Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.
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
(Physical Process of Digestion)

at Massey University, Turitea,

New Zealand.

Ian Lim Yuen Feung

2015
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-velocimetry 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.
Table of contents

Abstract ........................................................................................................................... iii

Table of contents .......................................................................................................... v

List of Figures .............................................................................................................. xvii

List of Tables .............................................................................................................. xxv

List of Videos Referenced Throughout this Thesis ...................................................... xxvi

Preface ......................................................................................................................... xxvii

Acknowledgements ...................................................................................................... xxix

Glossary ......................................................................................................................... xxxii

Chapter One - Introduction ........................................................................................... 1

Chapter Two - Literature review ................................................................................... 5

2.1. Foreword ............................................................................................................. 6

2.2. Small intestinal motility ..................................................................................... 7

2.2.1. Migrating motor complex (MMC) ............................................................... 8

2.2.2. Peristalsis .................................................................................................... 9

2.2.2.1. Promotion of mass transfer ................................................................. 11

2.2.3. Segmentation ............................................................................................. 16

2.2.3.1. Promotion of mass transfer ................................................................. 19

2.2.4. Pendular activity ........................................................................................ 20

2.2.4.1. Promotion of mass transfer ................................................................. 21
2.2.5. The postprandial period ................................................................. 22
2.2.6. Compartmental organization of mixing and mass transfer in the lumen.. 23
2.2.7. Concluding remarks on the effects of small intestinal motility patterns... 24

2.3. Small intestinal villi........................................................................... 26

2.3.1. Morphology of villi.......................................................................... 26
2.3.1.1. Shape.......................................................................................... 26
2.3.1.2. Dimensions .............................................................................. 29
2.3.1.3. Density...................................................................................... 30
2.3.2. Cellular composition of villi ........................................................... 31
2.3.2.1. Morphology and function of intestinal epithelium cells.............. 31
2.3.3. Villous internal structure................................................................. 34
2.3.4. Villous motility .............................................................................. 36
2.3.5. Possible villous functions................................................................. 39
2.3.5.1. Increased surface area for absorption ......................................... 39
2.3.5.2. Micro-mixing system................................................................. 40
2.3.5.3. ‘Cape Canaveral’ for luminal hormones and enzymes............... 43
2.3.6. Concluding remarks on the influence of villi................................. 44

2.4. Mucus in the small intestine .............................................................. 46
2.4.1. Regional variation of mucin type..................................................... 48
2.4.2. Mucogenesis and organization of secreted mucin ......................... 51
2.4.2.1. Biogenesis of mucin secretory granules ....................................... 53
2.4.2.2. Discharge and expansion of mucin granules .............................. 55
Chapter Three - Studies of the microrheology and fluid environment of the perivillous space ................................................................. 75

3.1. Foreword ...................................................................................... 76

3.1.1. Background and methodology used by other workers in this field .. 76

3.2. Copy of the paper: An exploration of the microrheological environment around the distal ileal villi and proximal colonic mucosa of the possum (Trichosurus vulpecula) ......................................................................................... 80

3.2.1. Abstract ...................................................................................... 81

3.2.2. Introduction ............................................................................... 82

3.2.3. Materials and Methods ............................................................... 84

3.2.3.1. Preparation of intestinal samples ........................................... 84

3.2.3.2. Microrheological technique ................................................... 86

3.2.3.3. Assessing the homogeneity of the environments of bead ensembles 89
3.3.5. Assessment of tissue viability ................................................................. 131
3.3.6. Validation of the MPT technique .......................................................... 132

3.4. Ancillary work: A comparison of the microrheological environment around distal ileal villi and proximal colonic mucosa of the possum (*Trichosurus vulpecula*) using two types of microbeads of differing surface chemistry. .......................... 134

3.4.1. Introduction ............................................................................................. 134

3.4.1.1. Description of mucin structure ........................................................ 135
3.4.1.2. Mucus properties .............................................................................. 136

3.4.2. Methods ................................................................................................... 136

3.4.2.1. Choice of amine-coated (AC) microbeads ....................................... 137
3.4.2.2. Sampling and statistics ..................................................................... 137

3.4.3. Results ..................................................................................................... 138

3.4.3.1. Ileal mucosa ..................................................................................... 138
3.4.3.2. Colonic tissue .................................................................................. 141
3.4.3.3. Comparison of ileum and colon ....................................................... 144
3.4.3.4. Comparison of the results obtained with NP and AC microbeads .. 145

3.4.4. Discussion ............................................................................................... 146

3.5. Chapter conclusion ......................................................................................... 150

Chapter Four - LBM of mixing and mass transfer in the small intestine............ 153

4.1. Foreword ........................................................................................................ 154

4.2. Modelling strategy .......................................................................................... 155

4.3. Physical formulation of the computational models developed....................... 156
4.3.1. Fluid environment of the model .............................................................. 156

4.3.2. Determination of villous architecture and density ................................ 157

4.3.2.1. Determination of villous density ..................................................... 157

4.3.3. Villous profile ......................................................................................... 159

4.4. Lattice Boltzmann numerical formulation of mathematical model ............ 160

4.4.1. Dimensionless formulation .................................................................. 161

4.4.2. LBM modeling of flow by LBGK .......................................................... 163

4.4.3. Boundary conditions used in LBM environment ..................................... 165

4.4.3.1. Pendular contractions of gut wall in LBM environment ................. 165

4.4.3.2. Simulating moving and curved boundaries ..................................... 167

4.4.3.3. Symmetry boundaries ...................................................................... 169

4.4.4. Multi-scale meshing considerations ...................................................... 170

4.4.5. Code validation ....................................................................................... 170

4.5. Experimental parameters .......................................................................... 171

4.5.1. Physiological parameters ...................................................................... 171

4.5.2. Numerical Parameters .......................................................................... 173

4.5.3. Model’s experimental parameters ............................................................ 175

4.5.3.1. Flow and villi characteristics compared ........................................... 176

4.5.3.2. Simulation of advective and diffusive mass transfer of a solute tracer ...
..................................................................................................................... 177

4.6. LBM results .................................................................................................. 179

4.6.1. Effect of villous length .......................................................................... 181
4.6.2. Effect of villous numbers ................................................................. 183
4.6.3. Effect of varying flow parameters .................................................. 185
4.6.4. Mass transfer of a solute tracer ..................................................... 187
4.7. Discussion ...................................................................................... 189
4.8. Chapter Conclusion .......................................................................... 193

Chapter Five - Mucosal microfolding of gut wall ........................................ 195

5.1. Foreword ...................................................................................... 196
5.1.1. Background and justification of experimental apparatus used ...... 196
5.2. Additional materials and methods ................................................... 199
5.2.1. Eversion of gut segment ............................................................... 199
5.2.2. Organ bath design ...................................................................... 201
5.2.3. Experimental apparatus setup .................................................... 203
5.2.4. Alternative method of determining mucosal microfolds dimensions .... 203
5.3. Copy of the paper: Mucosal microfolds augment mixing at the wall of the distal ileum of the brushtail possum .................................................... 206
5.3.1. Abstract .................................................................................... 207
5.3.2. Introduction ............................................................................... 208
5.3.3. Materials and methods ............................................................... 209
5.3.3.1. Preparation of ileal segments ................................................ 209
5.3.3.2. Image acquisition and spatiotemporal mapping ....................... 211
5.3.3.3. Measurement of villous and microfold geometry .................. 212
5.3.3.4. Modelling of peripheral and bulk fluid mechanics ............... 213
Chapter Six - Passive mechanical properties of villi.................................243

6.1. Foreword .................................................................................................244

6.1.1. Background and justification of experimental techniques used........244

6.1.1.1. Determination of flow velocity in the perivillous space..............245

6.2. Supplementary methods and design of the equipment used.................247
6.2.1. Tissue flow cell design ................................................................. 247
6.2.1.1. Tissue flow cell probe .............................................................. 253
6.2.2. Overall setup of experimental apparatus ...................................... 256
6.2.2.1. Inverted microscope ................................................................. 258
6.2.2.2. Microscope objective used ...................................................... 258

6.3. Copy of the paper: Determination of villous rigidity and intervillous flow in the distal ileum of the brushtail possum (Trichosurus vulpecula) ........................................ 260

6.3.1. Abstract ...................................................................................... 261
6.3.2. Introduction ................................................................................ 262
6.3.3. Methods .................................................................................... 264
6.3.3.1. Preparation of intestinal samples ........................................... 264
6.3.3.2. Micro-PIV ............................................................................. 267
6.3.3.3. Analysis of micro-PIV results ................................................. 269
6.3.3.4. Mean villous length and width ................................................. 270
6.3.3.5. Total displacement (TD) of the villous tip ............................... 271
6.3.3.6. Assessment of bending of the villous shaft and angular displacement ......................................................................................... 272
6.3.3.7. Assessment of endogenous villous motility ............................. 273
6.3.3.8. Sampling and statistics ......................................................... 273
6.3.4. Results ..................................................................................... 274
6.3.4.1. Villus length and width ......................................................... 274
6.3.4.2. Flow profiles around villi ..................................................... 274
6.3.4.3. Total displacement (TD) of the villous tip ........................................ 276
6.3.4.4. Assessment of villous rigidity ........................................................... 277
6.3.4.5. Spatiotemporal maps along the longitudinal axis of villi .............. 278
6.3.5. Discussion .......................................................................................... 278
6.3.6. Journal article references .................................................................... 282
6.3.7. Figures and Figure Legends ............................................................... 285
6.3.8. Additional Notes on the Published Journal ......................................... 293
6.4. Additional Methods and Results .............................................................. 294
6.4.1. Physical formulation .......................................................................... 294
6.4.1.1. Villous profile .................................................................................. 295
6.4.2. Description of models developed ...................................................... 295
6.4.2.1. Model 1: Flow profile around an isolated villus ........................... 295
6.4.2.2. Model 2: Flow profile around an array of diagonally staggered villi 296
6.4.3. Lattice Boltzmann methods ............................................................... 296
6.4.4. Results ............................................................................................... 297
6.4.4.1. Fluid flow modelling around an isolated villous ............................ 297
6.4.4.2. Modelling of fluid flow around an infinite array of asymmetric villi 299
6.5. Ancillary discussion – significance of chapter findings ......................... 301
6.6. Chapter Conclusion ................................................................................ 305

Chapter Seven - 3D Models of Mucosal Microfolding .................................. 307
7.1. Foreword ........................................................................................................ 308
7.2. Background .................................................................................................... 309
7.3. Methods .......................................................................................................... 312
  7.3.1. Modelling strategy .................................................................................. 312
    7.3.1.1. Villous profile, dimensions and spacing .......................................... 313
    7.3.1.2. Villous flexibility and row configuration ........................................ 314
    7.3.1.3. Mucosal microfolding during pendular contractions ....................... 315
  7.3.2. Lattice Boltzmann methods..................................................................... 316
  7.3.3. Use of physiological and numerical parameters ..................................... 318
  7.3.4. Analysis and comparison of flow fields .................................................. 318
7.4. Results ............................................................................................................ 320
  7.4.1. 3D model of aligned villi configuration..................................................... 320
  7.4.2. 3D model of staggered villi configuration .............................................. 323
  7.4.3. Comparison of the aligned and staggered villi configurations................. 326
7.5. Discussion ...................................................................................................... 327
  7.5.1. Comparison between 2D and 3D models ................................................ 327
  7.5.2. Comparison between aligned and staggered villi configuration ............. 329
  7.5.3. Leading villi of mucosal microfolds. ...................................................... 330
7.6. Chapter conclusion ......................................................................................... 332

Chapter Eight - Overall Discussion ........................................................................... 335

  8.1. The perivillous fluid environment in the small intestine ......................... 336
  8.2. Formation of mucosal microfolds during non-propagating contractions ...... 339
8.3. Villous rigidity and perivillous flow conditions during lumen flow .......... 342
8.4. Computational modeling of mass transfer at the perivillous region .......... 345
8.5. The overall context of the work .................................................................. 347

Appendix ...................................................................................................................... 348

References .................................................................................................................... 356
List of Figures

Figure 2-1: Observations of the peristaltic reflex on an *ex vivo* preparation of a 10 cm segment of guinea pig ileum following the injection of a 0.8 ml bolus. ......................... 10

Figure 2-2: Suggested mechanism for mixing by peristaltic contractions. ...................... 12

Figure 2-3: A pair of spatiotemporal maps obtained from a segment of possum ileum undergoing peristaltic contractions. ................................................................. 14

Figure 2-4: Segmentative gut motility pattern. ............................................................... 16

Figure 2-5: The first published illustration of a possible mechanism of mixing by segmentation. .................................................................................................................. 17

Figure 2-6: Diameter ‘D’ map of the occurrence of non-propagating circular muscle contractions on a guinea pig duodenum (adapted from Lentle et al. 2012). .......... 18

Figure 2-7: Multiscale numerical model of mass transfer in the gut developed by Wang et al. (2010). .................................................................................................................... 24

Figure 2-8: Reproduced images of duodenal villi from endoscopy A) (Cammarota et al. 2004) and B) microscopy of fresh biopsy samples of jejunal villi (Holmes et al. 1964). ......................................................................................................................................... 27

Figure 2-9: Images of ileal villi ....................................................................................... 28

Figure 2-10: The intestinal epithelium and immuno-histochemical analysis of the four main cell types that are located on the epithelium. ......................................................... 32

Figure 2-11: The structural organization of selected constituents of the villi stroma.... 35

Figure 2-12: Expression of the B°AT1 amino acid transporter along the length of villi in the mouse small intestine. ................................................................. 40
Figure 2-13: Assuming that villi are rigid structures and may be approximated as a bluff body, Karman vortexes may form behind villi. The flows routes on opposite sides of the bluff object are given different colours to better illustrate that the vortices are shedded from alternate sides of the object. ................................................................. 43

Figure 2-14: Electron microscope picture as evidence for the possible function of villi as ‘launching pads’ for hormones and enzymes via their micro-villi. .........................44

Figure 2-15: Thicknesses of the 2 mucus gel layers *in vivo* in the corpus, antrum, midduodenum, proximal jejunum, distal ileum, and proximal colon of the rat gastrointestinal tract (GIT) (adapted from Atuma et al. 2001). ................................................. 48

Figure 2-16: The disposition and flow of the various types of mucins and gastric gland secretions..................................................................................................................51

Figure 2-17: The process of biogenesis of a goblet cell mucin granule to its exocytosis. .................................................................................................................................55

Figure 2-18: The ‘jack-in-the-box’ mechanism of exocytosis of a mucus secretory granule (MSG). ................................................................................................................58

Figure 2-19: Confocal microscopy image of mucus overlying the apices of villi indicating that they are discontiguous and heterogeneous............................. 61

Figure 2-20: Possible mucin structure type taken at 3 different magnifications and 4 levels of detail. ................................................................................................. 62

Figure 3-1: Tissue bath. .................................................................................................107

Figure 3-2: Spatial analyses of microrheological environments.............................109

Figure 3-3: Mapping of viscoelastic bodies...............................................................111

Figure 3-4: Stained sections of villi from mucosal sample following passive microrheology..............................................................................................................113
Figure 3-5: Variation in the rheological properties of the continuous phase and viscoelastic bodies with intestinal segment, distance from the mucosa and location around intestinal villi (i.e. tips and sides of villi) shown using boxplots. 114

Figure 3-6: Variation in the diameter and projected area of viscoelastic bodies near the ileal villous and colonic mucosa. 115

Figure 3-7: Alternatives for disposition of mucin around villi. 116

Figure 3-8: Final design of the tissue bath. 120

Figure 3-9: The tissue flow cell probe. 123

Figure 3-10: Custom made probe holder to secure the probe to the vertical positioning structure (VPS) of the tissue bath. The lock was used to secure the probe holder to the VPS. The complete tissue bath can be viewed in Figure 3-8. 124

Figure 3-11: The base of the tissue. 125

Figure 3-12: A sectional view of the Perspex baths through the baths centre showing the locations and diameters of the inlet and outlet flow spouts for carboxygenated and heated Earler-Hepes solution (HBS). 127

Figure 3-13: Basic setup of experimental apparatus on the optical microrheometer during recording of the Brownian motion of microbeads around villi on a live ileal segment. 128

Figure 3-14: The mean squared displacement (MSD) plot for 4 wt% solution polyethylene oxide (PEO) showing an agreement between data obtained using multiple particle tracking (MPT) and diffusive wave spectroscopy (DWS). 133

Figure 3-15: Main features of the mucin monomer glycoprotein. 135

Figure 3-16: Variation in the rheological properties of the A) continuous phase and B) viscoelastic bodies near the ileal villus and colonic mucosa obtained using NP (naked polystyrene; green plots) and AC (amine coated; red plots) microbeads. 140
Figure 3-17: Variation in the diameter of viscoelastic bodies with intestinal segment, distance from the mucosa and type of microbead.................................143
Figure 4-1: Lattice Boltzmann modelling (LBM) scheme used and the basic proceedings of any LBM algorithm.................................................................161
Figure 4-2: The simplified small intestinal model of 1 spatial domain of contraction (2l) of the rat duodenum (Lentle et al. 2012)..............................................166
Figure 4-3: Two situations where the standard ‘bounce-back’ scheme (Sukop and Thorne 2007) was needed to be modified to address the density distribution function when the propagation of a particle encounters a boundary that is less than a lattice unit from the last fluid node.........................................................168
Figure 4-4: Relationship between ‘% deviation from velocity fields of the base case’ (left Y-axis; blue plot with diamond shaped points) and simulation time (right Y-axis; red plot with square shaped points) against a range of assumed relaxation parameters (X-axis). .................................................................173
Figure 4-5: Relationship between ‘% error from the base case’ (left Y-axis; square shaped points plot) and simulation time (right Y-axis; diamond shaped points plot) against a range of relaxation parameters (X-axis). .........................................................174
Figure 4-6: Radial velocity intensity plots comparing the base case model against a model run without villi.................................................................179
Figure 4-7: The percentage difference of radial velocities between the model run with villi and the other without.................................................................180
Figure 4-8: Radial velocity intensity plots comparing the base case model against a model run with villi of half the full length.............................................181
Figure 4-9: The percentage difference in radial velocities between the full length villi (FL) and half length villi (HL) model.................................................182
Figure 4-10: Radial velocity intensity plots comparing models with different densities of villi. ................................................................. 183

Figure 4-11: The percentage difference in radial velocities between the model run with all 36 villi and a model run with just 9 villi. ................................................................. 184

Figure 4-12: Radial velocity intensity plots showing flow profiles characterized by different combinations of dimensionless parameters. .............................................. 185

Figure 4-13: The percentage difference of radial velocities between the model run with $W_o = 1.45$ and the model run with $W_o = 2.02$. ............................................................. 186

Figure 4-14: Plots of the advection and/or diffusion of a solute tracer that has the same diffusion coefficient as mannitol. ................................................................. 187

Figure 4-15: Plot comparing the percentage reduction of solute tracer concentrations between the model of pure diffusive mass transfer (red plot) of tracer and the model of advective and diffusive mass transfer (blue plot) of tracer. .............................................. 188

Figure 5-1: Everting probe used to evert gut segment samples. ........................................... 200

Figure 5-2: Basic setup of the experimental apparatus used for the recording of the disposition and movements of the mucosa and associated villi of gut segments maintained ex vivo during the recording of gut motility patterns of the everted gut. ... 202

Figure 5-3: Staining of villous tips following application and elution of methylene blue. ....................................................................................................................................... 224

Figure 5-4: Spatiotemporal maps of pendular activity in the terminal ileum of the possum. ............................................................................................................................................... 225

Figure 5-5: Everted mucosal surface of ileum at rest (A), and during a longitudinal (B), and a simultaneous longitudinal and circular (C) contraction. ................................. 226

Figure 5-6: Micro-scale simulation of the effect of villous apical crowding on velocity and mixing adjacent to the mucosa during a complete pendular contraction cycle*. ... 227
Figure 5-7: Simulated effect of villous length and molecular diffusivity on the absorption rate of readily absorbed compounds. .......................................................... 229

Figure 5-8: Macro-scale simulation of the effect of villi on radial velocity and shear rate across the lumen. ........................................................................................................... 230

Figure 5-9: Overview of geometry used in both micro- and macro-scale simulations. 234

Figure 5-10: Coarse and fine grid dimensions used in the villous micro-scale simulation ....................................................................................................................................... 238

Figure 5-11: Contact and access locations of perivillous digesta flow during both axial and radially oriented mucosal microfolds. ................................................................. 241

Figure 6-1: Photographs of the tissue flow cell. ........................................................... 248

Figure 6-2: Tissue flow cell core structure with dimensions – a machined stainless steel block............................................................................................................................. 249

Figure 6-3: The elbow quick-fit flow connectors attached to the Perspex lid to be inlet and outlet points for the inner flow chamber and outer flow channel. ....................... 250

Figure 6-4: The silicone sealant and positioning of the screws used to secure the Perspex lid to the stainless steel block. ........................................................................ 251

Figure 6-5: Underside of the stainless steel block. ...................................................... 252

Figure 6-6: Perspex base plate and its dimensions, which was attached to the tissue flow cell. .......................................................................................................................... 253

Figure 6-7: Tissue flow cell probe. .............................................................................. 254

Figure 6-8: The process of the mounting of the sample of gut wall on the flow cell probe ............................................................................................................................... 255

Figure 6-9: The various probe tips designs trialled during pilot study. ....................... 256
Figure 6-10: The basic setup of experimental equipment used for the recording of the movements of villi during lumen flow and trajectories of microbeads in the perivillous space ........................................................................................................................................... 257

Figure 6-11: Tissue flow cell used in experimental work .............................................. 285

Figure 6-12: Method for determining the total displacement of villus tips (TD) ........ 286

Figure 6-13: Relationship between local velocity of microbeads and the volumetric perfusion rate ........................................................................................................................................... 287

Figure 6-14: Variation of $U_x$ with lengthwise distance from the villous tip .............. 288

Figure 6-15: Variation of $U_y$ with lengthwise distance from the villous tip .............. 290

Figure 6-16: Variation of total displacement (TD) with volumetric flow rate .......... 291

Figure 6-17: Relationship between displacement of points along the villous length with distance from the villous tip ........................................................................................................... 292

Figure 6-18: Lattice Boltzmann modelling (LBM) output based on data derived from Lim et al. (2014) simulating flows around an isolated villus ................................................................. 298

Figure 6-19: Output from model based on data derived from experimental work simulating flow in the intervillous space ........................................................................................................ 300

Figure 7-1: ‘Three-dimensions’ (3D) plots of the two villi arrangements (i.e. configuration) of villi used in the computational models described in this chapter. ................................................................. 313

Figure 7-2: Overview of the geometry and movements used in the simulations of mixing and mass transfer in the perivillous space during non-propagating pendular contractions ........................................................................................................................................... 315

Figure 7-3: Computational simulation scheme ............................................................ 317

Figure 7-4: Velocity flow field of $U_{xy}$ velocity intensity plots for a model of the aligned villi configuration at two different planes in the Z-dimension ................................................................. 321
Figure 7-5: Velocity flow field of Uxz velocity intensity plots for a model of the aligned villi configuration.................................................................322

Figure 7-6: Velocity flow field of Uxy velocity intensity plots for a model of two rows of staggered villi at different planes in the Z-dimension. ..................324

Figure 7-7: Velocity flow field of Uxz velocity intensity plots for a model of staggered villi configuration.................................................................325
List of Tables

Table 2-1: Villous lengths for a selection of small mammals........................................ 29
Table 2-2: Villous widths for a selection of small mammals................................. 29
Table 3-1: Summary of the micro-rheological properties (viscosity and elastic moduli) of the continuous phase of Newtonian fluid and viscoelastic bodies, body diameters and percentage area occupied by viscoelastic bodies per 0.064 mm² field of view. ........... 117
Table 3-2: Summary of the microrheological properties (viscosity and elastic moduli) of the continuous Newtonian fluid phase and viscoelastic bodies. ................................. 141
Table 3-3: Summary of the viscoelastic body sizes (i.e. viscoelastic body diameters and the percentage area per (0.064 mm²) field of view) occupied by viscoelastic bodies for both types of microbeads at both distances in both the ileum and the colon.......... 144
Table 4-1: Physical and dimensionless parameters used in the Lattice Boltzmann modelling (LBM) models described in this chapter......................................................... 172
Table 5-1: Physiological parameters used for modelling at the villous scale .............. 239
Table 7-1: Physiological parameters used for the computational models of both configurations ................................................................................................................ 318
List of Videos Referenced Throughout this Thesis

Chapter 3 – Microrheo Movie.................................................................138

Chapter 5 – Microfold Movie1............................................................215

– Microfold Movie2........................................................................216

Chapter 6 – Villi bend Movie.............................................................278
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:


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

Chapter 6:


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

To God be the glory, great things He has done.

First of all, I thank God for the privilege of being given the opportunity to explore His design in His creation of the small intestine. Thank you for carrying me this far in the journey and for the way ahead. Thank you Jing Xiu, my wife and love of my life for your love, support, encouragement and great cooking to sustain me especially during the home straight of this leg of my journey. I also want to thank you, mum and dad for your love, inspiration and encouragement along the way.

I would like to thank all of my supervisors for putting up with me, freely provided me with access to your time, expertise and support. First of all, thank you Roger for your steadfastness in your desire to see me grow to be a better researcher. Regardless of how I felt at that point in time when the pressure was on, I know you had my best interest in mind. Thank you Pat for keeping me grounded in my engineering roots as I ‘traversed distally’ into the exciting but many times more unpredictable realm of gastrointestinal biology. I appreciate you hearing me out on my many ‘navel gazing’ moments especially nearer to the end and for the fine craftsmanship of the experimental apparatus that made my work possible. Finally, Bill, thank you for letting me use your precious equipment, for sparing me the time of your ‘underlings’ and for being a third voice for opinions that has been really useful to me. I appreciate the different (i.e. more ‘chilled out’) style of supervision from you that can be a real ‘pressure release valve’.

At this space, though you were not my formal supervisor, I just want to thank you Clement for your patience in helping me further develop my computational modelling skills and for bearing with me during times when our conversation gets perdue dans la traduction. Also Richard Love for your help looking through few chapters and for
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.

I also want to thank Dick and Mary Earle for their generosity in providing the scholarship administered by the Riddet Institute that enabled me to do the PhD. I too appreciate the Riddet Institute for their work in facilitating comraderie amongst all their PhD students in diverse disciplines through the various student symposiums, trips and activities organized – it has been fun and enlightening to be involved in something larger than my little ‘PhD world’ whilst being involved with the CoRE Future Foods programme.

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’.

To my fellow ‘comrade-in-arms’ of Ivana, Yen and Corrin under the ‘bearded one’, thank you for your support, friendship and to share the load of high expectations. In addition, to the crew who regularly hangs out for a cuppa in the tearoom of the ‘secret third floor’ that I never knew existed until commencing my PhD – thank you for all the yummy food that you feed to a ‘starving grad student’ and for the conversations as well

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

A big ‘shout-out’ also to my ‘office-mates’ (i.e. Team TWO-THREE-EIGHT) past and present: Sandra, Teresa, Oni, Soffa, Jeremy, Elham, Hayley, Chalida, Haoran, Sina and others. Thank you for the conversations, fun, laughter, parties and craziness shared with people who walk and know the journey towards the PhD that can many times be lonely.

Last but certainly in no way least, thank you also to friends not mentioned, mentors and other family for your encouragements, prayers and support of me in this time. Among them, a special mention is to be made of Yuen Leung, Yuen Xin, Janeen, Teng Yang, Mark G, Michael Loh, Kellis, Dawn, Srikanth, Horng Yuan, DJ, Julian, Natalia, Neil, Shoichi and Thomas. Finally, I also would like to thank Paul Stock and Terry McGrath for their help in proof-reading my various chapters.
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.
Copyright and permissions

Permissions to reproduce the figures from other authors/publishers and material from my published journal articles have either been obtained or are in the process of hearing back from the relevant authorities at the time of submission of this thesis.