Modeling lung capillary perfusion and gas exchange in alveolar microstructures

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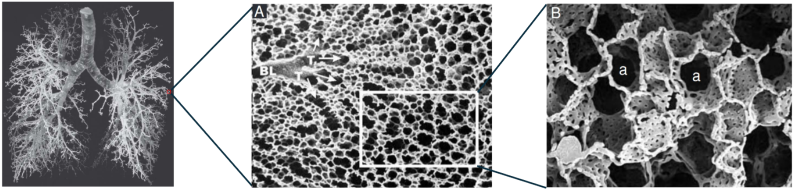
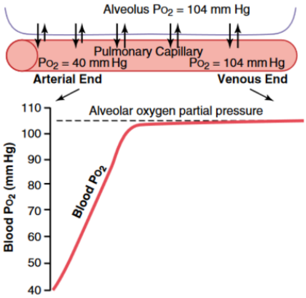
Lung tissue organization and microstructure

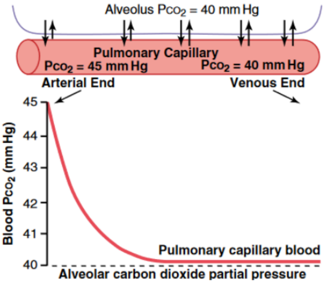


whole lung | alveolar tissue | pulmonary microcapillaries

- Lung parenchyma is a porous tissue in two different scales!
- Continuous sheet of blood with posts
- Very low Reynolds number, Re $\sim 10^{-4}$

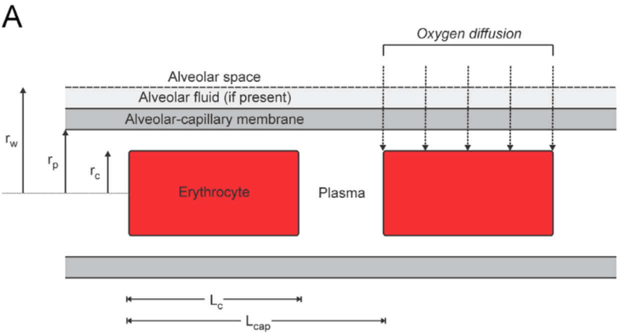
Gas exchange





- Deoxygenated blood: $p_{O_2} = 40$ mmHg, $p_{CO_2} = 45$ mmHg
- Oxygenated blood: $p_{O_2} = 100$ mmHg, $p_{CO_2} = 40$ mmHg
- Partial pressure difference-driven gas exchange between blood and alveolar air

Perfusion and gas exchange models



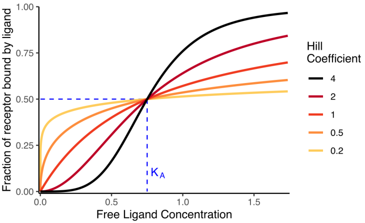
- Cylindrical geometry for a single capillary
- Poiseuille (laminar) flow driven by pressure difference
- Simplified, one-dimensional gas exchange with radial gas flow

Hill (1973)

Let p_{O_2} and S_{HbO_2} be the O_2 partial pressure and HbO_2 saturation in RBCs. Then,

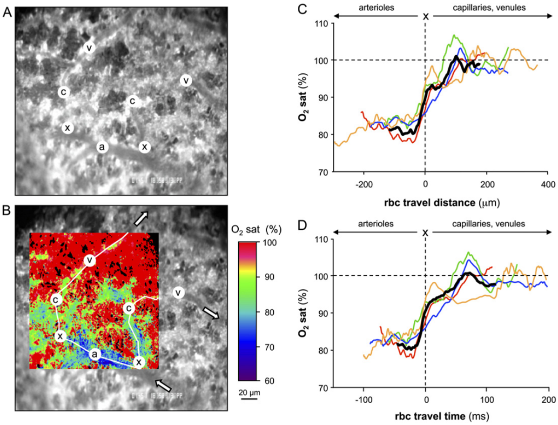
$$S_{HbO_2} = \frac{(p_{O_2}/p_{50})^n}{1 + (p_{O_2}/p_{50})^n}, \tag{1}$$

where $n \approx 2.7$, and $p_{50} \approx 26.8$ mmHg correlates with $S_{HbO_2} = 0.5$.

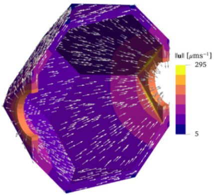


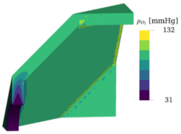
- Ignores relevant physiological parameters, e.g. blood pH and velocity
- Inaccurate at very low/high p_{O_2}
- Does not model CO_2 dynamics
- More complex models include temperature, [DPG] and pH effects

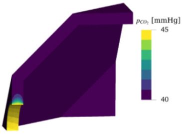
Gas exchange as a local process

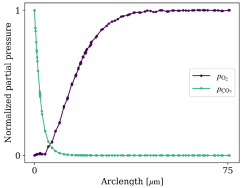


- *In vivo* setup (Tabuchi et al., 2013): multispectral oxymetry + intravital fluorescent microscopy
- Flow-dependent behaviour
- Irregular oxygenation profile along capillaries









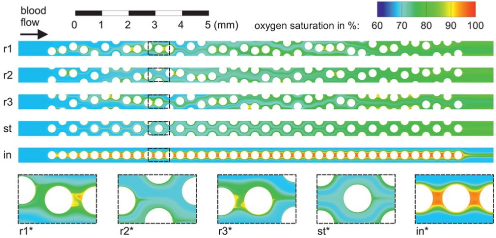
- Perfusion as Darcy porous media flow
- Gas exchange multiphysics: convection + diffusion + reaction
- First-order kinetics: $HbO_2 \xleftrightarrow{k_{O_2}} Hb + O_2$, $HbCO_2 \xleftrightarrow{k_{CO_2}} Hb + CO_2$
- Alveolar geometry approximation: slab, spherical, TKD

Why do we need a better model?

- Realistic, 3D alveolar geometries yet to be considered
- Lack of CO_2-O_2 competitivity and synergystic effects
- CO_2 dynamics are decoupled from bicarbonate buffer system

$$HCO_3^- + H^+ \longleftrightarrow CO_2 + H_2O$$

- Lack of whole-lung efficiency metrics based on microscale gas exchange
- Predictive models serve for artificial lung design



Our model

Perfusion: Darcy blood flow

Darcy's law for porous media flow (1856)

Let $\boldsymbol{u}$ and p be the fluid velocity field and pressure. Then, for a porous media,

$$\boldsymbol{u} = -\frac{1}{\mu}\boldsymbol{\kappa}\nabla p, \tag{2}$$

where μ is the fluid viscosity and $\boldsymbol{\kappa}$ is the permeability tensor.

Perfusion: Darcy blood flow

We define a compact set Ω that represents a blood-perfused region of alveolar tissue. We split its boundary as $\partial\Omega = S_{\text{in}} \cup S_{\text{air}} \cup S_{\text{out}}$.

Perfusion model (Zurita & Hurtado, 2023)

Find the velocity $\boldsymbol{u}$ and pressure p that satisfy (2) and

$$\begin{aligned} \nabla \cdot (\kappa \nabla p) &= 0 && \text{in } \Omega && \text{(3a)} \\ \kappa \nabla p \cdot \boldsymbol{n} &= \mu u^{\text{in}} && \text{in } \Gamma_{\text{in}} && \text{(3b)} \\ p &= p_{\text{min}} && \text{in } \Gamma_{\text{out}} && \text{(3c)} \\ \kappa \nabla p \cdot \boldsymbol{n} &= 0 && \text{in } \Gamma_{\text{air}}, && \text{(3d)} \end{aligned}$$

where κ is the isotropic permeability (i.e. $\boldsymbol{\kappa} = \kappa \boldsymbol{I}$).

Boundary conditions: velocity prescribed at the inlet, pressure prescribed at the outlet.

- Detailed chemical equilibrium derived by Dash & Bassingthwaighte (2006, 2010, 2016)
- Multi-step reactions between Hb and gases
- Equilibrium with hydrogen ions
- Coupling with the bicarbonate buffer system (K_1'')

Dash & Bassingthwaighte (2016)

$$K_1'[CO_2] = [H_2CO_3],$$

$$K_1''[H_2CO_3] = [HCO_3^-][H^+],$$

$$K_2'[CO_2][HmNH_2] = [HmNHCOOH],$$

$$K_2''[HmNHCOOH] = [HmNHCOO^-][H^+],$$

$$K_3'[CO_2][O_2HmNH_2] = [O_2HmNHCOOH],$$

$$K_3''[O_2HmNHCOOH] = [O_2HmNHCOO^-][H^+],$$

$$K_4'[O_2][HmNH_2] = [O_2HmNH_2],$$

$$K_5''[HmNH_3^+] = [HmNH_2][H^+],$$

$$K_6''[O_2HmNH_3^+] = [O_2HmNH_2][H^+],$$

- Oxygen is transported as oxyhemoglobin or dissolved gas
- Carbon dioxide is transported as carbaminohemoglobin, dissolved gas, or as HCO_3^- ions, in equilibrium with the bicarbonate buffer system

Gas concentrations in blood

$$c_{O_2}(p_{O_2}, p_{CO_2}) = W_{bl}\beta_{O_2}p_{O_2} + 4[Hb]_{bl}S_{HbO_2} \tag{4}$$

$$c_{CO_2}(p_{O_2}, p_{CO_2}) = W_{bl}\beta_{CO_2}p_{CO_2} + 4[Hb]_{bl}S_{HbCO_2} + [HCO_3^-]_{bl}(p_{CO_2}) \tag{5}$$

HCO_3^- equilibrium (Dash & Bassingthwaighte, 2010)

$$[HCO_3^-]_{bl}(p_{CO_2}) = ((1 - Hct)W_{pl} + Hct\, W_{rbc}R_{rbc})\, \frac{K_1\beta_{CO_2}p_{CO_2}}{[H^+]} \tag{6}$$

Dash & Bassingthwaighte model (2006, 2010, 2016)

$$S_{HbO_2}(p_{O_2}, p_{CO_2}) \equiv \frac{[HbO_2]_{rbc}}{[Hb]_{rbc}} = \frac{K_{HbO_2}[O_2]_{rbc}}{1 + K_{HbO_2}[O_2]_{rbc}} \tag{7a}$$

$$S_{HbCO_2}(p_{O_2}, p_{CO_2}) \equiv \frac{[HbCO_2]_{rbc}}{[Hb]_{rbc}} = \frac{K_{HbCO_2}[CO_2]_{rbc}}{1 + K_{HbCO_2}[CO_2]_{rbc}} \tag{7b}$$

- Nonlinear functions that depend on both partial pressures:

$$K_{HbO_2} = K_{HbO_2}(p_{O_2}, p_{CO_2})$$
$$K_{HbCO_2} = K_{HbCO_2}(p_{O_2}, p_{CO_2})$$

- Implicit dependence on physiological parameters: pH, Hct, [DPG], T°
- Accurately predicts saturations given any pair of partial pressures between 0 and 150 mmHg

We employ the following continuum balance laws for our derivation, where $X \in \{O_2, CO_2\}$:

Conservation of mass

$$\frac{\mathrm{D}}{\mathrm{D}t} \int_{E_t} c_X \mathrm{d}x + \int_{\partial E_t} \boldsymbol{j}_X \cdot \boldsymbol{n} \mathrm{d}s = 0 \tag{8}$$

Fick's law of diffusion

$$\boldsymbol{j}_X = -d_X^{\text{pla}} \nabla c_X \tag{9}$$

Robin condition for membrane gas exchange (Zurita & Hurtado, 2023)

$$\nabla c_X \cdot \boldsymbol{n} = \frac{d_X^{\text{b-a}} \beta_X}{d_X^{\text{pla}} h^{\text{b-a}}} (p_X^{\text{air}} - p_X) \qquad \text{in } \Gamma_{\text{air}} \tag{10}$$

Now, we derive our steady-state convection-diffusion system as following:

Gas exchange model

Find the oxygen partial pressure p_{O_2} and carbon dioxide partial pressure p_{CO_2} that satisfy

$$-d_{O_2}^{\text{pla}}\nabla^2 c_{O_2} + \boldsymbol{u}\cdot\nabla c_{O_2} = 0 \qquad \text{in } \Omega \tag{11a}$$

$$-d_{CO_2}^{\text{pla}}\nabla^2 c_{CO_2} + \boldsymbol{u}\cdot\nabla c_{CO_2} = 0 \qquad \text{in } \Omega \tag{11b}$$

$$p_{O_2} = p_{O_2}^{\text{in}}, \quad p_{CO_2} = p_{CO_2}^{\text{in}} \qquad \text{in } S_{\text{in}} \tag{11c,d}$$

$$\nabla p_{O_2}\cdot\boldsymbol{n} = 0, \quad \nabla p_{CO_2}\cdot\boldsymbol{n} = 0 \qquad \text{in } S_{\text{out}} \tag{11e,f}$$

$$\nabla c_{O_2}\cdot\boldsymbol{n} = \frac{d_{O_2}^{\text{b-a}}\beta_{O_2}}{d_{O_2}^{\text{pla}}h^{\text{b-a}}}(p_{O_2}^{\text{air}} - p_{O_2}) \qquad \text{in } S_{\text{air}} \tag{11g}$$

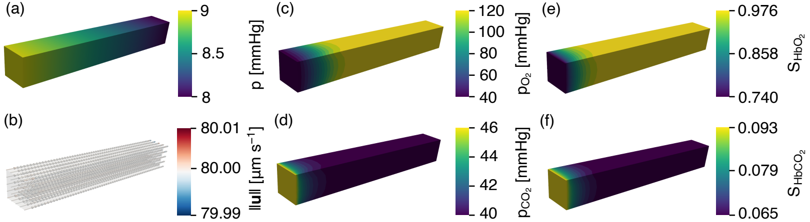
$$\nabla c_{CO_2}\cdot\boldsymbol{n} = \frac{d_{CO_2}^{\text{b-a}}\beta_{CO_2}}{d_{CO_2}^{\text{pla}}h^{\text{b-a}}}(p_{CO_2}^{\text{air}} - p_{CO_2}) \qquad \text{in } S_{\text{air}} \tag{11h}$$

Computational aspects

- Developed on Python 3.10.2 + FEniCSx 0.7.2
- Lagrange finite elements P^2-P^1 (Taylor-Hood) for $(p, \boldsymbol{u})$, and P^1 for both p_{O_2} and p_{CO_2}, defined on tetrahedral cells
- Direct (MUMPS) numerical method for perfusion
- Damped Newton method for gas exchange
- Parallel execution on 16GB RAM w/ Intel Core i7-11800H @ 2.30GHz

We begin by defining a single-capillary slab geometry as

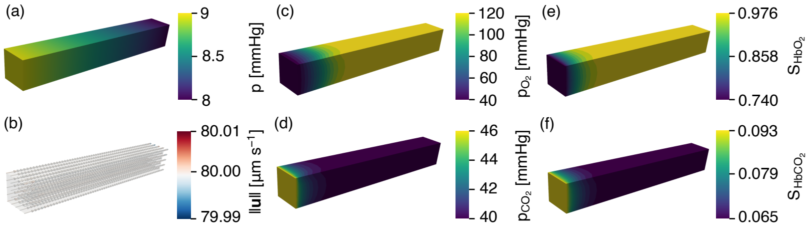
$$\Omega = [0, 60]\ \mu\text{m} \times [-4, 4]\ \mu\text{m} \times [-4, 4]\ \mu\text{m}$$



Single-capillary perfusion and gas exchange

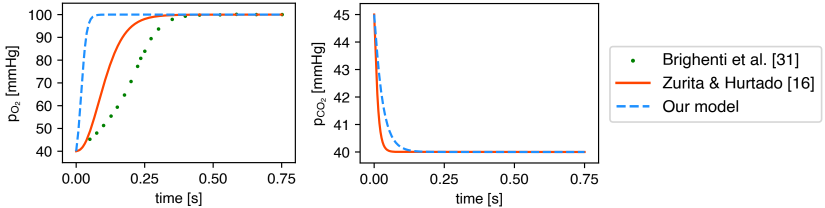
We begin by defining a single-capillary slab geometry as

$$\Omega = [0, 60]\ \mu\text{m} \times [-4, 4]\ \mu\text{m} \times [-4, 4]\ \mu\text{m}$$



- Linear pressure drop and uniform velocity field
- Gas exchange is completed in $\sim 80 - 100$ ms

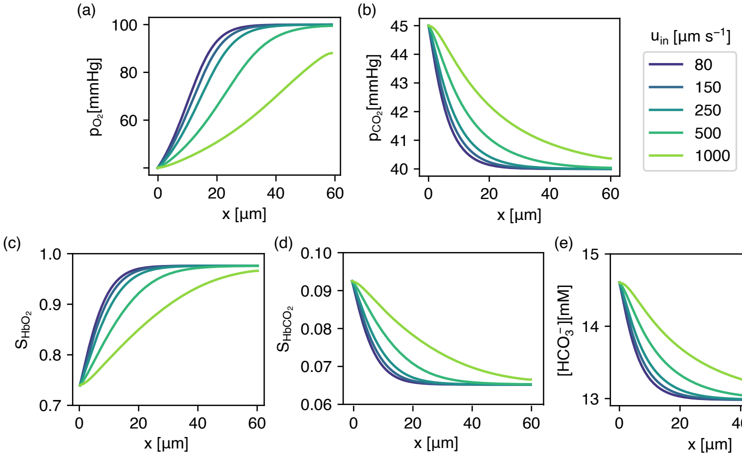
Benchmark perfusion and gas exchange tests



- Markedly faster O_2 uptake, slower CO_2 release than existing models
- O_2 reaches equilibrium at 83 μs, similar to the $80 - 100$ ms observed equilibrium time
- CO_2 dynamics slowed by the bicarbonate buffer system

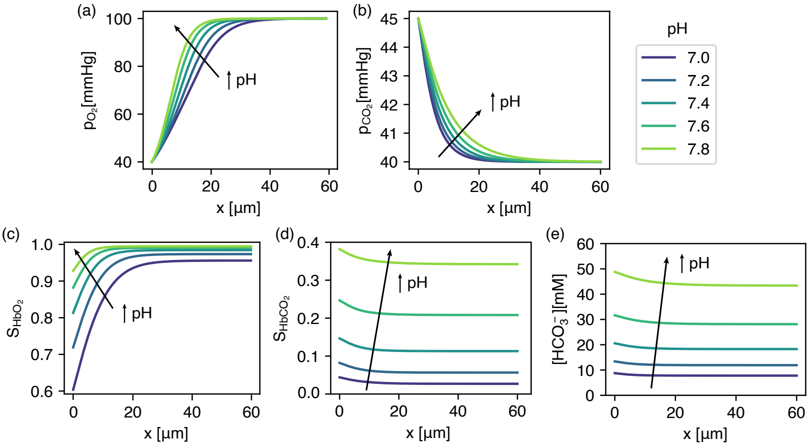
$$HCO_3^- + H^+ \longleftrightarrow CO_2 + H_2O$$

Velocity-dependent gas exchange



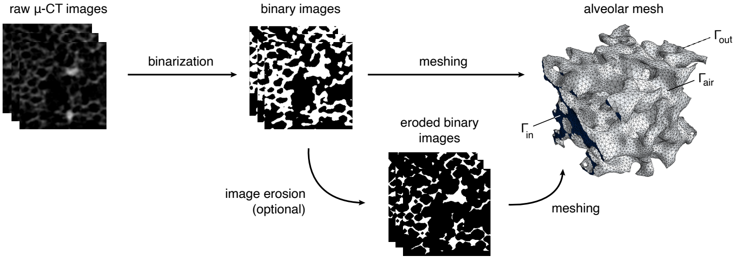
- As expected, shorter transit times limit O_2 uptake and CO_2 release
- Microstructural basis for exercise-induced hypoxia

pH-dependent gas exchange



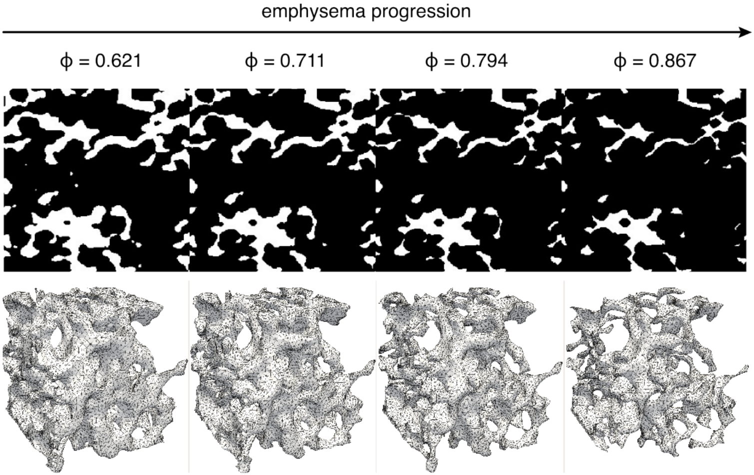
- Increasing pH raises Hb affinity for O_2 (Bohr effect)
- Coupled HCO_3^--CO_2 dynamics through the bicarbonate buffer system

Lung microstructure reconstruction

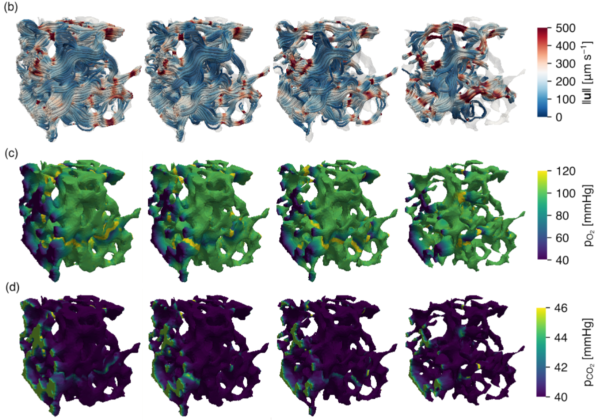


- Raw μ-CT images obtained from a murine alveolar morphology study (Sarabia-Vallejos et al., 2021)
- Custom thresholding and Delaunay triangulation to match observed porosity $\phi = 0.65$
- Image erosion to generate emphysematous lung meshes

Normal and emphysematous lung geometries



Alveolar perfusion and gas exchange



- Poorly-perfused tissue regions
- Regional variations in p_{O_2}, p_{CO_2}
- Emphysema does not prevent gas equilibrium, but reduces effective gas flux

Whole-lung diffusing capacity

Lung efficiency is often calculated as a ratio of effectively transferred gas to partial pressure differences.

Diffusing capacity ratio

$$\mathrm{DL}_X = \frac{\dot{V}_X}{|p_X^{\text{air}} - p_X^{\text{in}}|} \tag{12}$$

We propose a locally-informed estimation for lung diffusing capacity.

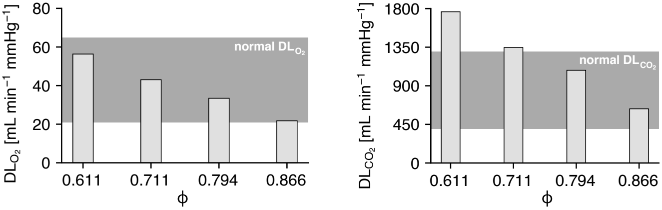
Upscaled local diffusing capacity

$$\mathrm{DL}_{O_2} = \frac{V_{\text{lung}}}{V_{\text{RVE}}} \frac{1}{p_{O_2}^{\text{air}} - p_{O_2}^{\text{in}}} \int_{\Gamma_{\text{air}}} \underbrace{\frac{d_{O_2}^{\text{b-a}} \beta_{O_2}}{h^{\text{b-a}}} \left(p_{O_2}^{\text{air}} - p_{O_2} \right)}_{j_{CO_2} \cdot \boldsymbol{n}} \mathrm{d}s \tag{13a}$$

$$\mathrm{DL}_{CO_2} = \frac{V_{\text{lung}}}{V_{\text{RVE}}} \frac{1}{p_{CO_2}^{\text{in}} - p_{CO_2}^{\text{air}}} \int_{\Gamma_{\text{air}}} \underbrace{\frac{d_{CO_2}^{\text{b-a}} \beta_{CO_2}}{h^{\text{b-a}}} \left(p_{CO_2} - p_{CO_2}^{\text{air}} \right)}_{j_{CO_2} \cdot \boldsymbol{n}} \mathrm{d}s \tag{13b}$$

Whole-lung diffusing capacity

We can now estimate DL_X using the solution of the gas exchange model.



- Estimations within normal physiological ranges for both gases
- Higher degree of emphysema $\rightarrow$ lower DL_{O_2} and DL_{CO_2}
- Decrease is only caused by microstructure geometry alterations

Thank you!

Variational form of gas exchange system

$$
\begin{aligned}
F_{O_2}(p_{O_2}, p_{CO_2}, v) = & \int_\Omega d_{O_2}^{\text{pla}} \nabla c_{O_2} \cdot \nabla v dx + \int_{S_{\text{out}}} c_{O_2} v \boldsymbol{u} \cdot \boldsymbol{n} ds - \int_\Omega c_{O_2} \boldsymbol{u} \cdot \nabla v dx \\
& + \int_{S_{\text{air}}} \frac{d_{O_2}^{\text{b-a}} \beta_{O_2}}{h^{\text{b-a}}} p_{O_2} v ds - \int_{S_{\text{air}}} \frac{d_{O_2}^{\text{b-a}} \beta_{O_2}}{h^{\text{b-a}}} p_{O_2}^{\text{air}} v ds
\end{aligned} \tag{14}
$$

$$
\begin{aligned}
F_{CO_2}(p_{O_2}, p_{CO_2}, w) = & \int_\Omega d_{CO_2}^{\text{pla}} \nabla c_{CO_2} \cdot \nabla w dx + \int_{S_{\text{out}}} c_{CO_2} w \boldsymbol{u} \cdot \boldsymbol{n} ds - \int_\Omega c_{CO_2} \boldsymbol{u} \cdot \nabla w dx \\
& + \int_{S_{\text{air}}} \frac{d_{CO_2}^{\text{b-a}} \beta_{CO_2}}{h^{\text{b-a}}} p_{CO_2} w ds - \int_{S_{\text{air}}} \frac{d_{CO_2}^{\text{b-a}} \beta_{CO_2}}{h^{\text{b-a}}} p_{CO_2}^{\text{air}} w ds
\end{aligned} \tag{15}
$$

$$
(WE) \begin{cases}
F_{O_2}(p_{O_2}, p_{CO_2}, v) = 0 & \forall v \in \mathcal{V}_e \quad (16a) \\
F_{CO_2}(p_{O_2}, p_{CO_2}, w) = 0 & \forall w \in \mathcal{V}_e \quad (16b) \\
p_{O_2} = p_{O_2}^{\text{in}} & \text{in } S_{\text{in}} \quad (16c) \\
p_{CO_2} = p_{CO_2}^{\text{in}} & \text{in } S_{\text{in}} \quad (16d)
\end{cases}
$$