Factors influencing mixing and mass transfer in the small intestine

A thesis presented in partial fulfilment of the

requirements for the degree of Doctor of Philosophy in Digestive Biomechanics

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Abstract

This work sought to determine the factors influencing mixing and mass transfer in the small intestine. Specifically, the work was focussed on the gut periphery (i.e. perivillous region) of the terminal ileum in the brushtail possum (*Trichusurus vulpecula*). The salient questions to answer were;

1. What are the microrheological properties and disposition of mucus in the perivillous space?
2. What are the disposition and movements of the mucosa and the associated villi during postprandial gut motility patterns of pendular contractions?
3. Are villi rigid structures during physiological levels of lumen flow?

The following three main experimental works of this thesis were all conducted using live gut wall samples maintained *ex vivo*. In addition, computational models were developed incorporating the novel findings detailed in this thesis to assist in visualizing mixing and mass transfer in the perivillous space.

1. The properties of the perivillous fluid environment were assessed by multiple-particle-tracking of the Brownian motion of fluorescent microbeads on gut samples.
2. The movements and disposition of the mucosal surface and associated villi during pendular contractions were observed for whole lengths of everted gut samples.
3. Flow velocities in the perivillous space of gut samples were determined by microparticle-image-velocimetery of microbeads. The movement of villi in response to physiological levels of lumen flow were quantified by image analysis.

The following are the main findings and implications of the work.

1. The perivillous fluid environment consisted of discrete viscoelastic bodies dispersed within a watery Newtonian phase. Such characteristics of the fluid environment were thought to be conducive for mixing and mass transfer, and likened to the processes of gel filtration.
2. Gut pendular contractions generated transient mucosal microfolds, which resulted in the formation of periodic congregation and separation of villous tips. Such a mechanism was predicted (using computational simulations) to augment mixing and mass transfer of nutrients at the gut periphery.
3. Villi were rigid structures, which were more prone to pivot than to bend, while intervillous fluid was predicted to be quasi-static during physiological levels of lumen flow. Such a feature of villi supports a perivillous mixing and mass transfer mechanism driven by mucosal microfolding

In conclusion, mixing and mass transfer in the perivillous space are governed by more complex dynamics than previously assumed and by factors previously unknown.

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Preface

This thesis is written according to the regulations stipulated in the latest version of the Handbook for Doctoral Study, published by the Doctoral Research Committee in January 2011 (GRS version 7).

All animal works were carried out in strict accordance with the 'New Zealand Code of Practice for the Care and Use of Animals for Scientific Purposes'. The procedures carried in this thesis were also approved by the Massey University Animal Ethics Committee (MUAEC approval no. 10/31, 11/45 and 12/77).

The thesis format complies with the format of a thesis based on publications, as described on page 63-64 under the section 'Submission of a thesis based on publications'. My journal articles have been reproduced in this thesis in its entirety at the relevant chapters and are interspersed in between introductory and additional material that were not included in the articles. At each chapter that contains a publication, a 'DRC 16 – Statement of contribution to doctoral thesis containing publications' is attached as a page just before the sections of the journal article.

Below, details of the journal articles that have been published and the chapter of which it may be found are listed in the order they would appear in my thesis.

Chapter 3:

Yuen Feung Lim, Martin A. K. Williams, Roger G. Lentle, Patrick W. M. Janssen, Bradley Mansel, Stephen Keen, and Paul Chambers (2013). An exploration of the microrheological environment around the distal ileal villi and proximal colonic mucosa of the possum (*Trichosurus vulpecula*).

Published in: **Journal of the Royal Society Interface 10(81):** 20121008

Chapter 5:

Roger G. Lentle, Patrick W. M. Janssen, Clement de Loubens, Yuen Feung Lim, Corrin Hulls, Paul Chambers (2013). Mucosal microfolds augment mixing at the wall of the distal ileum of the brushtail possum.

Published in: **Neurogastroenterology and Motility 25(11):** 881-e700

Chapter 6:

Yuen Feung Lim, Roger G. Lentle, Patrick W. M. Janssen, Martin A. K. Williams, Clement de Loubens, Bradley Mansel, and Paul Chambers (2014). Determination of villous rigidity and intervillous flow in the distal ileum of the brushtail possum (*Trichosurus vulpecula*).

Published in: **Plos One 9(6):** e100140

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advice with MatLab in the absence of Clement. I too want to acknowledge John Bronlund my masters supervisor who found and suggested the PhD to me in addition to the help you provided with MatLab to get me started early in my work.

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Thank you as well to all those who have assisted me in my work either in the experimental preparations, during the experiments or post experiments as well as 'outside' advice for my PhD work; Paul Chambers, Gordon Reynolds, Byron McKillop, William Thielicke, Shampa De, Fran Wolber, Marlena Kruger, Chua Wei-Hang, Kevin Pedley, John Pedley, Corrin Hulls, Stephen Keen and Brad Mansel. I would also like to give a special mention to the latter three guys who were willing to drag themselves out of bed to help with experiments in the early hours of the morning and for allowing me to contact you 'after hours'.

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xxx

as laughter that helps place the challenging aspects of the PhD into a different perspective.

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Glossary

Postprandial period – The period following the consumption of a meal a.k.a. the fed state

Interdigestive period – The period that commences after and precludes the postprandial period a.k.a. the fasting/intercibal period

Unstirred water layer – Commonly abbreviated as the 'UWL'. Initially thought to be an actual diffusion barrier of unstirred fluid overlying the intestinal mucosa that acts as a barrier to mass transfer

Perivillous region – The region encompassing the intervillous space as well as the region directly above villi up to a distance of no more than a length of a villous from the villous tips

Small intestinal villi – Small, often finger-like projections that protrude from the epithelial lining of the intestinal wall. Its outer surfaces are composed of a variety of epithelial cells of which absorptive enterocytes are the pre-dominant type

Mucus islands – Mucin secreted by goblet cells into the extracellular regions that is undergoing swelling by hydration

Mass transfer – Net movement of mass from one location to another. It usually refers to movement by diffusive (i.e. the diffusion of solute within the bulk phase) and/or advective (i.e. mass movement of the bulk phase with contained solute) mass transfer.

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