Modelling the role of ion transport in controlling airway surface liquid

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Introduction

ATP and protease activity in the airway surface liquid (ASL), are thought to control ASL depth. Many experiments have examined this control system by measuring absorption rates when excess fluid is added to the ASL. However, these experiments often use saline solutions that are not well matched to the ASL ion composition. We have developed a simple mathematical model of ion transport (Figure 1) and simulated the impact of changing ion composition alone without any ASL regulatory pathways.

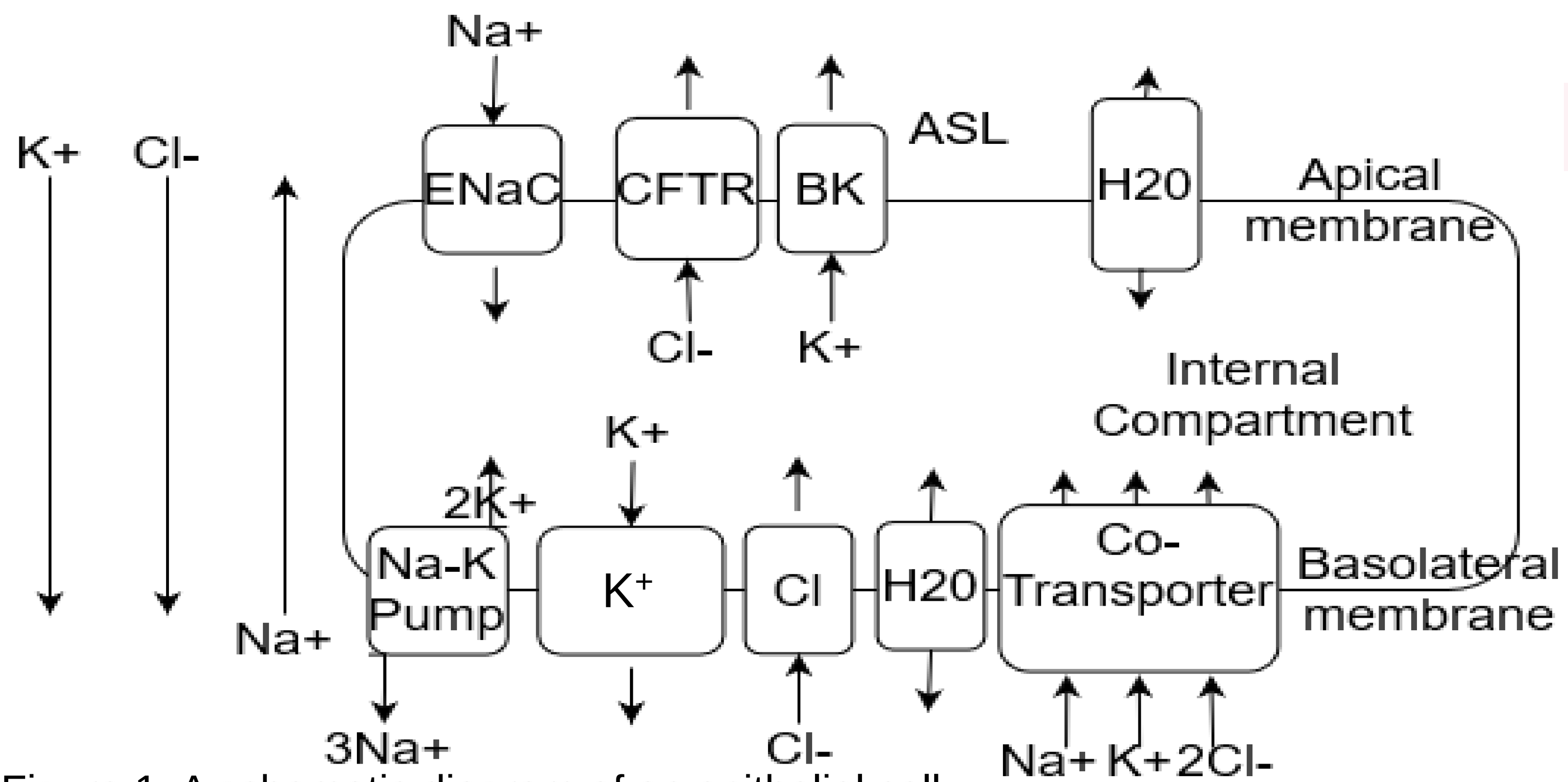

Figure 1: A schematic diagram of an epithelial cell

Parameter Estimation

We examined a variety of ASL ion compositions reported in the literature (Table 1).

Table 1.

Study	$[Na^+]_{ASL}$(mM)	$[Cl^-]_{ASL}$(mM)	$[K^+]_{ASL}$(mM)
Joris et al. [1]	82	84	29
Knowles et al. [2]	80	88	21
Jayaraman et al. [3]	103	93	N/A (25 used)
Song et al. [4]	122	123	N/A (25 used)

We estimated steady state transport parameters for the apical ion channels with MATLAB's Fmincon function using the SQP algorithm to solve, with constraints to find steady state conditions in the model.

The model predicts multiple solutions for each ASL composition, but shows correlation in its predictions of apical permeability (Figure 2). The predictions suggest that each ASL composition can be produced with a large variation in CFTR permeability.

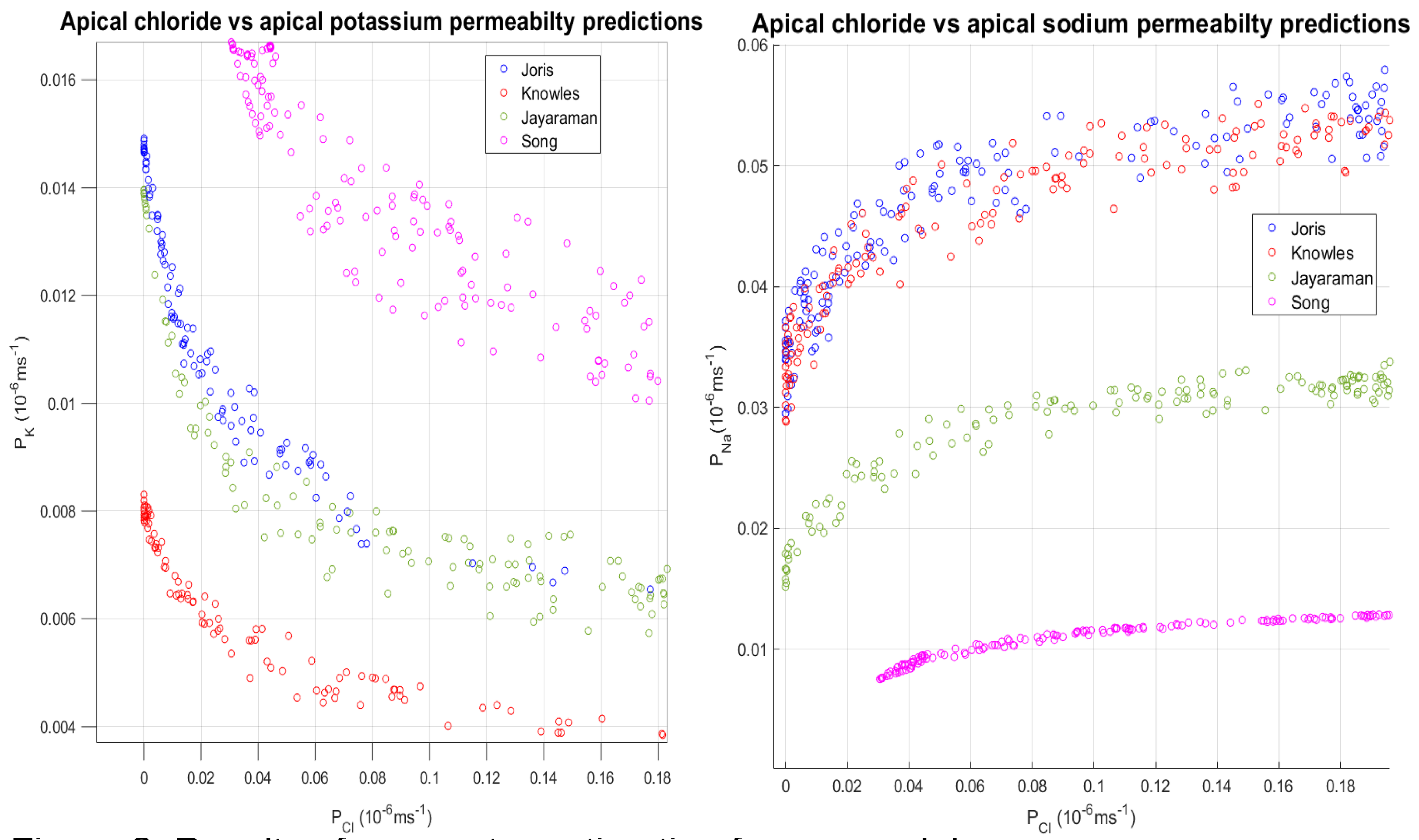

Figure 2: Results of parameter estimation for our model

Validation

We validated the model against data by Namkung et al. [5], comparing changes in ASL potassium concentration following changes in epithelial call permeabilites (Figure 3).

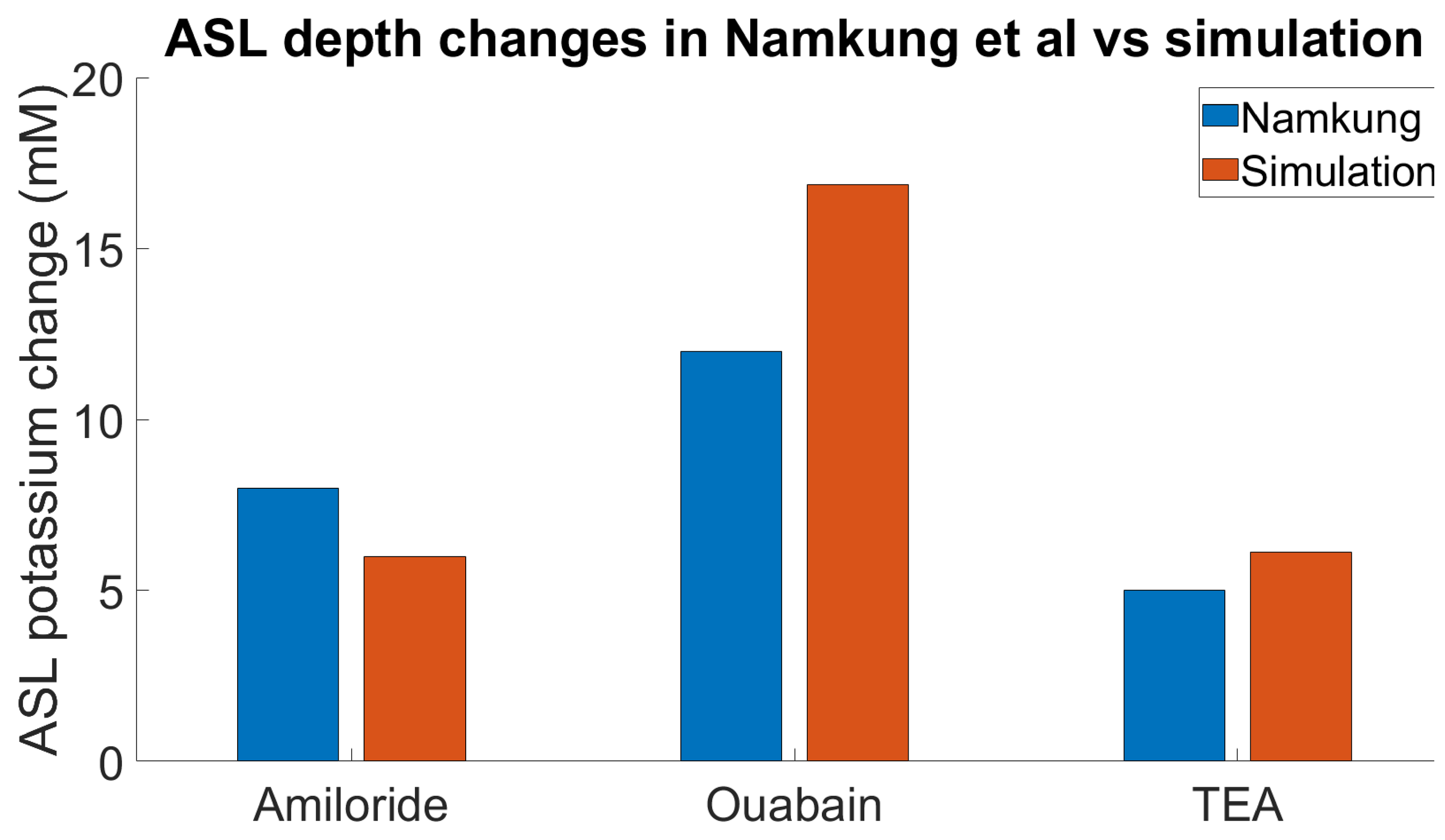

Figure 3: Model validation results compared to Namkung et al. [5]

Saline absorption

We simulated saline absorption using the model. The composition of the each of the saline solutions tested is shown in Table 2.

Table 2.

Solution	$[Na^+]_{ASL}$ (mM)	$[Cl^-]_{ASL}$ (mM)	$[K^+]_{ASL}$ (mM)
Solution 1	140	145	5
Solution 2	90	145	55

Water and ion absorption rates vary, including that of chloride, despite the same concentration of chloride in both solutions (Figure 4).

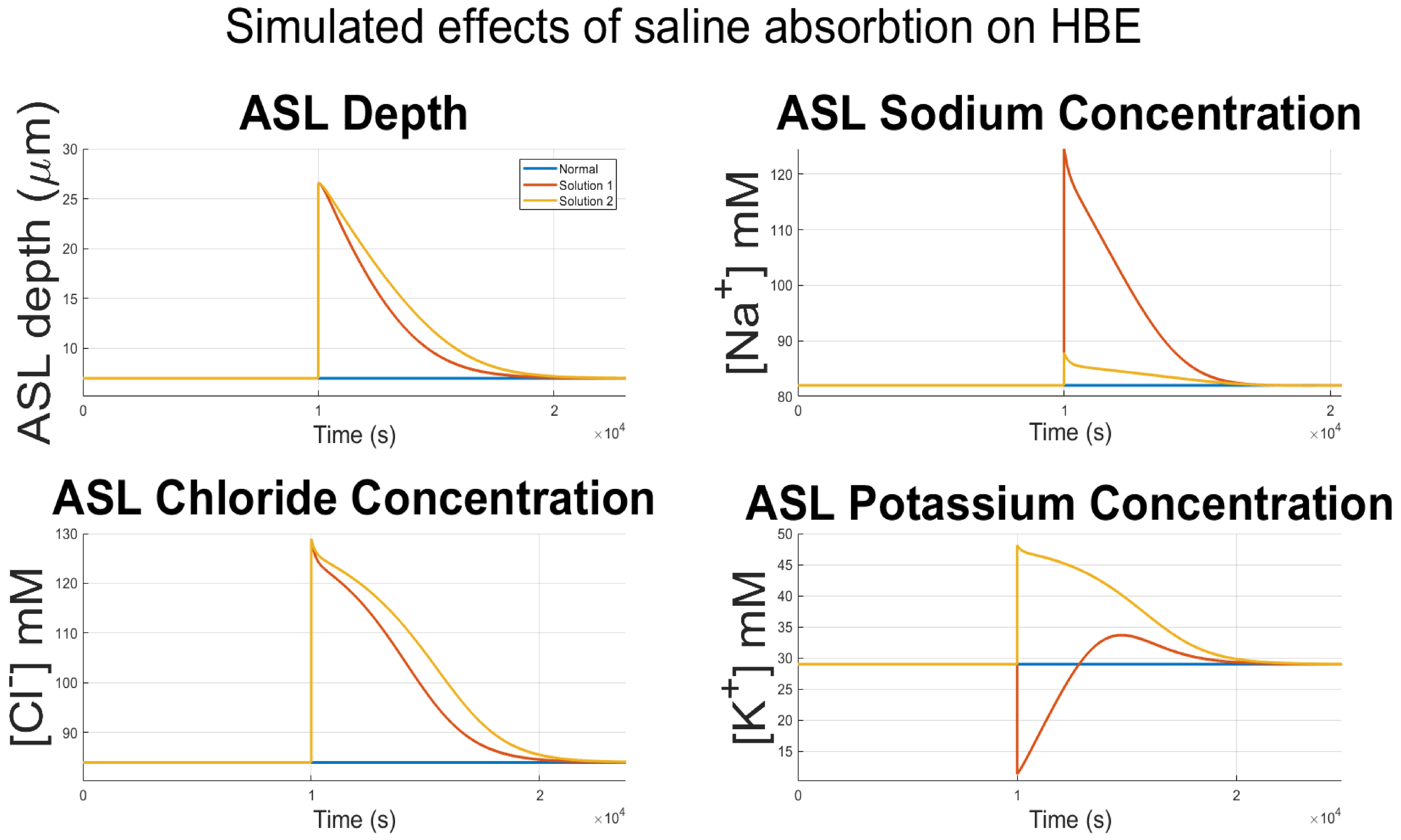

Figure 4: Simulated results for saline absorption from different saline solutions

Conclusion

Our model shows that saline absorption is to be expected whenever there are concentration gradients and osmotic driving forces. Regulation is not necessary. This does not rule out a central role for regulation but rather shows that other contributions must be accounted for when comparing absorption rates in different experimental conditions.

References:

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[2] Knowles, M.R., Robinson, J.M., Wood, R.E., Pue, C.A., Mentz, W.M., Wager, G.C., Gatzy, J.T. and Boucher, R.C., 1997. Ion composition of airway surface liquid of patients with cystic fibrosis as compared with normal and disease-control subjects. *The Journal of clinical investigation*, *100*(10), pp.2588-2595.

[3] Jayaraman, S., Song, Y. and Verkman, A.S., 2001. Airway surface liquid pH in well-differentiated airway epithelial cell cultures and mouse trachea. *American Journal of Physiology-Cell Physiology*, *281*(5), pp.C1504-C1511.

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[5] Namkung, W., Song, Y., Mills, A.D., Padmawar, P., Finkbeiner, W.E. and Verkman, A.S., 2009. In situ measurement of airway surface liquid [K+] using a ratioable K+-sensitive fluorescent dye. *Journal of Biological Chemistry*, *284*(23), pp.15916-15926.