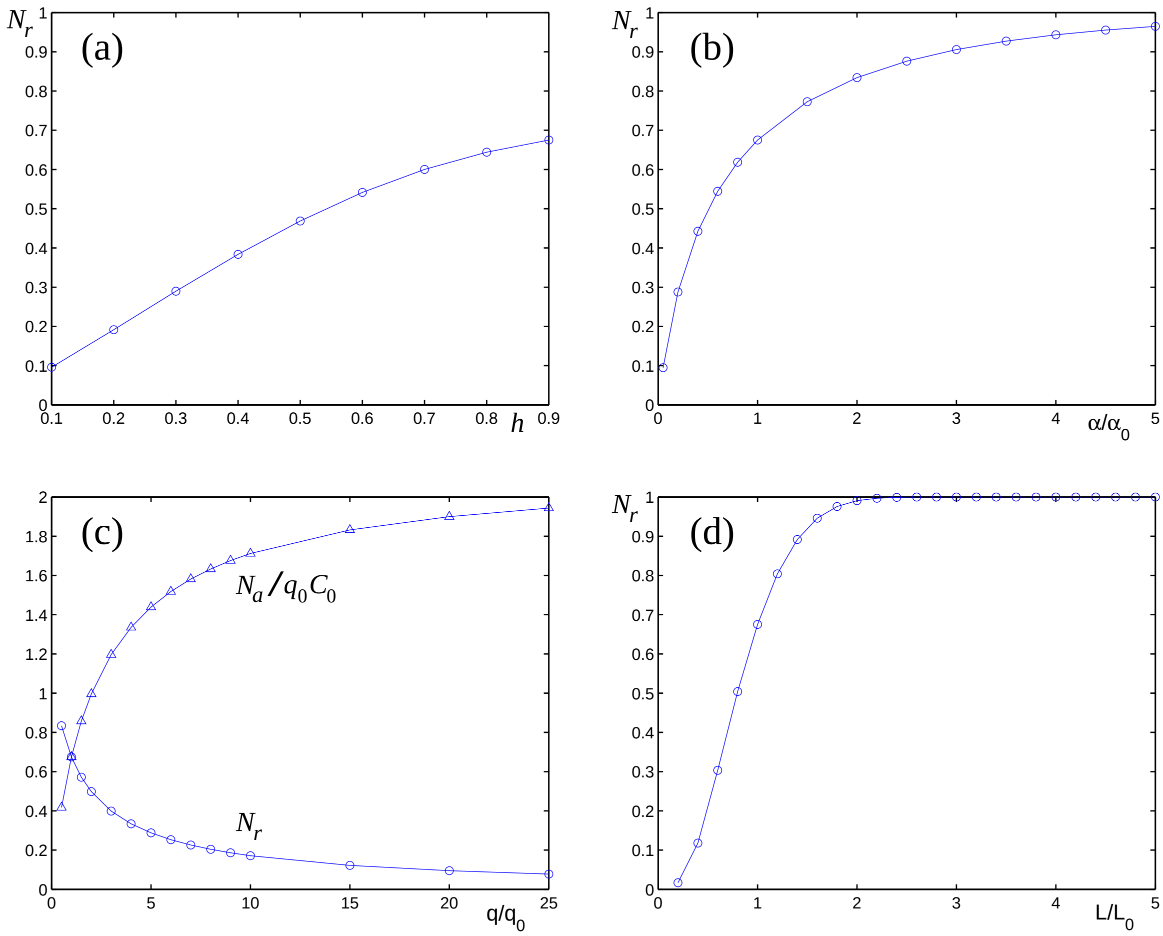

Figure S1. Effect of basal vessels' position and solute consumption rate on a net uptake rate. Dependence of the net uptake rate N_r on: (a) decidual artery-vein distance $h = z_v/L$ ($Da = 1$); (b) solute consumption rate α relative to the reference consumption rate α_0 at fixed inlet flux of maternal blood ($h = 0.9$, $q = q_0$); (c): inlet blood flow rate q relative to the reference flow rate q_0 ($h = 0.9$, $\alpha = \alpha_0$); (d): size of the placentone L relative to the reference placentone radius L_0 ($h = 0.9$, $\alpha = \alpha_0$, $q = q_0$). See Table 2 for parameter values.

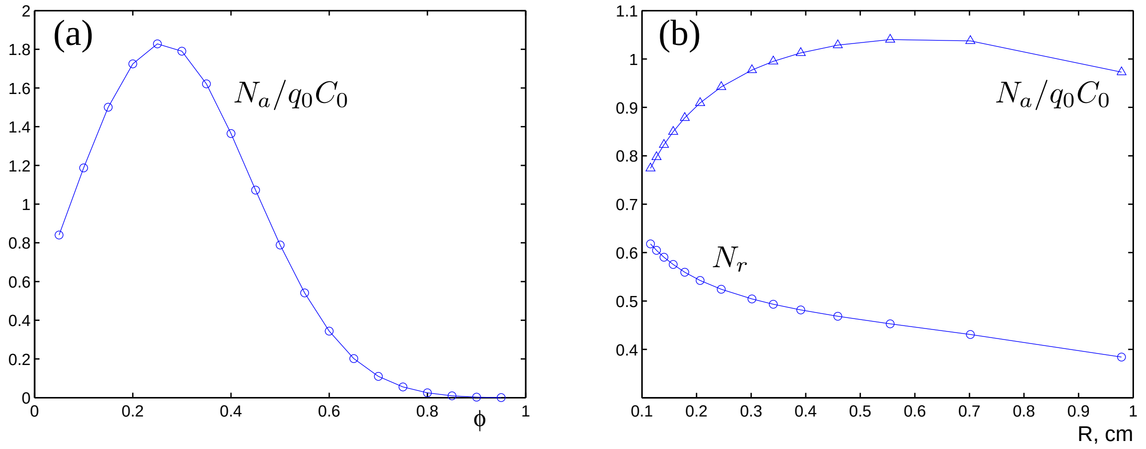

Figure S2. Dependence of absolute net uptake rate N_a on: (a) volume fraction ϕ of homogeneous villous tissue; (b) size of the central cavity R at constant pressure drop ΔP between the basal artery and veins ($h = 0.9$).