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Developing and testing a theoretical framework for airway surface liquid homeostasis

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Background

- Airway epithelium is covered by a thin airway surface liquid (ASL)
  - ASL depth integral to function
    - ~10 µm in trachea
    - ~0.1 µm in alveoli

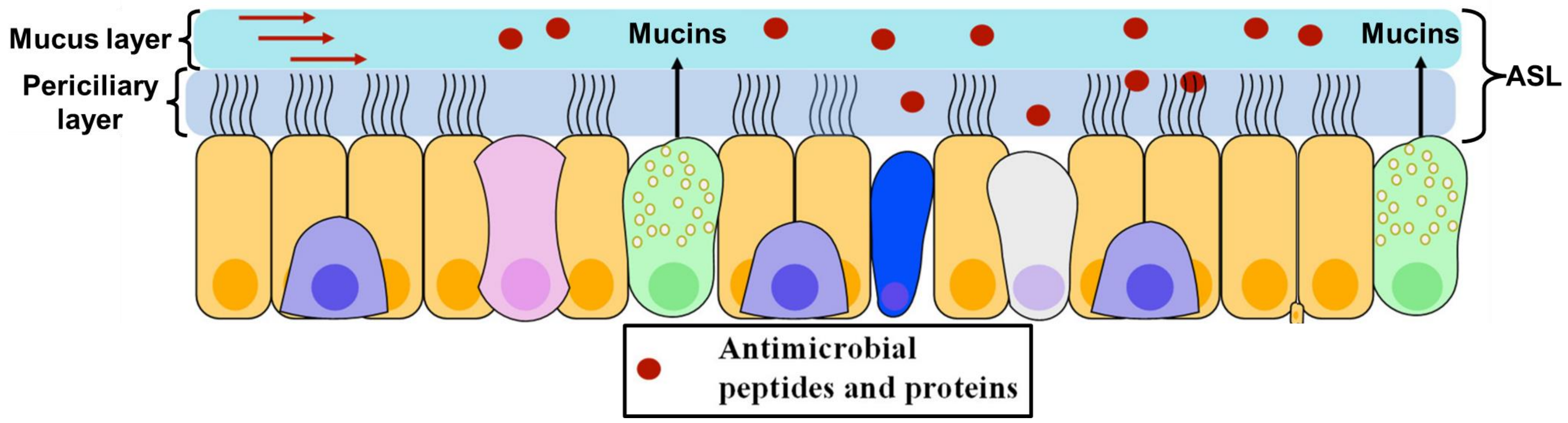
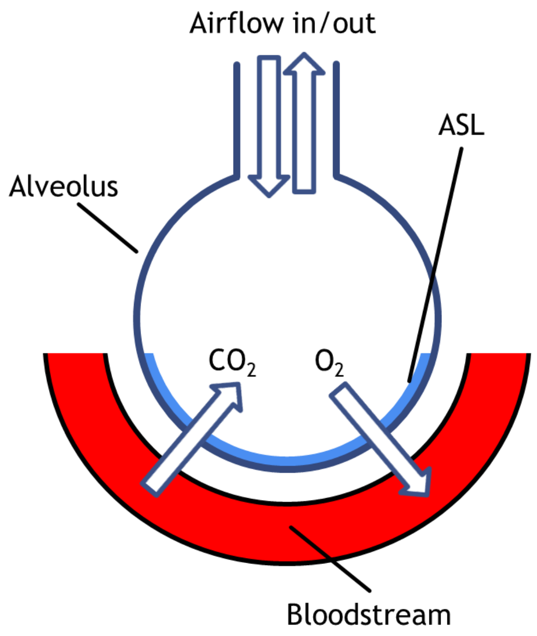


Image adapted from Zajac et al. (2021)



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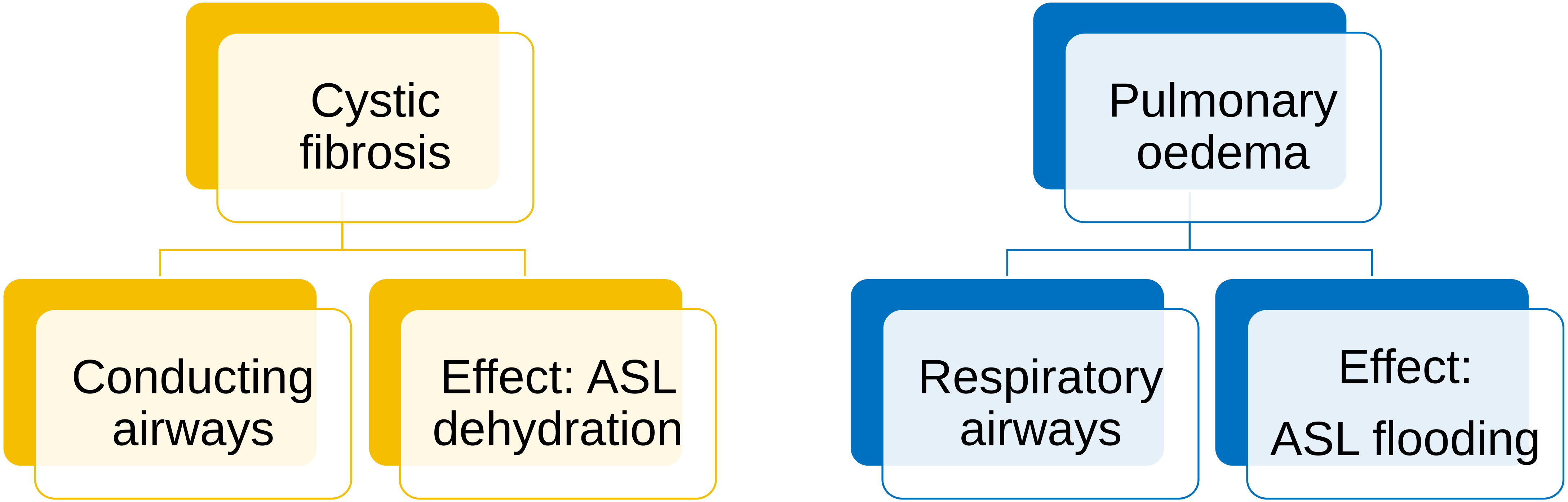
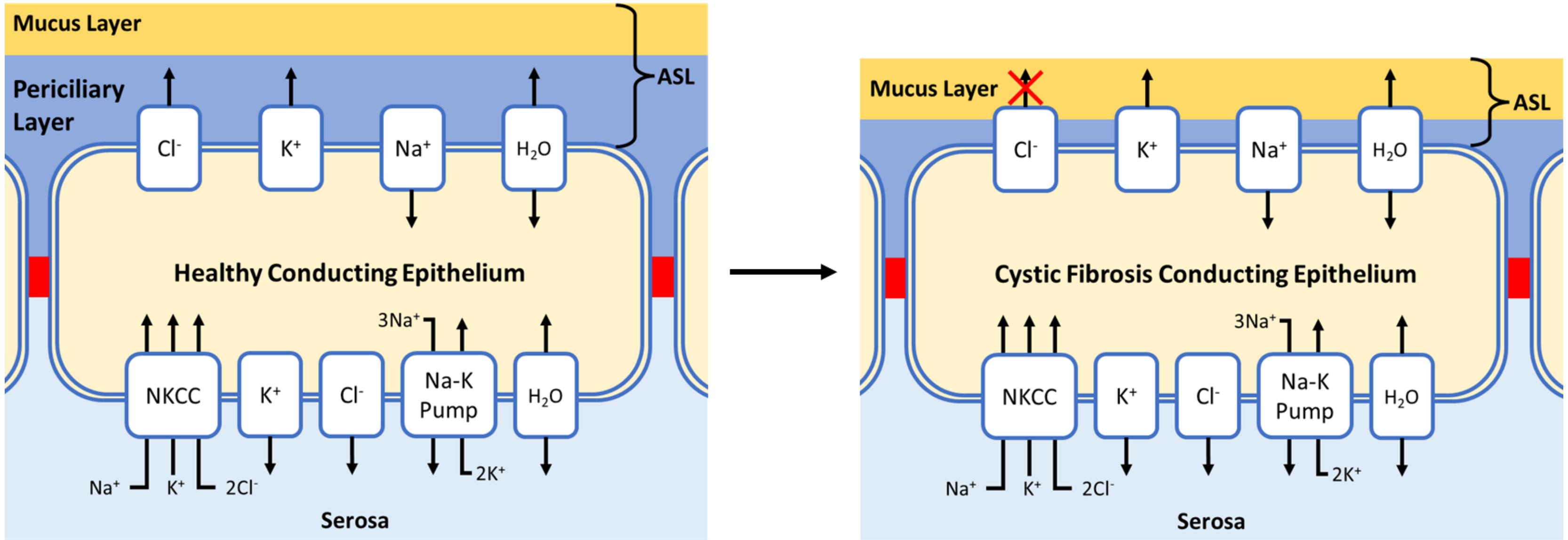
Motivation

- ASL dysregulation associated with airway diseases



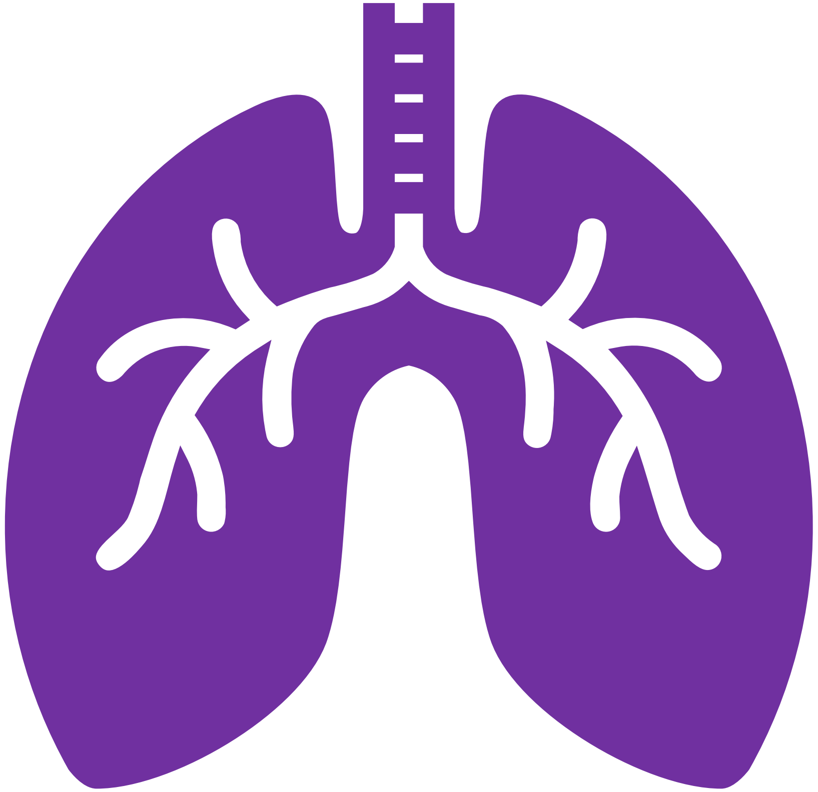
Cystic fibrosis (CF)

- Cystic fibrosis is a lethal genetic disorder
  - 1 in 25 Europeans are carriers of the disease
  - Caused by loss-of function mutations in CFTR anion channel
  - Reduced anion conductance → ASL dehydration → Chronic infection



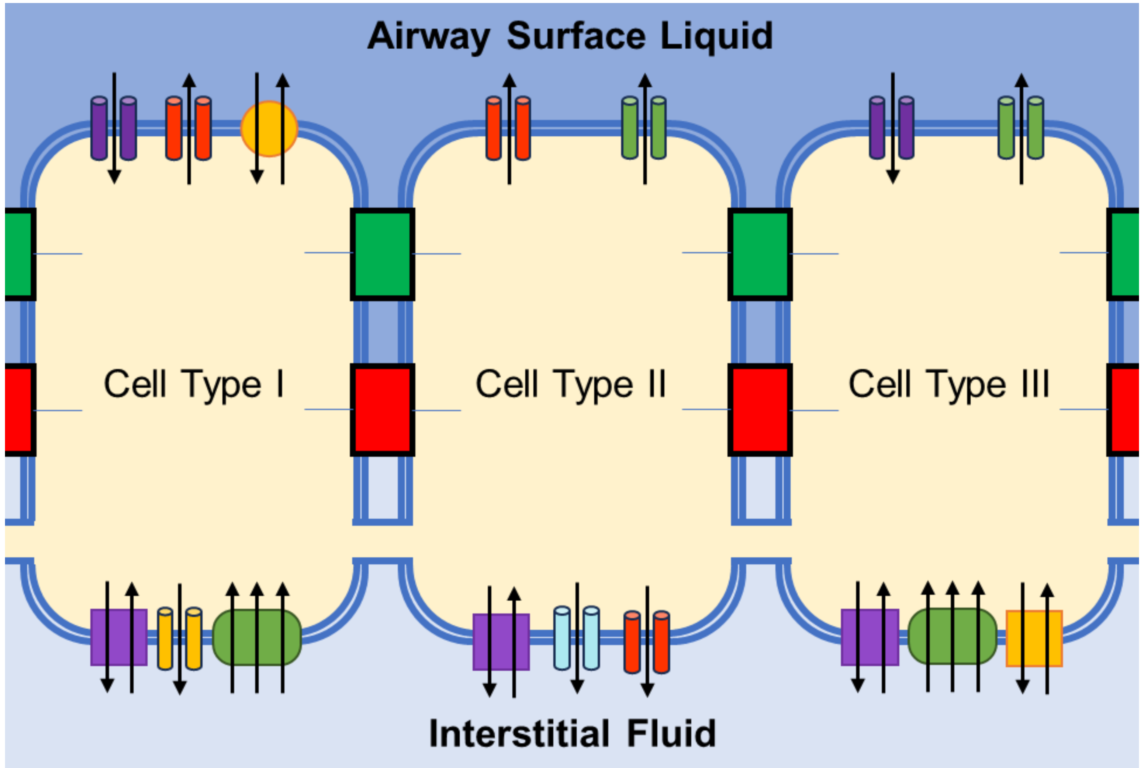
Contents

- Fluid/ion transport in airway epithelia
- Modelling to understand CF airway epithelial characteristics
- Airway epithelial cell types
- A framework for multicellular modelling of airway epithelia



Fluid/ion transport in airway epithelia

- Fluid and ion transport controlled by:
  - Ion channels
  - Transporters
  - Tight junctions
- Computational modelling can aid analysis of complex processes



Fluid/ion transport in airway epithelia

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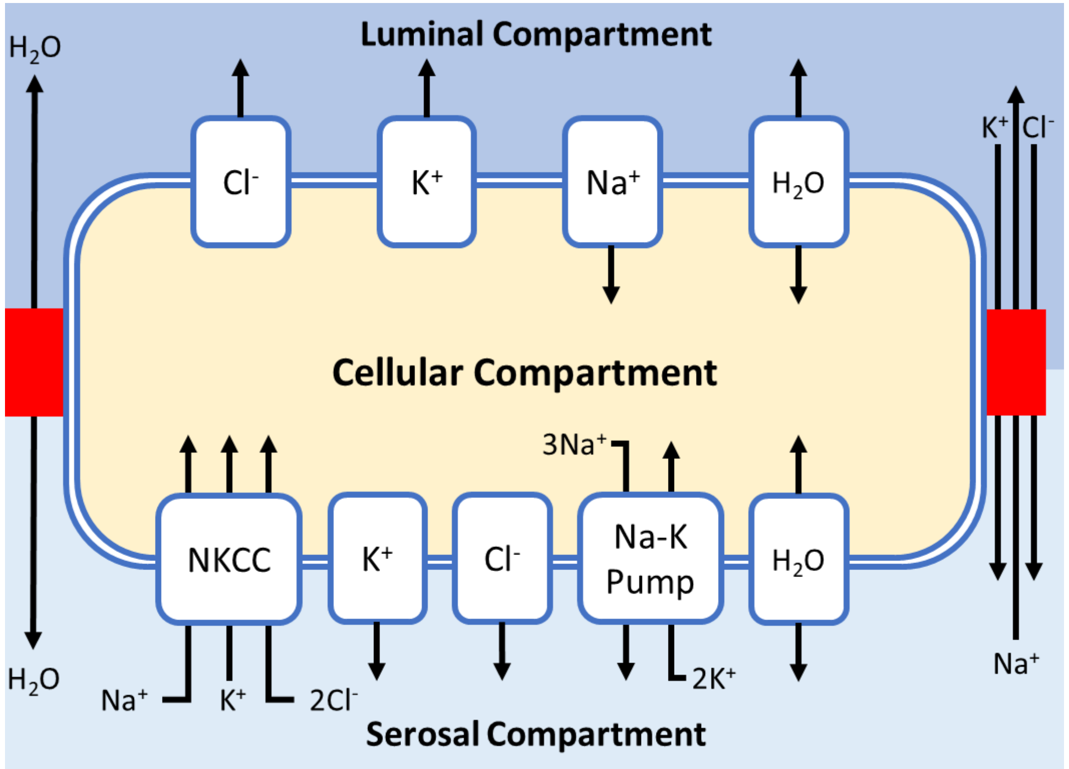
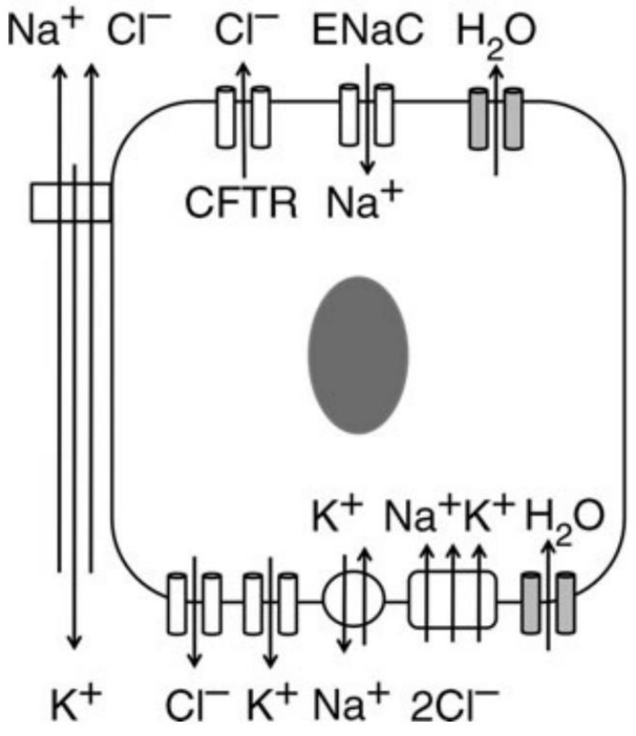


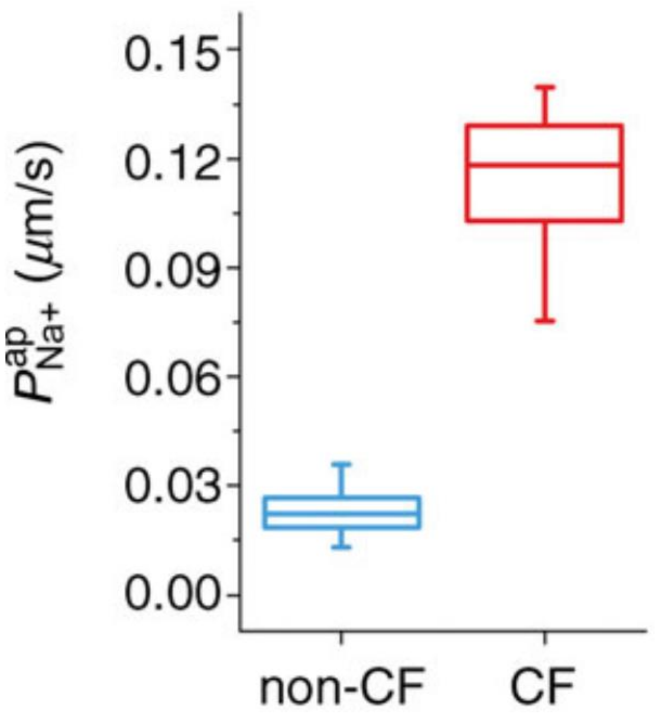
BUT… almost all models treat airway epithelium as single, idealised cell!

Modelling to understand CF airway epithelial characteristics

O'Donoghue D.L., Dua V., Moss G.W.J., Vergani P. ***Increased apical Na+ permeability in cystic fibrosis is supported by a quantitative model of epithelial ion transport***. J Physiol. 2013 doi: 10.1113/jphysiol.2013.253955



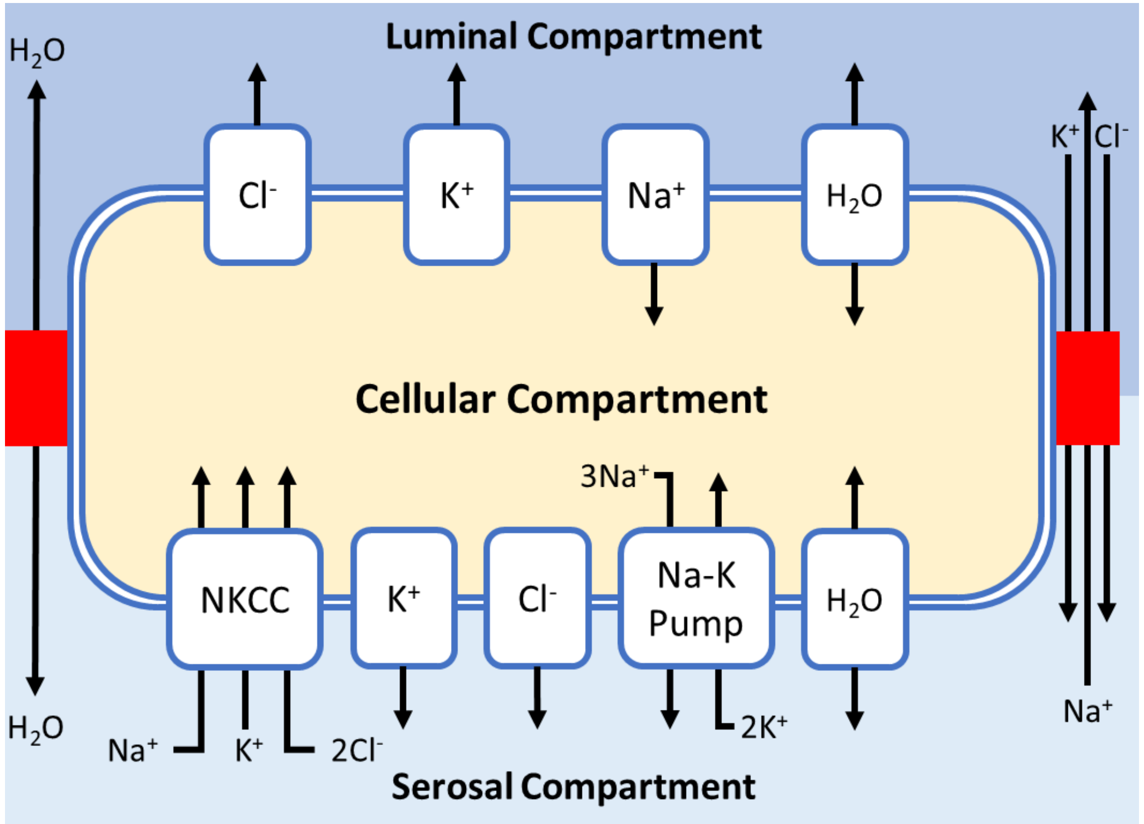
Schematic diagram of airway epithelial cell



Na^+ permeability (P_{Na+}) estimated from 10^6 parameter sets.

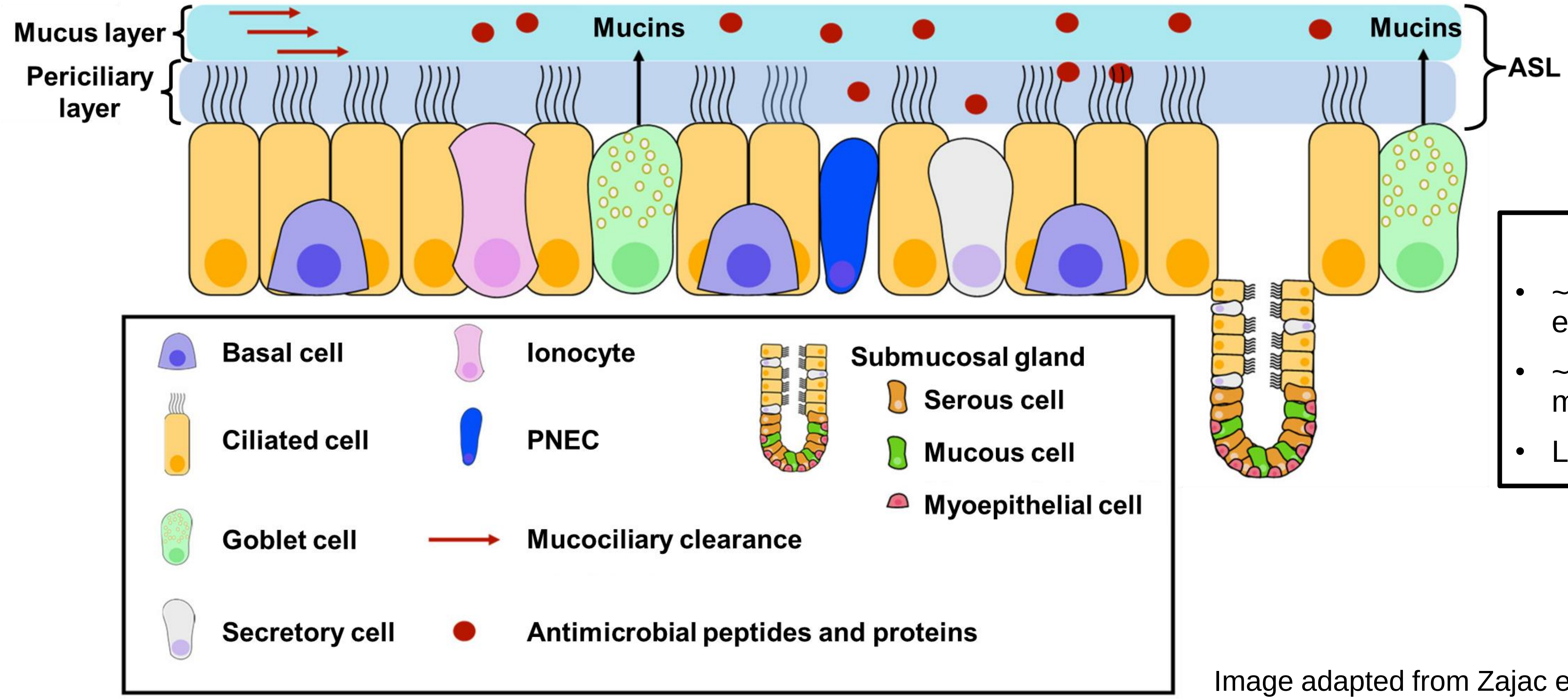
Modelling fluid/ion transport in airway epithelia

- Epithelium modelled as its equivalent electrical circuit
- Three ionic species modelled
  - Na^+, Cl^-, K^+
- Channel currents described by GHK flux
- Existing literature models used for Na-K pump and NKCC
- Water transport occurs via osmosis



A multicellular framework for modelling airway epithelia

Pulmonary ionocytes and the multicellular airway epithelium



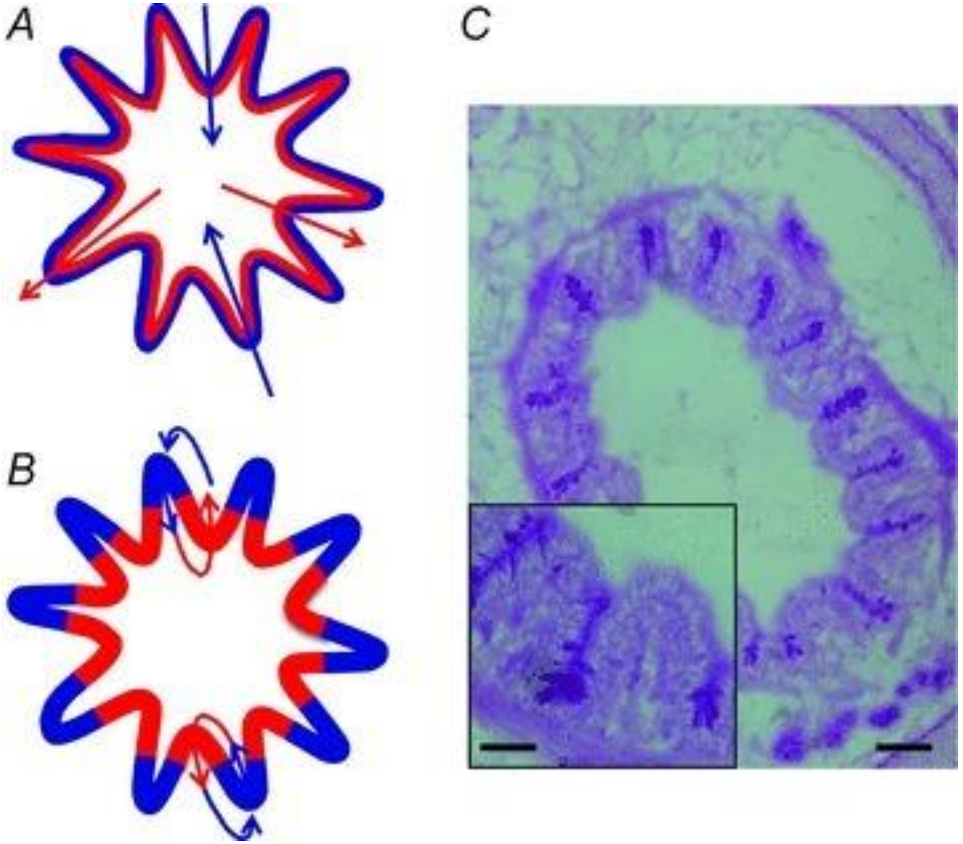
Ionocytes

- ~1% of airway epithelial cells
- ~50% of CFTR mRNA transcripts
- Lei, L., et al., (2023)

Image adapted from Zajac et al. (2021)

Secretory-absorptive theory of fluid/ion transport in airway epithelia

- Typical airway fluid/ion transport models are bidirectional
- Classical epithelial transport is unidirectional
  - Small intestine: secretion by crypt cells and absorption by villous cells



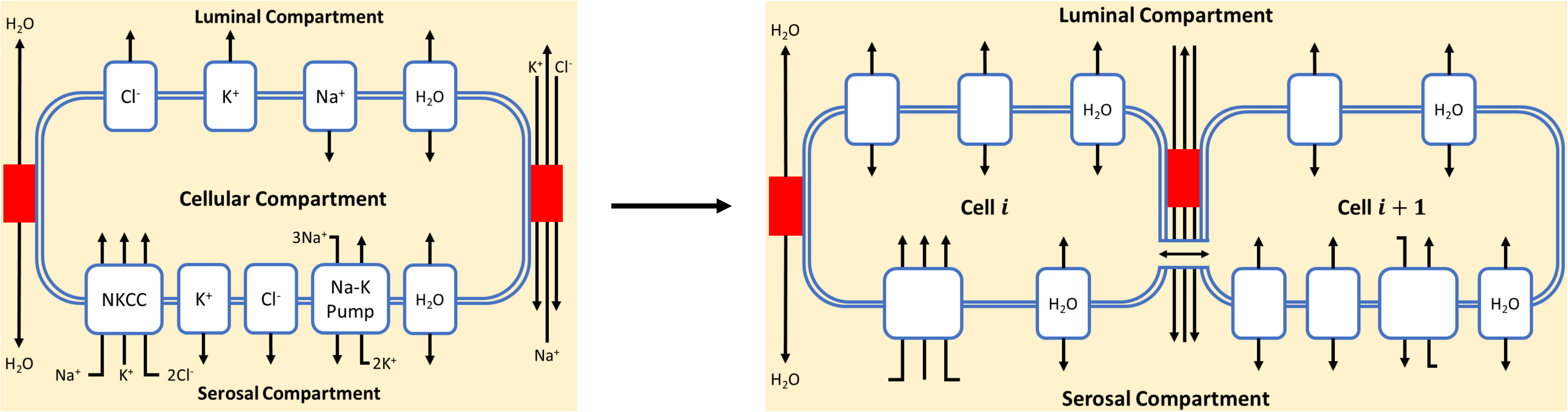
Blue = Secretory

Red = Absorptive

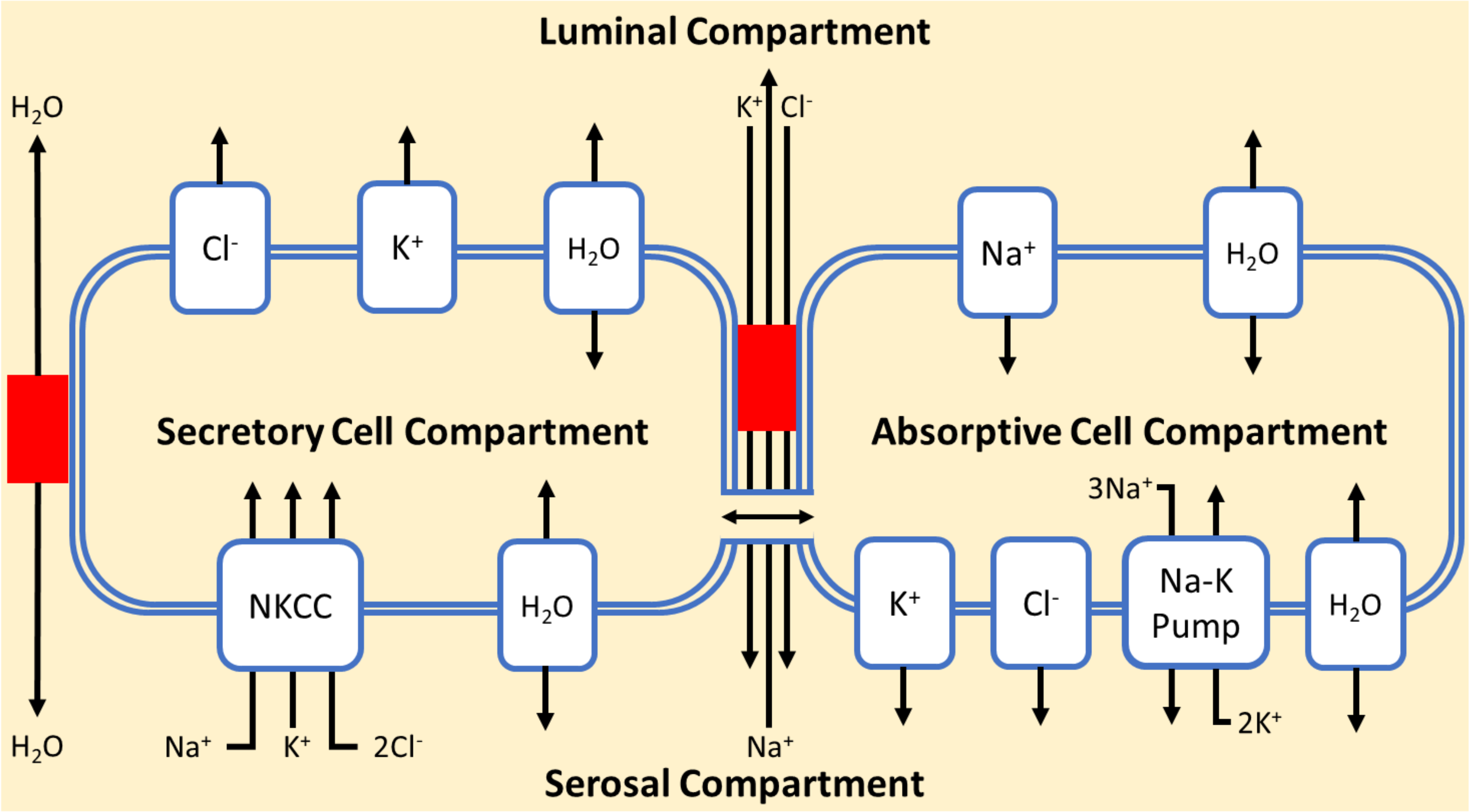
Image from Shamsuddin and Quinton (2012)

A framework for multicellular modelling of airway epithelia

- Based on the equivalent electrical circuit and fluid/ion fluxes

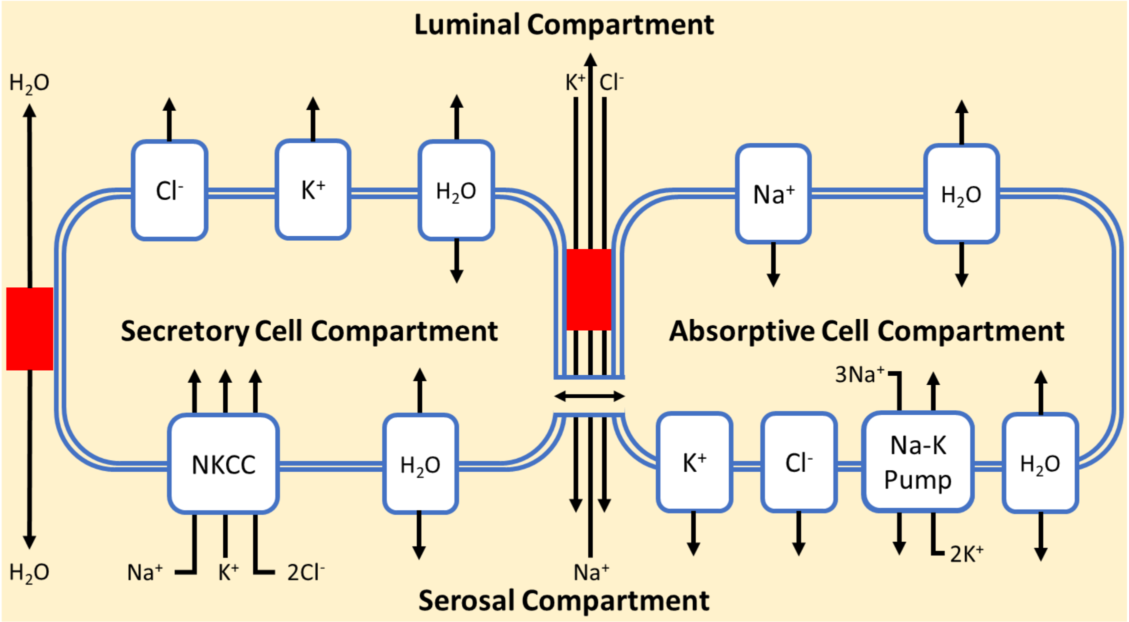


A *secretory-absorptive* model of fluid/ion transport in airway epithelia



What can the *secretory-absorptive* model tell us?

- Can a multicellular model provide stable and realistic outputs?
  - Steady-state AND dynamic
- Under what conditions does the model approximate a single-cell model?
- Can model cells feasibly maintain distinct conditions from their neighbours?



Secretory-absorptive model outputs: Low cell-cell resistance

Variable	Initial Guess	Composition 1		Composition 2		Composition 3		Composition 4	
		Cell 1	Cell 2	Cell 1	Cell 2	Cell 1	Cell 2	Cell 1	Cell 2
H_i (µm)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$[Na^+]_i$ (mM)	26.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$[Cl^-]_i$ (mM)	57.2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$[K^+]_i$ (mM)	116.9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
V_m^{ap} (mV)	-16.6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
V_m^{ba} (mV)	-31.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
V_t (mV)	-14.4	[illegible]		[illegible]		[illegible]		[illegible]	
H_{ASL} (µm)	***Fixed***	[illegible]		[illegible]		[illegible]		[illegible]	
$[Na^+]_{ASL}$ (mM)	***Fixed***	[illegible]		[illegible]		[illegible]		[illegible]	
$[Cl^-]_{ASL}$ (mM)	***Fixed***	[illegible]		[illegible]		[illegible]		[illegible]	
$[K^+]_{ASL}$ (mM)	***Fixed***/*Variable*	[illegible]		[illegible]		[illegible]		[illegible]	

Table 1: Steady state estimations run for four different literature ASL compositions for a two-cell model with **low** cell-cell lateral resistance. Model data displayed is the average value predicted by the model for ~1000 estimations with randomly generated parameter start points.

Secretory-absorptive model outputs: High cell-cell resistance

Variable	Initial Guess	Composition 1		Composition 2	
		Cell 1	Cell 2	Cell 1	Cell 2
H_i (µm)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]
$[Na^+]_i$ (mM)	26.0	[illegible]	[illegible]	[illegible]	[illegible]
$[Cl^-]_i$ (mM)	57.2	[illegible]	[illegible]	[illegible]	[illegible]
$[K^+]_i$ (mM)	116.9	[illegible]	[illegible]	[illegible]	[illegible]
V_m^{ap} (mV)	-16.6	[illegible]	[illegible]	[illegible]	[illegible]
V_m^{ba} (mV)	-31.0	[illegible]	[illegible]	[illegible]	[illegible]
V_t (mV)	-14.4	[illegible]		[illegible]	
H_{ASL} (µm)	***Fixed***	[illegible]		[illegible]	
$[Na^+]_{ASL}$ (mM)	***Fixed***	[illegible]		[illegible]	
$[Cl^-]_{ASL}$ (mM)	***Fixed***	[illegible]		[illegible]	
$[K^+]_{ASL}$ (mM)	***Fixed/****Variable*	[illegible]		[illegible]	

Table 2: Steady state estimations run for two different literature ASL compositions for a two-cell model with **high** cell-cell lateral resistance.

Potential of multicellular modelling

Single-cell models capable of biologically feasible outputs

- Not an accurate representation of epithelium and limited applications for investigation

Multicellular modelling provides a way to…

- Analyse cell type-specific contributions to ASL regulation
- Investigate how to influence ASL hydration in CF by targeting specific cells
    - e.g., targeting CFTR across all cell types might not be beneficial

Proof-of-concept, *secretory-absorptive* model

- Realistic outputs despite “extreme” modelling scenario

Summary

ASL dysregulation associated with diseases

Modelling airway epithelia can aid analysis of complex ASL regulation

Airway epithelia are not homogenous

Developed a multicellular modelling framework for airway epithelia

Multicellular models can highlight cell type-specific regulatory roles to understand bioelectric properties and suggest therapeutic strategies for ASL rehydration

Thank you for listening!

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- Professor Vivek Dua
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- Dr. Arthur Mitchell
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- Saidi Li
- Zeyu Chen

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Supplementary Slides

Single cell ionic model outputs

Variable	Initial Guess	ASL Composition			
		Joris	Jayaraman	Song	Knowles
H_i (µm)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]
$[Na^+]_i$ (mM)	26.0	[illegible]	[illegible]	[illegible]	[illegible]
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H_l (µm)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]
$[Na^+]_l$ (mM)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]
$[Cl^-]_l$ (mM)	***Fixed***	[illegible]	[illegible]	[illegible]	[illegible]
$[K^+]_l$ (mM)	***Fixed***/*Variable*	[illegible]	[illegible]	[illegible]	[illegible]

Table 3: Steady state estimations run for four different literature ASL compositions for single cell model. Model data displayed is the average value predicted by the model for ~1000 estimations with randomly generated parameter start points.

Recent successes in CF therapeutics but…

- In recent years, CFTR correctors and potentiators have significantly improved quality of life in CF patients
  - e.g., elexacaftor/tezacaftor/ivacaftor
- Yet, these do not fully restore CFTR function!
- Patients with certain CF mutations are ineligible for treatments

K^+ channel stimulation as a supplement to CF therapeutics

Number of channels

Driving force

$$I_{an^-} = \gamma N P_o (E_{ap} - E_{an^-})$$

Single channel conductance

Channel open probability

- Existing CF therapies seek to modify N and P_o
- Alternatively, amplify the effects of the drug by increasing driving force
- Several K^+ channel activators have passed phase I/II clinical trials

A nanosensor approach to multi-property evaluation of CF therapies

Culture human bronchial epithelia from healthy and CF-donors at air-liquid-interface conditions

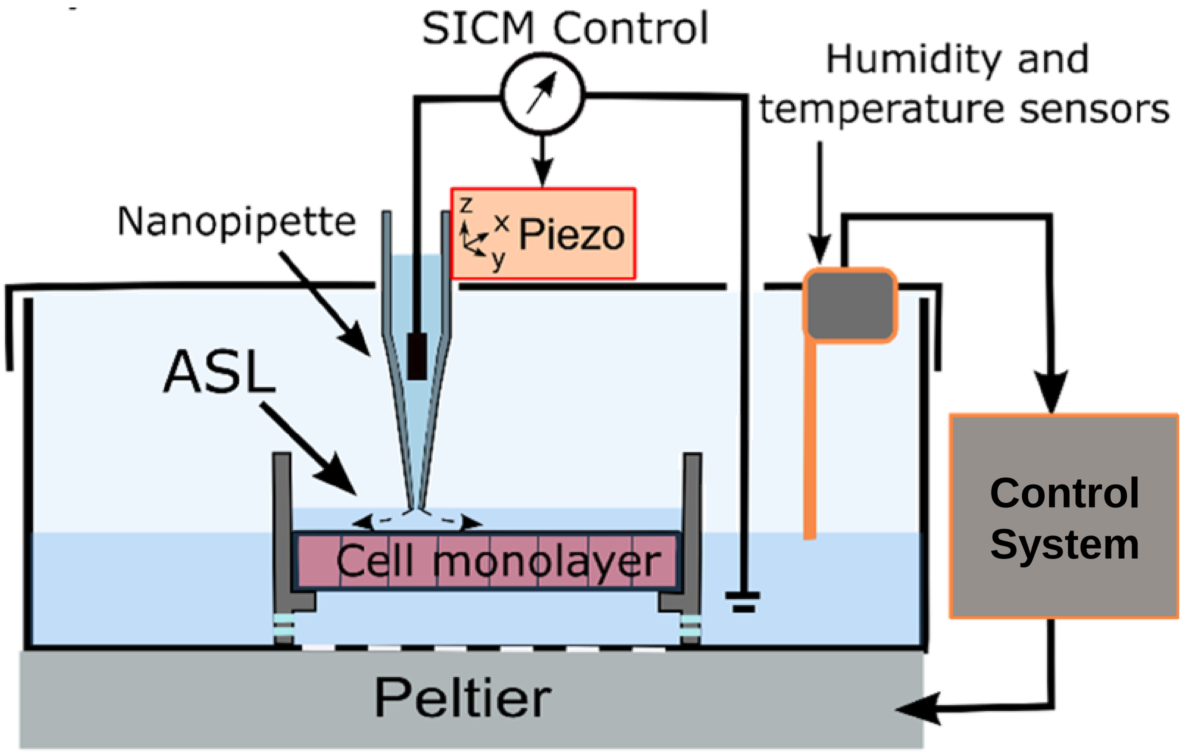
Apply drugs to basolateral medium of CF cells

Nanosensor probes mounted on a scanning ion-conductance microscope (SICM)

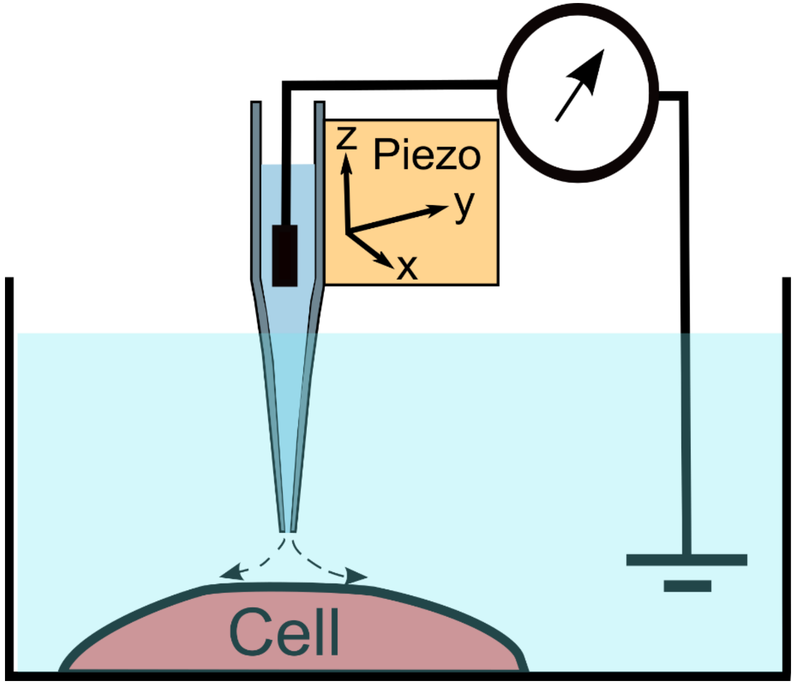
Evaluate key epithelial properties

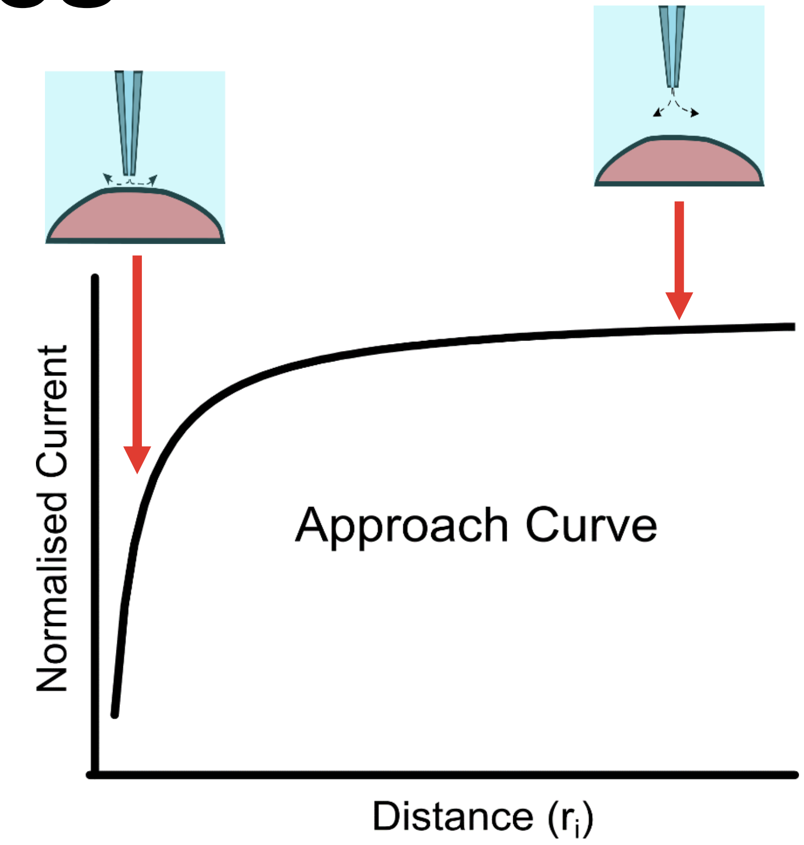
A nanosensor approach to multi-property evaluation of CF therapies

Ivanova R., Benton D.C.H., Munye M.M., Rangseesorranan S., Hart S.L., Moss G.W.J., ***A Nanosensor Toolbox for Rapid, Label-Free Measurement of Airway Surface Liquid and Epithelial Cell Function***. ACS Applied Materials & Interfaces, 2019. 11(9): p. 8731-8739.



A nanosensor approach to multi-property evaluation of CF therapies





The surface can be detected when the probe is at ~1ri

Measurement of key ASL properties