A Multi-Scale Computational Model of Fluid Transport in the Human Bronchial Airways

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Abstract

Mucociliary transport provides the airways' vanguard of defence against inspired noxious materials. Without adequate hydration of the thin layer of liquid that lines the airways, mucociliary transport would cease, leading to build up of mucus and the development of infection. Within this thesis a multi-scale computational model was used to investigate the fluid transport within the airways which is necessary for maintenance of the mucociliary transport system.

A mathematical description of the fluid secretion elicited by a rise in $[Ca^{2+}]_i$ from a single airway epithelial cell was developed. The model indicates that apical membrane Ca^{2+} activated Cl^- channels are not required for Ca^{2+} induced fluid secretion. It was shown that when $[Ca^{2+}]_i$ followed an oscillatory profile the resulting fluid secretion displayed different properties to when the model stimulated a tonic rise in $[Ca^{2+}]_i$ due to saturation of the Ca^{2+} gated ion channels. Furthermore, consistent with known physiology, cell volume returned to equilibrium more rapidly after a hypotonic challenge when Ca^{2+} gated ion channels were activated by a rise in $[Ca^{2+}]_i$.

A description of intercellular Ca^{2+} signalling was developed and used to investigate the relative roles of IP_3 and ATP diffusion in mediating $[Ca^{2+}]_i$ waves in airway epithelial tissue. It was shown that for greater amounts of released ATP, there is a diminishing return in the radius of $[Ca^{2+}]_i$ wave propagation. In addition to this, the radial profile of maximal $[Ca^{2+}]_i$ response from the stimulated cell does not match the flat profile seen in experimental studies. This suggests that for $[Ca^{2+}]_i$ waves to propagate large distances an additional mechanism such as regenerative release of ATP from cells down stream of the stimulated cell may be important.

The epithelial cell model was incorporated into a geometric representation of the human conducting airways. This "cell to organ" coupling was used to investigate the transport of water and heat within the airways. The current work indicates that energy neutrality on its own is an unsatisfactory metric of inspired air's temperature and humidity for invasive mechanical ventilation and can lead to airway dehydration. It was shown that with inspiration of air significantly above body core temperature, a redistribution of airway surface liquid can theoretically occur. This condition represents an extreme which is unlikely to occur clinically, and suggests that mild heating of the air within the ventilator circuit would not cause mucociliary transport dysfunction.

The model presented here provides a firm platform for further study of pathological conditions, such as cystic fibrosis, which lead to mucociliary failure.

Preface

At the forefront of medical exploration, theories are no longer simple and intuitive. Where once a hypothesis could be formulated from an intuitive understanding of the mechanisms at play, as we increasingly appreciate the fractal complexity underlying the systems we investigate, producing a rigourous hypothesis is no longer so straightforward.

In the past, science has been founded on a reductionist approach, whereby each component is individually dissected and analysed. While this is obviously important, and provides a foundation for our knowledge, if we fail to join the dots and understand the interconnectivity, then we never see the big picture. This means we fail to understand the relationship between the constituent components and the whole system. Such perspective can be achieved through the use of quantitative methods. This approach allows the scientist to develop hypotheses for systems which have complex relationships between their constituent mechanisms which are not necessarily intuitive upon first inspection.

There is a particular anecdote which is appropriate here, and it is made ever the sweeter by the fact that it is: one of the greatest contributions to medical science, debunked theories more than a millennium old, and was perhaps the very first use of quantitative methods in medical science. It was the discovery of the circulatory system by William Harvey as published in his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings) in 1628.

At that time Galenic[1] theory ruled supreme. It was thought that once ingested, food passed from the stomach into the liver through the portal vein, where it was used to make blood. Once manufactured, the blood would flow from the liver to all parts of the body where it was then consumed. Harvey's experiment was to estimate how much blood would pass through the heart each day. He estimated the stroke volume of the heart at 1/6th of an ounce, and that the heart beats approximately 1000 times every half an hour. Taking the product of these two numbers he arrived at the number 10 pounds 6 ounces of blood being pumped every half an hour. Multiplying this by 48 (the number of half hours in a day) he realised that the liver would have to produce 540 pounds of blood in a day. Realising that no one consumes 540 pounds of food in a day (the amount which would be required to produce that quantity of blood), Harvey considered it was necessary to propose an alternate mechanism– a circulatory system. Using his careful observations from animal vivisection and cadaver dissection, he proposed that blood flowed through the heart in two separate closed loops. One loop, the pulmonary circulation, connected the circulatory system to the lungs. The second loop, the systemic circulation, allowed blood to flow to the vital organs and body tissue.

The purpose of the anecdote is to illustrate how even the most simple quantitative measure can provide hugely useful insights when combined with inductive reasoning. However, while Harvey's discovery illustrates the immense power of a juxtaposition of experimental

[1] Aelius Galenus (AD 129 -200), who was better known as Galen of Pergamum was almost certainly the most accomplished medical researcher of the Roman period. His theories dominated and influenced Western medical science for well over a millennium.

and quantitative measures, it is also an indictment on the progress of medical science until that point. Consider the huge contributions made to science within the 17th century which provided insights into the natural world, such as Galileo Galilei (1564-1642) and Johannes Kepler (1571-1630) and their laws of planetary motion which provided some of the foundations for Isaac Newton's (1643-1727) theory of universal gravitation. This is of course the same Newton who we hold jointly responsible with Gottfried Leibniz (1646-1716) for the invention of calculus. The same time in history as Blaise Pascal (1623-1662) and his contributions to the construction of mechanical calculators, and the field of fluids, pressure and vacuum. The list could go on.

And yet, medical physiology was revolutionised, almost overnight, by Harvey's multiplication of three numbers. It is naïve to think that medical science will again be changed so remarkably by such rudimentary arithmetic. However, the story illustrates the immense power of quantitative methods combined with scientific experiment. Mathematical modelling is no more than an advanced quantitative method. It is about attempting to describe a phenomenon, and using that to place bounds upon the mechanism thought responsible. By bounds we merely mean a numerical value above or below which the proposed mechanism could not be responsible.

This thesis presents a mathematical framework which can be used to establish numerous hypotheses about the transport and regulation of fluid through the airway epithelium. For it to be most beneficial it must be combined with experiment. Indeed, I hope this will occur in the future.

Acknowledgements

"It was the best of times, it was the worst of times; it was the age of wisdom, it was the age of foolishness; it was the epoch of belief, it was the epoch of incredulity; it was the season of Light, it was the season of Darkness; it was the spring of hope, it was the winter of despair; we had everything before us, we had nothing before us...."

A tale of two cities. Charles Dickens

Throughout this study my mental state has been anything but constant. It has been a roller-coaster on which I have experienced the biggest highs and the biggest lows. While I would not trade the experience for anything, I could not have endured such turbulence alone, but have survived only due to the support of many people.

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Acronyms and Abbreviations

2D	Two dimensions
3D	Three dimensions
8-SPT	8-sulfophenyltheophylline
AC	Adenylate cyclase
ACh	Acetylcholine
ADO	Adenosine
ADP	Adenosine diphosphate
AH	Absolute humidity
AMP	Adenosine monophosphate
AQP	Aquaporin
ASL	Airway surface liquid
ATP	Adenosine triphosphate
ATP γS	Adenosine 5'-O-(3-thio)triphosphate
BCC	Basolateral chloride channel
CaCC	Calcium activated chloride channel
CaKC	Calcium activated potassium channel
cAMP	Cyclic adenosine mono-phosphate
CBF	Ciliary beat frequency
CF	Cystic fibrosis
CFD	Computational fluid dynamics
CFTR	Cystic fibrosis transmembrane conductance regulator
CICR	Calcium induced calcium release
CNT	Concentrative nucleoside transporter
CT	Computed tomography
DAG	Diacylglycerol

ENaC	Epithelial sodium channel
E-NPPs	Ecto-nucleotide pyrophosphatase/phosphodiesterase
E-NTDPases	Ecto-nucleotide triphosphate diphosphohydrolases
ER	Endoplasmic reticulum
ETT	Endotracheal tube
FDM	Finite difference method
FEM	Finite element method
GDP	Guanosine diphosphate
GHK	Goldman-Hodgkin-Katz
GPCR	GTP binding protein coupled receptor
GTP	Guanosine triphosphate
BHE	Human bronchial epithelium
HH	Heated humidifier
HME	Heat and moisture exchanger
INO	Inosine
IP_2	Inositol biphosphate
IP_3	Inositol 1,4,5-triphosphate
IP_4	Inositol tetraphosphate
IP_3-R	Inositol 1,4,5-triphosphate receptor
ISB	Isothermal saturation boundary
LIS	Lateral intercellular space
MRI	Magnetic resonance imaging
NSAP	Nonspecific alkaline phosphatase
ODE	Ordinary differential equation
PCL	Periciliary Liquid
PDE	Partial differential equation
PIP_2	Phosphotidylinositol 4,5-biphosphate
PKA	Protein kinase A

PKC	Protein kinase C
PLC	Phospholipase C
PMCC	Plasma membrane calcium channel
PPADS	Pyridoxal-phosphate-6-azophenyl-2', 4'-disulfonate
RH	Relative humidity
RVD	Regulatory volume decrease
RyR	Ryanodine receptor
SEM	Scanning electron micrograph
SMG	Submucosal gland
UTP	Uridine-5'-triphosphate

List of Symbols

$\mathscr{P}_\star$	Membrane permeability for the species $\star$
$\psi_\star$	Non-permeable osmolytes, for the $\star$ cellular compartment
$A_\star$	Area, for the $\star$ membrane
$C_\star$	Membrane capacitance, for the $\star$ membrane
$D_\star$	Diffusivity of the species $\star$
F	Faraday's constant
G	Maximum ion channel conductance density
g	Maximum ion channel conductance
$I_\star$	Ion current for the ion $\star$
$L_\star$	Hydraulic permeability, for the $\star$ membrane
$P_\star$	Open probability for the channel $\star$
R	Universal Gas constant
$V_\star$	Membrane potential, for the $\star$ membrane
$w_\star$	Volume of cellular compartment, where $\star$ denotes the PCL, cell, ER, or serous
$z_\star$	Valency of the ion $\star$
$\mathcal{D}$	Differentiation operator
$\mathscr{L}$	A linear differential operator
Γ	The boundary of the domain of interest. $\Gamma = \partial\Omega$
$\mathbb{W}$	Gaussian quadrature weight
$\mathcal{I}_K\star$	Local interpolant on K for the function $\star$.
$\mathcal{N}$	$\mathcal{N}$ is the set of nodal variables. $\mathcal{N}_k = \{N_1, N_2, N_3, \ldots, N_k\}$.
$\mathcal{P}$	The space of polynomials
ϕ_i	Nodal basis funcion
ξ_g	Affine Gaussian quadrature location

K_i	The element domain. Where $K_i \subseteq \Omega \subset \Re^n$ such that the domain $\Omega = \bigcup_{i=1}^{N} K_i$
$[\cdot, \cdot]$	Closed interval
$[f]_b^a$	$f(b) - f(a)$
$\cap$	Intersection of sets
$\cup$	Union of sets
δ_{ij}	Kronecker delta. $\delta_{ij} = 1$ if $i = j$, else $\delta_{ij} = 0$
$\dot{V}$	Ventilation rate in ℓmin^{-1}
$\exists$	Existance of an element
$\forall$	Is read as, "For every"
$\in$	Membership to a set
inf	Infimum
$(\cdot, \cdot)$	Inner Product
$\{x \in A : P\}$	The set of elements x, which is a member of A, satisfying condition P
$\mathcal{O}$	Order of approximation
$\mathscr{H}$	Hilbert Space
$\mathscr{H}^1(\Omega)$	Hilbertian-Sobolev Space of order $m = 1$, $p = 2$ on Ω
$\mathscr{H}^m(\Omega)$	Hilbertian-Sobolev Space of order m, $p = 2$ on Ω
$\mathscr{K}_n$	Krylov subspace of dimension n
$\mathscr{V}$	Real vector space
$\mathscr{D}(\Omega)$	Space of functions which are compact on the Ω
$\notin$	Negates membership to a set
Ω	The domain of interest: an open set in $\Re^n$
$\Re$	The space of real numbers
$\Re^n$	A space of n-truples of real numbers. Where $\Re^n = \Re \times \Re \times ... \, (n - times)$
supp	Support
sup	Supremum
$\triangle$	Laplacian differential operator: $\triangle f = \sum_{i=1}^{n} \frac{\partial^2 f}{\partial x_i^2}$ for n dimensions.
ξ	Affine coordinate, where $\xi \in [0, 1]$
$A \Rightarrow B$	A implies B
$A \subset B$	A is a subset of B
$C[a, b]$	Space of continuous functions on $[a, b]$

$C^\infty[a,b]$	Space of smooth functions on $[a,b]$
$C_0^\infty(\Omega)$	Space of smooth functions with compact support in Ω
$C_0^\infty[a,b]$	Space of smooth functions vanashing at $[a,b]$
$C^n[a,b]$	Space of n times continuously differentiable functions on $[a,b]$
$C_0[a,b]$	Space of continuous functions vanashing at $[a,b]$
$f : X \to Y$	f maps elements of X to elements of Y
$L_2(\Omega)$	Space of square integratable distributions on Ω
$L_2[a,b]$	Space of square integratable functions on $[a,b]$
$W_p^m(\Omega)$	Sobolev Space of order m, p on Ω
$\lim_{n\to\infty} x_n = x$	The sequence x_n converges to the point x as $n \to \infty$
$\lvert\cdot\rvert$	Semi norm
$\lVert\cdot\rVert$	Norm
$\lVert\cdot\rVert_\infty$	(essential) sup norm
$\lVert\cdot\rVert_{L_p}$	Lebesque integratable L_p norm

Prefixes

Prefix	**Symbol**	**Factor**
yotta	Y	10^{24}
zetta	Z	10^{21}
exa	E	10^{18}
peta	P	10^{15}
tera	T	10^{12}
giga	G	10^{9}
mega	M	10^{6}
kilo	k	10^{3}
hecto	h	10^{2}
deka	da	10^{1}
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
micro	μ	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}
atto	a	10^{-18}
zepto	z	10^{-21}
yocto	y	10^{-24}