Model for DQ reaction-exchange in capillary

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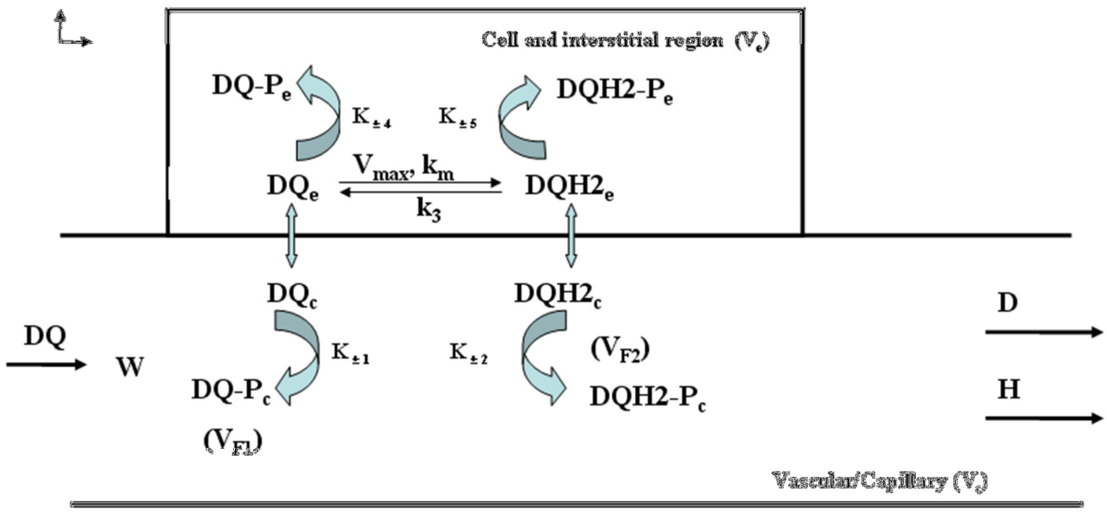


Assumption:

I. Two regions compartments are involved in this model, the capillary and the tissue space whose volume is Vc and Ve respectively. The concentration of free DQ in capillary and tissue represent as [DQ] and [DQ]e, the concentration of binded DQ in capillary and tissue represent as [DQ-P]c and [DQ-P]e respectively. The free DQH2 in capillary and tissue represent as [DQH2] and [DQH2]e, the binded DQH2 in capillary and tissue represent as [DQH2-P]c and [DQH2-P]e respectively. The total concentration of DQ in the capillary and tissue represent as $[\overline{DQ}]$ and $[\overline{DQ}]e$ respectively, the total concentration of DQH2 in the capillary and tissue represent as $[D\overline{QH}2]$ and $[D\overline{QH}2]e$ respectively.

II. DQ and DQH2 can diffuse across the cell membrane easily whose PS is PS1 and PS2 respectively following Fick's Law. Since the quick equilibration between capillary and tissue, we assume further that the concentrations of DQ in the capillary and tissue are the same.

III. DQ and DQH2 bind to protein in the capillary and tissue space respectively whose reaction rate is $K_{\pm i}$ (bidirectively) respectively.

IV. In the tissue, DQ is reduced into DQH2 by enzyme such as NQO1 following M-M kinetics whose parameter is vmax and km. DQH2 can be oxidized into DQ by complex III whose reaction rate is k3.

V. The flow velocity through the capillary is w, w=F/Ac, F is the flow rate and Ac is section area of capillary.

VI. The concentration of oxygen is stable due to the sufficient supply of oxygen.

VII. The concentration of electron donor for reduction of DQ is stable due to the sufficient supply, though in some degree, this assumption may be not true.

VI. To simplify the model, the effect of the binding of DQ, DQH2 to proteins can be represented by visual volume. For DQ, the visual volume of capillary can be represented as α1Vv where $\alpha 1=1+[Pv]k_1/k_{-1}$, for DQH2, the visual volume of capillary can be represented as α2Vv where $\alpha 21=1+[Pv]k_2/k_{-2}$. Similarly, there are α3Ve for DQ in the tissue and α4Ve for DQH2 in the tissue.

I. Without considering the chemical reactions, for the free DQ, it has:

$$\frac{\partial Dc}{\partial t}+W\frac{\partial Dc}{\partial x}=\frac{PS}{Vc}(De-Dc) \qquad \text{(in the capillary)}$$

$$\frac{\partial De}{\partial t}=-\frac{PS}{Ve}(De-Dc) \qquad \text{(in the tissue)}$$

Thus, $\frac{\partial Dc}{\partial t}+W\frac{\partial Dc}{\partial x}=\frac{PS}{Vc}(De-Dc)=-\frac{Ve}{Vc}\frac{\partial De}{\partial t}$

$$\frac{\partial Dc}{\partial t}+W\frac{\partial Dc}{\partial x}+\frac{Ve}{Vc}\frac{\partial De}{\partial t}=0$$

Since PS is extremely large, thus we regard Dc=De,

hence, $W\frac{\partial Dc}{\partial x}+\left(1+\frac{Ve}{Vc}\right)\frac{\partial Dc}{\partial t}=0$

The same, for free DQH2, it has, $W\frac{\partial Hc}{\partial x}+\left(1+\frac{Ve}{Vc}\right)\frac{\partial Hc}{\partial t}=0$

II. Now, take the chemical reaction into the consideration,
For free DQ,
According to mass balance,

Equ. a: $Vc\frac{\partial Dc}{\partial t}+WVc\frac{\partial Dc}{\partial x}=PS(De-Dc)$

Equ. b: $Ve\frac{\partial De}{\partial t}=-PS(De-Dc)-\frac{V_{\max 1}De}{k_{m1}+De}-\frac{V_{\max 2}De}{k_{m2}+De}+\frac{V_{\max 3}He}{k_{m3}+He}$

Add Equa and Equ b together,

Equ. c: $Ve\frac{\partial De}{\partial t}+Vc\frac{\partial Dc}{\partial t}+WVc\frac{\partial Dc}{\partial t}=-\frac{V_{\max 1}De}{k_{m1}+De}-\frac{V_{\max 2}De}{k_{m2}+De}+\frac{V_{\max 3}He}{k_{m3}+He}$

Equ. d: $De=Dc$, $He=Hc$

Combine Equ. c and Equ. d,

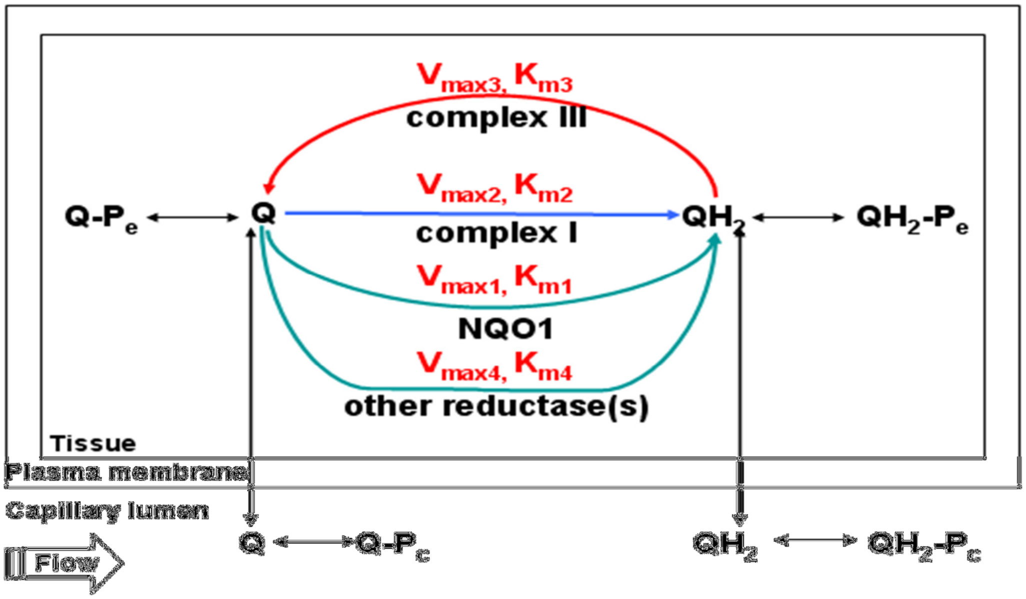
$$(Ve+Vc)\frac{\partial Dc}{\partial t}+WVc\frac{\partial Dc}{\partial t}=-\frac{V_{\max 1}De}{k_{m1}+De}-\frac{V_{\max 2}De}{k_{m2}+De}+\frac{V_{\max 3}He}{k_{m3}+He}$$

(note, the unit of Vmax is mol/s)

For free DQH$_2$,

$$(Ve+Vc)\frac{\partial H_c}{\partial t}+WV_c\frac{\partial H_c}{\partial x}=\frac{V_{\max 1}De}{k_{m1}+De}+\frac{V_{\max 2}De}{k_{m2}+De}-\frac{V_{\max 3}He}{k_{m3}+He}$$

III. Further, consider the binding of Quinone, hydroquinone to protein,



$Q + P_c \underset{k-1}{\overset{k1}{\rightleftarrows}} Q - P_c$

(in capillary lumen), $Q + P_e \underset{k-2}{\overset{k2}{\rightleftarrows}} Q - P_e$ (in tissue)

$QH_2 + P_c \underset{k-3}{\overset{k3}{\rightleftarrows}} QH_2 - P_c$ (in capillary), $QH_2 + P_e \underset{k-4}{\overset{k4}{\rightleftarrows}} QH_2 - P_e$ (in tissue)

For bound quinone and hydroquinone,
In capillary:

$$Vc\frac{\partial Q-P_c}{\partial t} + WVc\frac{\partial Q-P_c}{\partial x} = Vc(k_1 Q \times P_c - k_{-1}Q - P_c) \quad \text{(EQ1)}$$

→ since fast equilibrium, thus $Q - P_c = \frac{k_1 Q \times P_c}{k_{-1}} == \frac{QP_c}{k_{eq1}}$

$$Vc\frac{\partial QH_2-P_c}{\partial t} + WVc\frac{\partial QH_2-P_c}{\partial x} = Vc(-k_2 QH_2 \times P_c + k_{-2}QH_2 - P_c) \quad \text{(EQ2)}$$

→ $QH_2 - P_c = \frac{k_3 QH_2 \times P_c}{k_{-3}} = \frac{QH_2P_c}{k_{eq3}}$

In tissue:

$$Ve\frac{\partial Q-P_e}{\partial t} = Ve(k_3 Q \times P_e - k_{-3}Q - P_e) \quad \text{(EQ3)}$$

→ $Q - P_e = \frac{k_2 Q \times P_e}{k_{-2}} == \frac{QP_e}{k_{eq2}}$

$$Ve\frac{\partial QH_2-P_e}{\partial t}=V_e\left(-k_4QH_2\times P_e-k_{-4}QH_2-P_e\right)$$ (EQ4)

→ $$QH_2-P_e=\frac{k_4QH_2\times P_e}{k_{-4}}=\frac{QH_2P_e}{k_{eq4}}$$

For free quinone and hydroquinone,

$$(Ve+Vc)\frac{\partial Q}{\partial t}+WVc\frac{\partial Q}{\partial t}=-\frac{V_{\max 1}Q}{k_{m1}+Q}-\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}-V_c\ (k_1QP_c-k_{-1}Q-P_c)-V_e(k_3QP_e-k_{-3}Q-P_e)$$

(EQ5)

$$(Ve+Vc)\frac{\partial QH_2}{\partial t}+WVc\frac{\partial QH_2}{\partial t}=\frac{V_{\max 1}Q}{k_{m1}+Q}+\frac{V_{\max 2}Q}{k_{m2}+Q}-\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}--V_c\ (k_2QH_2P_c-k_{-2}QH_2-P_c)-V_e(k_4QH_2P_e-k_{-4}QH_2-P_e)$$

(EQ6)

Taking EQ1, EQ2, EQ3 into EQ5, EQ6, we have:

$$(Ve+Vc)\frac{\partial Q}{\partial t}+WVc\frac{\partial Q}{\partial t}=-\frac{V_{\max 1}Q}{k_{m1}+Q}-\frac{V_{\max 2}Q}{k_{m2}+Q}-\frac{V_{\max 4}Q}{k_{m4}+Q}+\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}-V_c\ \frac{\partial Q-P_c}{\partial t}-WVc\frac{\partial Q-P_c}{\partial x}-V_e\frac{\partial Q-P_e}{\partial t}$$

$$(Ve+Vc)\frac{\partial QH_2}{\partial t}+WVc\frac{\partial QH_2}{\partial t}=\frac{V_{\max 1}Q}{k_{m1}+Q}+\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 4}Q}{k_{m4}+Q}-\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}-V_c\ \frac{\partial QH_2-P_c}{\partial t}-WVc\frac{\partial QH_2-P_c}{\partial x}-V_e\frac{\partial QH_2-P_e}{\partial t}$$

→

Since Pc, Pe are sufficient, the concentration of Pc is regarded as a constant, thus $\frac{\partial QP_c}{\partial t}=P_c\frac{\partial Q}{\partial t}$

$$(Ve+Vc)\frac{\partial Q}{\partial t}+WVc\frac{\partial Q}{\partial t}=-\frac{V_{\max 1}Q}{k_{m1}+Q}-\frac{V_{\max 2}Q}{k_{m2}+Q}-\frac{V_{\max 4}Q}{k_{m4}+Q}+\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}-V_c\ \frac{\partial Q-P_c}{\partial t}-WVc\frac{\partial Q-P_c}{\partial x}-V_e\frac{\partial Q-P_e}{\partial t}$$

$$(Ve+Vc)\frac{\partial QH_2}{\partial t}+WVc\frac{\partial QH_2}{\partial t}=\frac{V_{\max 1}Q}{k_{m1}+Q}+\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 4}Q}{k_{m4}+Q}-\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}--V_c\ \frac{\partial QH_2-P_c}{\partial t}-WVc\frac{\partial QH_2-P_c}{\partial x}-V_e\frac{\partial QH_2-P_e}{\partial t}$$

→

$$(V_e+V_c)\frac{\partial Q}{\partial t}+WV_c\frac{\partial Q}{\partial t}+V_c\frac{\partial Q-P_c}{\partial t}+WVc\frac{\partial Q-P_c}{\partial x}+V_e\frac{\partial Q-P_e}{\partial t}=-\frac{V_{\max 1}Q}{k_{m1}+Q}-\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}-\frac{V_{\max 4}Q}{k_{m4}+Q}$$

$$(Ve+Vc)\frac{\partial QH_2}{\partial t}+WVc\frac{\partial QH_2}{\partial t}=\frac{V_{\max 1}Q}{k_{m1}+Q}+\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 4}Q}{k_{m4}+Q}-\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}--V_c\ \frac{\partial QH_2-P_c}{\partial t}-WVc\frac{\partial QH_2-P_c}{\partial x}-V_e\frac{\partial QH_2-P_e}{\partial t}$$

Set

$$\overline{Q}=Q+Q-P_c=\left(1+\frac{P_c}{k_{eq1}}\right)Q=\alpha_1 Q$$

$$\overline{QH_2}=QH_2+QH_2-P_c=\left(1+\frac{P_c}{k_{eq3}}\right)QH_2=\alpha_3 QH_2$$

$$Q+Q-P_e=\left(1+\frac{P_e}{k_{eq2}}\right)Q=\alpha_2 Q$$

$$Q+QH_2-P_e=\left(1+\frac{P_e}{k_{eq4}}\right)QH_2=\alpha_4 QH_2$$

$\overline{Q}$ is the total quinone in venous efflux sample, the measured quinone.

$\overline{QH_2}$ is the total hydroquinone in venous efflux sample, the measured hydroquinone.

Thus,

$$\left[V_e\left(1+\frac{P_e}{k_{eq2}}\right)+V_c\left(1+\frac{P_c}{k_{eq1}}\right)\right]\frac{\partial Q}{\partial t}+WV_c\left(1+\frac{P_c}{k_{eq1}}\right)\frac{\partial Q}{\partial x}=\left(V_e\,\alpha_2+V_c\alpha_1\right)\frac{\partial Q}{\partial t}+WV_c\alpha_1\frac{\partial Q}{\partial x}=-\frac{V_{\max 1}Q}{k_{m1}+Q}-\frac{V_{\max 2}Q}{k_{m2}+Q}-\frac{V_{\max 4}Q}{k_{m4}+Q}+\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}$$

$$\left[V_e\left(1+\frac{P_e}{k_{eq4}}\right)+V_c\left(1+\frac{P_c}{k_{eq2}}\right)\right]\frac{\partial QH_2}{\partial t}+WV_c\left(1+\frac{P_c}{k_{eq2}}\right)\frac{\partial QH_2}{\partial x}=\left(V_e\,\alpha_4+V_c\alpha_3\right)\frac{\partial QH_2}{\partial t}+WV_c\alpha_3\frac{\partial QH2}{\partial x}=\frac{V_{\max 1}Q}{k_{m1}+Q}+\frac{V_{\max 2}Q}{k_{m2}+Q}+\frac{V_{\max 4}Q}{k_{m4}+Q}-\frac{V_{\max 3}QH_2}{k_{m3}+QH_2}$$

=>

$$\left(\frac{V_e\,\alpha_2}{\alpha_1}+V_c\right)\alpha_1\frac{\partial Q}{\partial t}+WV_c\alpha_1\frac{\partial Q}{\partial x}=\left(\frac{V_e\,\alpha_2}{\alpha_1}+V_c\right)\frac{\partial \overline{Q}}{\partial t}+WV_c\frac{\partial \overline{Q}}{\partial x}=-\frac{V_{\max 1}\overline{Q}}{\alpha_1 k_{m1}+\overline{Q}}-\frac{V_{\max 2}\overline{Q}}{\alpha_1 k_{m2}+\overline{Q}}-\frac{V_{\max 4}\overline{Q}}{\alpha_1 k_{m4}+\overline{Q}}+\frac{V_{\max 3}\overline{QH_2}}{\alpha_3 k_{m3}+\overline{QH_2}}$$

$$\left(\frac{V_e\,\alpha_4}{\alpha_3}+V_c\right)\alpha_3\frac{\partial Q}{\partial t}+WV_c\alpha_3\frac{\partial Q}{\partial x}=\left(\frac{V_e\,\alpha_4}{\alpha_3}+V_c\right)\frac{\partial \overline{QH_2}}{\partial t}+WV_c\frac{\partial \overline{QH_2}}{\partial x}=\frac{V_{\max 1}\overline{Q}}{\alpha_1 k_{m1}+\overline{Q}}+\frac{V_{\max 2}\overline{Q}}{\alpha_1 k_{m2}+\overline{Q}}+\frac{V_{\max 4}\overline{Q}}{\alpha_1 k_{m4}+\overline{Q}}-\frac{V_{\max 3}\overline{QH_2}}{\alpha_3 k_{m3}+\overline{QH_2}}$$

=>

$$\left(\frac{V_e\,\alpha_2}{\alpha_1}+V_c\right)\frac{\partial \overline{Q}}{\partial t}+WV_c\frac{\partial \overline{Q}}{\partial x}=-\frac{V_{\max 1}\overline{Q}}{k_{m1a}+\overline{Q}}-\frac{V_{\max 2}\overline{Q}}{k_{m2a}+\overline{Q}}-\frac{V_{\max 4}\overline{Q}}{k_{m4a}+\overline{Q}}+\frac{V_{\max 3}\overline{QH_2}}{k_{m3a}+\overline{QH_2}}$$

$$\left(\frac{V_e\,\alpha_4}{\alpha_3}+V_c\right)\frac{\partial \overline{QH_2}}{\partial t}+WV_c\frac{\partial \overline{QH_2}}{\partial x}=\frac{V_{\max 1}\overline{Q}}{k_{m1a}+\overline{Q}}+\frac{V_{\max 2}\overline{Q}}{k_{m2a}+\overline{Q}}+\frac{V_{\max 4}\overline{Q}}{k_{m4a}+\overline{Q}}-\frac{V_{\max 3}\overline{QH_2}}{k_{m3a}+\overline{QH_2}}$$

=>

Set $V_{F1}=\frac{V_c\,\alpha_2}{\alpha_1}$, $V_{F2}=\frac{V_e\,\alpha_4}{\alpha_3}$

Then,

$$\frac{\partial \overline{Q}}{\partial t}+W\left(\frac{V_c}{V_c+V_{F1}}\right)\frac{\partial \overline{Q}}{\partial x}=\frac{1}{V_c+V_{F1}}\left(-\frac{V_{\max 1}\overline{Q}}{k_{m1a}+\overline{Q}}-\frac{V_{\max 2}\overline{Q}}{k_{m2a}+\overline{Q}}-\frac{V_{\max 4}\overline{Q}}{k_{m4a}+\overline{Q}}+\frac{V_{\max 3}\overline{QH_2}}{k_{m3a}+\overline{QH_2}}\right)$$

$$\frac{\partial \overline{QH_2}}{\partial t}+W\left(\frac{V_c}{V_c+V_{F2}}\right)\frac{\partial \overline{QH_2}}{\partial x}=\frac{1}{V_c+V_{F2}}\left(\frac{V_{\max 1}\overline{Q}}{k_{m1a}+\overline{Q}}+\frac{V_{\max 2}\overline{Q}}{k_{m2a}+\overline{Q}}+\frac{V_{\max 4}\overline{Q}}{k_{m4a}+\overline{Q}}-\frac{V_{\max 3}\overline{QH_2}}{k_{m3a}+\overline{QH_2}}\right)$$