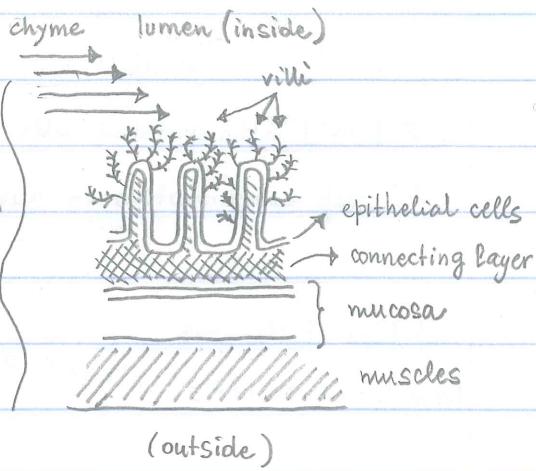


LECTURE 10

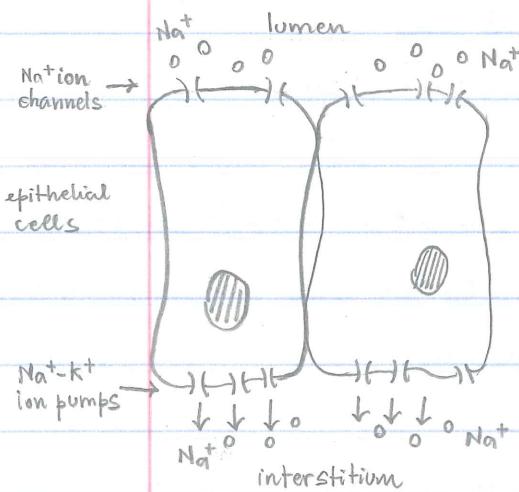
The main function of the gastrointestinal tract is to absorb nutrients from the mix of food and liquid ("chyme") that moves through it

CROSS-SECTION
GASTRO INTESTINAL
TRACT IN HUMANS

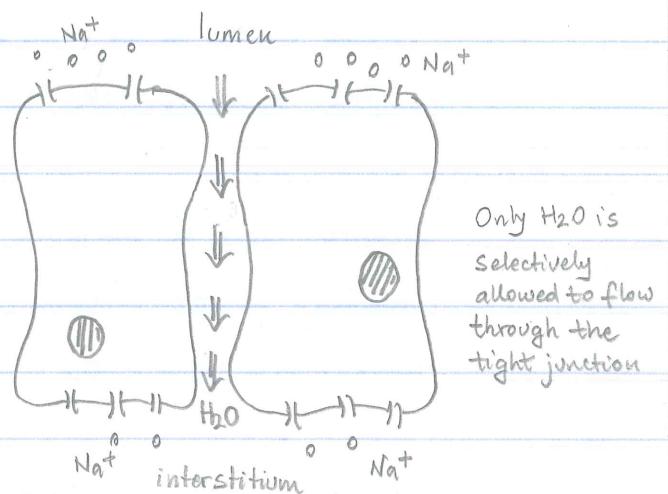


* A model of fluid absorption

The epithelial cells are depicted to interface with the chyme but their membrane on the luminal side (i.e., the side facing the chyme) is not permeable to H_2O (water)
 \Rightarrow There are tight junctions between cells to let water flow into the connecting layer (interstitium) \Rightarrow The diffusion of H_2O occurs by osmosis according to the following paradigm:



Because of the change in $[Na^+]$ in lumen and interstitium



Na^+ ions passively enter the epithelial cells via ion channels and actively transition into the interstitium via Na^+-K^+ pumps \Rightarrow

To equilibrate the Na^+ concentration gradient from lumen to interstitium, the tight junctions selectively let H_2O molecules flow toward the interstitium

(2)

$$s_L \triangleq [\text{Na}^+] \text{ in the lumen}$$

$$s_E \triangleq [\text{Na}^+] \text{ in the epithelial cells}$$

$$c_I \triangleq \text{lump concentration of substrates (of any kind) in the interstitium}$$

Net flux of Na⁺ ions

from lumen to cells:

$$J_{L \rightarrow E} = g(s_L - s_E)$$

$g \triangleq$ conductance of the ion channels (in appropriate units)

Net flux of Na⁺ ions

from cells to interstitium:

$$J_{E \rightarrow I} = f(s_E)$$

$f \triangleq$ function that describes the Na⁺-K⁺ pump's operation

$$\text{At steady state we expect: } J_{L \rightarrow E} = J_{E \rightarrow I} \Leftrightarrow g(s_L - s_E) = f(s_E)$$

Net flux of H₂O from the

lumen to the interstitium:

$$q_{L \rightarrow I} = \frac{1}{R}(c_I - s_L)$$

$R \triangleq$ resistance offered by the junction to the passage of H₂O (in appropriate units)

Note that c_I is determined by two fluxes:

1) The influx of Na⁺ ions from the epithelial cells

2) The influx of molecules due to capillary microcirculation



Denoted with Q the flux of fluid arriving into the interstitium because of capillary microcirculation, and denoted with c_0 the lump concentration of substrates (of any kind) in the influx Q , we have:

$$(Q + q_{L \rightarrow I})c_I = Qc_0 + f(s_E) \Rightarrow \text{Since } c_I = Rq_{L \rightarrow I} + s_L, \text{ we have:}$$

$$(Q + q_{L \rightarrow I})(Rq_{L \rightarrow I} + s_L) = Qc_0 + f(s_E)$$

(3)

$$R q_{L \rightarrow I}^2 + (QR + s_L) q_{L \rightarrow I} + Q (s_E - c_0) - f(s_E) = 0 \quad (*)$$

A typical, data-driven formulation for $f(s_E)$ in $(*)$ is:

$$f(s_E) = Q_f \frac{s_E^3}{k_f^3 + s_E^3} \quad \text{where } Q_f \text{ and } k_f \text{ are parameters estimated from actual data}$$

We want to solve equation $(*)$ for $q_{L \rightarrow I}$ and use s_L to control the value of $s_E \Rightarrow$ We must take into account, though, that s_E depends on s_L and the relationship is nonlinear:

$$s_L = s_E + \frac{1}{g} f(s_E) = s_E + \frac{Q_f}{g} \frac{s_E^3}{k_f^3 + s_E^3} \quad (**) \quad (*)$$

We can determine, though, conditions under which equation $(*)$ has an admissible solution. Let us call:

$$\left. \begin{array}{l} u_L \triangleq s_L/k_f \\ u_E \triangleq s_E/k_f \\ u_0 \triangleq c_0/k_f \\ y \triangleq q_{L \rightarrow I}/Q \end{array} \right\} \Rightarrow RQ^2 y^2 + \left(RQ + k_f u_L \right) Qy + Q k_f (u_L - u_0) - Q_f \frac{u_E^3}{1+u_E^3} = 0$$

↓

Dividing by $Q k_f$ we have:

$$\underbrace{\frac{RQ}{k_f} y^2}_{P} + \underbrace{\left(\frac{RQ}{k_f} + u_L \right) y}_{P+u_L} + \underbrace{u_L - u_0 - \frac{Q_f}{Q k_f} \frac{u_E^3}{1+u_E^3}}_{K} = 0 \quad (***)$$

In this polynomial equation, $P > 0$ and $P + u_L > 0$ by construction \Rightarrow The sign of the solution depends on the sign of K , i.e., there is at most one solution $y > 0$ ($\Rightarrow q_{L \rightarrow I} > 0$, influx of H₂O from the lumen to the interstitium) and this happens iff

$$K < 0 \Leftrightarrow u_L - u_0 - \frac{Q_f}{Q k_f} \frac{u_E^3}{1+u_E^3} < 0$$

(4)

By using (***) we can write:

$$k < 0 \Leftrightarrow u_E - u_0 + \frac{Q_f}{g k_f} \frac{u_E^3}{1+u_E^3} - \frac{Q_f}{Q k_f} \frac{u_E^3}{1+u_E^3} < 0$$

$$\Leftrightarrow u_E + \underbrace{\beta}_{\gamma} \left(1 - \underbrace{\frac{g}{Q}}_{\beta} \right) \frac{u_E^3}{1+u_E^3} < u_0$$

If we impose $u_L = 0$ (i.e., no more Na^+ ions available in the lumen) \Rightarrow From (**):

$$u_E + \beta \frac{u_E^3}{1+u_E^3} = 0 \Rightarrow k = -u_0 - \beta \gamma \frac{u_E^3}{1+u_E^3} < 0$$

Since $\beta > 0, \gamma > 0$ by construction, there will always be a positive solution y . Also, if $u_L > 0$ but small (i.e., $u_L \approx 0$), the condition $k < 0$ will be preserved, but the value of k will increase \Rightarrow There must exist a critical value u_L^*

such that:

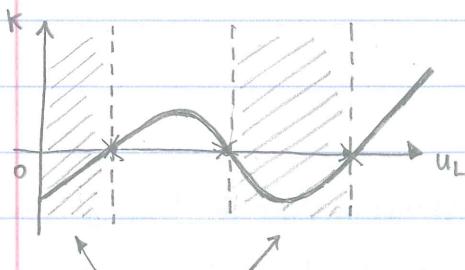
$$\begin{cases} u_E + \beta \frac{u_E^3}{1+u_E^3} = u_L^* \\ k = u_L^* - u_0 - \beta \gamma \frac{u_E^3}{1+u_E^3} = 0 \end{cases} \Rightarrow \begin{cases} \beta \frac{u_E^3}{1+u_E^3} = \frac{u_L^* - u_0}{\gamma} \\ u_E + \frac{u_L^* - u_0}{\gamma} = u_L^* \end{cases}$$

From these equations we can determine:

- $u_E = u_L^* - \frac{u_L^* - u_0}{\gamma}$ when $k=0$

- There are actually three values of u_L^* that satisfy the condition $k=0$ (since there is a polynomial equation of the 3rd order in u_L^*) \Rightarrow k will have an N-shaped behavior as a function of u_L \Rightarrow This behavior will be shown by the solution y of (****) as well.

(5)



For s_L falling into these regions ($k < 0$), there will be flow of H_2O from the lumen into the interstitium

Depending on the actual value of s_L , we can modulate the value of $q_{L \rightarrow I}$ (i.e., make it higher or lower) \Rightarrow We can achieve faster hydration by controlling the concentration of Na^+ ions in the lumen, e.g., by drinking fluids that contain electrolytes

Similarly, in case of dehydration, an hormone secreted by the adrenal glands (the aldosterone) enhances the transport of Na^+ ions by epithelial cells \Rightarrow This enhancement increases the value of model parameters g (i.e., more ion channels) and Q_f (i.e., more pumps across the cell membrane) \Rightarrow There is an upper bound though:

$$\left. \begin{array}{l} \lim_{g \rightarrow \infty} \frac{1}{g} f(s_E) = 0 \\ \frac{1}{g} f(s_E) = s_L - s_E \end{array} \right\} \Rightarrow s_E = s_L \text{ asymptotically} \Rightarrow \lim_{g \rightarrow \infty} J = f(s_L)$$

$$R q_{L \rightarrow I}^2 + (QR + s_L) q_{L \rightarrow I} + Q(s_L - c_0) - f(s_E) = 0$$

\Updownarrow Assuming $R=0$ (i.e., most favourable case for the flux)

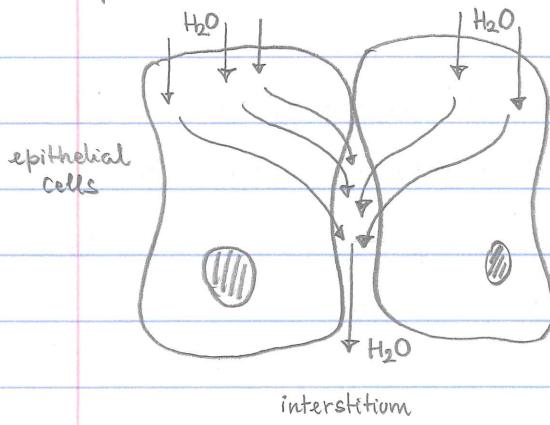
$$s_L q_{L \rightarrow I} + Q(s_L - c_0) - f(s_E) = 0 \Leftrightarrow q_{L \rightarrow I} = Q \left(\frac{c_0}{s_L} - 1 \right) + \frac{f(s_E)}{s_L}$$

$$\text{Hence, } \lim_{g \rightarrow \infty} q_{L \rightarrow I} = Q \left(\frac{c_0}{s_L} - 1 \right) + \frac{f(s_L)}{s_L}$$

⑥

- * A refined model of fluid absorption

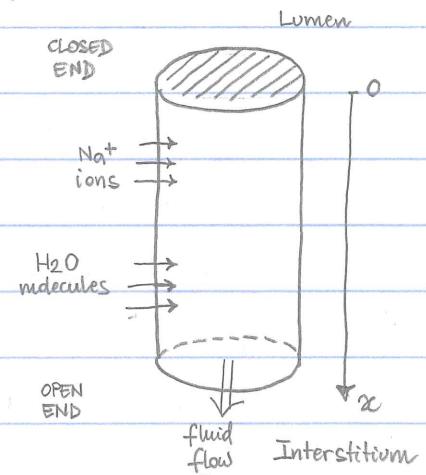
The previous model was based on the assumption that the tight junctions let H₂O pass from the lumen to the interstitium. However, tight junctions are "tight", i.e., they do not open to let H₂O molecules pass \Rightarrow Water must pass through the epithelial cells via osmosis



We want to model the influx of H₂O into the tight junctions via osmosis across the cell membrane



Let us model the junction as a tube with only one end open:



In this model, Na⁺ ions are introduced by the Na⁺-K⁺ pumps from the epithelial cells, H₂O molecules enter because of osmosis \Rightarrow The following steps occur:

- Na⁺ ions enter the junction because of active transport (i.e., pumps)



- There is a gradient in [Na⁺] across membrane



- Water passively flows to equilibrate the concentrations (osmosis)



- The flow of water clears the (local) concentration of Na⁺ ions and transports them in the

interstitium.

To model this phenomenon, let us define:

$v = v(x)$ - velocity of the fluid moving in the junction toward the interstitium

$s = s(x, t)$ - concentration of Na^+ ions in the junction at position x and time t

$n = n(x)$ - rate of transport of Na^+ ions into the junctions (moles/area-time)

Recall the equations for diffusion of molecules:

$$\begin{array}{c} \text{change in the} \\ \text{amount of } \text{Na}^+ \\ \text{ions at pos. } x \end{array} = \begin{array}{c} \text{amount of} \\ \text{injected } \text{Na}^+ \\ \text{ions} \end{array} = \begin{array}{c} \text{amount of} \\ \text{transported} \\ \text{Na}^+ \text{ ions} \end{array}$$

$$A \frac{\partial s}{\partial t} = \delta_x n(x) - A \frac{\partial}{\partial x} \left(v(x) s(x, t) - D_{\text{Na}} \frac{\partial s}{\partial x} \right)$$

$A \triangleq$ cross-section area ($A = \pi r^2$ in a cylinder of radius r)

$\delta_x \triangleq$ perimeter of the cross-section ($\delta_x = 2\pi r$ in a cylinder of radius r)

$J_d \triangleq -D_{\text{Na}} \frac{\partial s}{\partial x}$ - flux density of Na^+ ions in the junction due to diffusion

$J_g \triangleq v(x) s(x, t)$ - flux density of Na^+ ions in the junction due to concentration gradient

At steady-state we have:

$$\frac{\delta_x}{A} n(x) - \frac{\partial}{\partial x} (v s) + D_{\text{Na}} \frac{\partial^2 s}{\partial x^2} = 0$$

Differently from other problems of similar nature seen in previous lectures, velocity v cannot be approximated to a constant value. In particular, we have that the difference in concentration of Na^+ ions across the membrane of the epithelial cell causes a flow of water from inside the cell into the junction. Because this flow is typically

(8)

small, we can approximate it with a linear relationship:

$$J_{W_{E \rightarrow J}} = \eta (s(x,t) - s_E)$$

$J_{W_{E \rightarrow J}}$ \triangleq flux density of water from the cell into the junction

$s_E \triangleq [Na^+]$ inside the epithelial cell

$\eta \triangleq$ constant

Note that $s_x \cdot J_{W_{E \rightarrow J}}$ gives the total flux of water that enters the junction at position $x \Rightarrow$ The only way to accommodate this flux is varying the velocity of the fluid \Rightarrow

Hence we have:

$$s_x \cdot J_{W_{E \rightarrow J}} = A \cdot \frac{\partial v}{\partial x} \Rightarrow \frac{\partial v}{\partial x} = \frac{s_x \eta}{A} \cdot (s(x,t) - s_E)$$

Going back to the steady-state equation, we have:

$$\frac{s_x \cdot n(x)}{A} - \frac{\partial v}{\partial x} s(x) - v(x) \frac{\partial s}{\partial x} + D_{Na} \frac{\partial^2 s}{\partial x^2} = 0$$

↑
 we dropped
 the dependence
 on t because
 of steady-state

$$(a) \quad \begin{cases} \frac{s_x}{A} n(x) - \frac{\partial v}{A} \eta (s(x) - s_E) s(x) - v(x) \frac{\partial s}{\partial x} + D_{Na} \frac{\partial^2 s}{\partial x^2} = 0 \\ \frac{\partial v}{\partial x} = \frac{s_x}{A} \eta (s(x) - s_E) \end{cases}$$

This is an ODE system of the 3rd order (two derivatives of $s(x)$, one derivative of $v(x)$) \Rightarrow We need three boundary conditions:

- $v(0) = 0$ (this accounts the fact that the junction is closed at one end)
- $\frac{\partial s}{\partial x}(0) = 0$ (this accounts the fact that no Na^+ ions are exchanged at the closed end)
- $s(L) = s_0$ (uniform concentration of Na^+ in the interstitium)

(9)

Solving system (a) is beyond the scope of the lecture but interesting inferences can be made by working w/e the ODEs. For sake of simplicity, let us assume that the junction is a cylinder of radius $r \Rightarrow A = \pi r^2$; $\delta x = 2\pi r$; $\delta x/A = 2/r$

$$\frac{\partial v}{\partial x} = \frac{2}{r} \eta (s(x) - s_E) \Leftrightarrow v(L) - v(0) = \frac{2}{r} \eta \int_0^L (s(x) - s_E) dx$$

Assuming s_E -constant (QSS approximation) and using $v(0)=0$, we have:

$$v(L) = \frac{2L}{r} \eta \left[\frac{1}{L} \int_0^L s(x) dx - s_E \right] \quad (1)$$

$$\frac{2}{r} n(x) - \frac{\partial}{\partial x} (v s) + D_{Na} \frac{\partial^2 s}{\partial x^2} = 0 \Leftrightarrow -v(x) s(x) \Big|_0^L + D_{Na} \frac{\partial s}{\partial x} \Big|_0^L = -\frac{2}{r} \int_0^L n(x) dx$$

$$\Leftrightarrow -v(L) s(L) + v(0) s(0) + D_{Na} \frac{\partial s}{\partial x}(L) - D_{Na} \frac{\partial s}{\partial x}(0) = -\frac{2}{r} \int_0^L n(x) dx \Leftrightarrow$$

↑
 $v(0) = 0 \quad s(L) = s_0$
 $\frac{\partial s}{\partial x}(0) = 0$

$$\frac{2L}{r} \eta \left[\frac{1}{L} \int_0^L s(x) dx - s_E \right] s_0 - D_{Na} \frac{\partial s}{\partial x}(L) = \frac{2}{r} \int_0^L n(x) dx \quad (2)$$

From equation (1) we can determine that the higher the average concentration of Na^+ ions in the junctions, the higher the efflux velocity $v(L)$

From equation (2), since the concentration of Na^+ ions in the efflux is:

$$s_{\text{efflux}} = \frac{\text{amount of } \text{Na}^+ \text{ pumped in the junction}}{\text{flow leaving the junction}} = \frac{2\pi r \int_0^L n(x) dx}{\pi r^2 v(L)}$$

$$\text{we can write: } s_{\text{efflux}} = \frac{\frac{2}{r} \int_0^L n(x) dx}{v(L)} = \frac{v(L) s_0 - D_{Na} \frac{\partial s}{\partial x}(L)}{v(L)} = s_0 - \frac{D_{Na} \frac{\partial s}{\partial x}(L)}{v(L)}$$

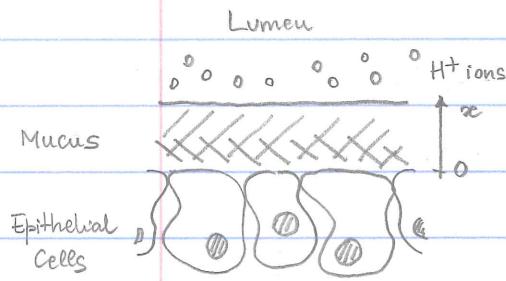
(10)

Hence, the concentration of Na^+ ions in the efflux is not the same as the concentration s_0 in the interstitium. Moreover, since $\frac{\partial s}{\partial x}(L) < 0$, the higher the velocity $v(L)$, the lower s_{efflux} .

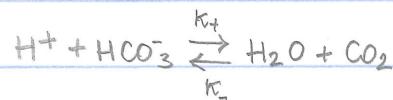
If $s_0 \approx s_E$ and $v(L)$ is large (which can happen, for instance, if the junction is short enough) then, we have an efflux of water from the epithelial cells into the junction even though $s_{\text{efflux}} \approx s_E \Rightarrow$ This is consistent with the fact that epithelial cells are able to transport water even in the absence of an osmotic gradient.

* Gastric protection

The abundance of H_2O in the chyme is due, in part, to the chemical reactions that occur within the lumen to reduce the acidity caused by other gastric secretions (e.g., hydrochloric acid) \Rightarrow In the stomach, the abundance of H^+ ions in the lumen does not hurt the epithelial cells thanks to a layer of mucus on top of the cells.



The H^+ ions that react with the mucus layer (which contains bicarbonate HCO_3^-) form H_2O molecules according to the scheme:



The products CO_2 and H_2O will eventually be released in the lumen. Molecules of HCO_3^- , H^+ , H_2O , and CO_2 diffuse through the mucus layer \Rightarrow We must use the equations for reaction-diffusion:

$$\left. \begin{array}{l} h \triangleq [H^+] \\ b \triangleq [HCO_3^-] \\ w \triangleq [H_2O] \\ c \triangleq [CO_2] \end{array} \right\} \Rightarrow \begin{aligned} \frac{\partial h}{\partial t} &= -k_+ hb + k_- wc + D_{H^+} \frac{\partial^2 h}{\partial x^2} \\ \frac{\partial b}{\partial t} &= -k_+ hb + k_- wc + D_{HCO_3^-} \frac{\partial^2 b}{\partial x^2} \\ \frac{\partial w}{\partial t} &= k_+ hb - k_- wc + D_{H_2O} \frac{\partial^2 w}{\partial x^2} \\ \frac{\partial c}{\partial t} &= k_+ hb - k_- wc + D_{CO_2} \frac{\partial^2 c}{\partial x^2} \end{aligned}$$

At steady-state conditions we have:

$$(b) \quad \left. \begin{aligned} D_{H^+} \frac{\partial^2 h}{\partial x^2} &= D_{HCO_3^-} \frac{\partial^2 b}{\partial x^2} = -k_- wc + k_+ hb \\ D_{H_2O} \frac{\partial^2 w}{\partial x^2} &= D_{CO_2} \frac{\partial^2 c}{\partial x^2} = +k_- wc - k_+ hb \end{aligned} \right.$$

Equations (b) can be solved for boundary conditions at the interface with lumen ($x=l$):

$h(l) = h_0$ - constant (concentration of H^+ ions in the lumen. It can be measured)

$c(l) = c_0$ - constant (concentration of CO_2 in the lumen. It can be measured)

$$b(l) = \frac{k_- c_0}{k_+ h_0} \text{ because of QSS approximation}$$

In fact, at the interface between mucus layer and lumen ($x=l$), HCO_3^- reaches equilibrium much faster than the other substances while $w \approx 1$.

Equations (b) involve 2nd order derivatives of h , b , and c \Rightarrow We need boundary conditions on the derivatives $\partial h / \partial x$, $\partial b / \partial x$, and $\partial c / \partial x$. It is reasonable to set these conditions at the interface between epithelial cells and mucus layer ($x=0$) by using the Fick's Law:

$$J_{HCO_3^-} = -D_{HCO_3^-} \frac{\partial b}{\partial x} - \text{constant} \Rightarrow \frac{\partial b}{\partial x}(0) = -\frac{J_{HCO_3^-}}{D_{HCO_3^-}}$$

(12)

$$J_{CO_2} = -D_{CO_2} \frac{\partial c}{\partial x} - \text{constant} \Rightarrow \frac{\partial c}{\partial x}(0) = -\frac{J_{CO_2}}{D_{CO_2}}$$

$$J_{H^+} = -D_{H^+} \frac{\partial h}{\partial x} - \text{constant} \Rightarrow \frac{\partial h}{\partial x}(0) = -\frac{J_{H^+}}{D_{H^+}}$$

Note that fluxes J_{CO_2} , $J_{HCO_3^-}$, and J_{H^+} can be assumed constant only at the interface with the epithelial cells (i.e., $x=0$) because:

$J_{H^+} \approx 0$ (epithelial cells do not typically release H^+ ions)

J_{CO_2} , $J_{HCO_3^-}$ are measurable because the cells transport CO_2 and HCO_3^- actively

Note that the ODE systems (a) and (b) encountered in this lecture have two-point boundary conditions, i.e., the boundary conditions are not imposed on the same point. \Rightarrow
More sophisticated methods are required to numerically solve systems (a) and (b) but this goes beyond the scope of the course.

REFERENCE:

Textbook (volume 2): chapter 18, sec. 18.1; 18.1.1; 18.1.2 (up to page 860);
18.2; 18.2.1 (up to page 868)