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REVIEW

A review of mixing and propulsion of chyme in the small intestine: fresh insights from new methods

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Abstract The small intestine is a convoluted flexible tube of inconstant form and capacity through which chyme is propelled and mixed by varying patterns of contraction. These inconstancies have prevented quantitative comparisons of the manner in which contractile activity engenders mixing of contained chyme. Recent quantitative work based on spatiotemporal mapping of intestinal contractions, macro- and micro-rheology, particle image velocimetry and real-time modelling has provided new insights into this process. Evidence indicates that the speeds and patterns of the various types of small intestinal contraction are insufficient to secure optimal mixing and enzymatic digestion over a minimal length of intestine. Hence particulate substrates and soluble nutrients become dispersed along the length of the lumen. Mixing within the lumen is not turbulent but results from localised folding and kneading of the contents by contractions but is augmented by the inconstant spatial disposition of the contractions and their component contractile processes. The latter include inconstancies in the sites of commencement and the directions of propagation of contraction in component groups of smooth muscle cells and in the coordination of the radial and circular components of smooth muscle contraction. Evidence suggests there is ongoing augmentation of mixing at the periphery of the lumen, during both the post-prandial and inter-meal periods, to promote flow around and between adjacent villi. This results largely from folding of the relatively inelastic mucosa during repeated radial and longitudinal muscular contraction, causing chyme to be displaced by periodic crowding and separation of the tips of the relatively rigid villi. Further, micro-rheological studies indicate that such peripheral mixing may extend to the apices of enterocytes owing to discontinuities in the mobile mucus layer that covers the ileal mucosa.

Keywords Small intestine · Luminal mixing · Stochastic vortices · Real-time modelling

Abbreviations

Annealing of mucins	Process of union of individual masses of mucin secreted from individual goblet cells by inter-diffusion of their respective carbohydrate side chains
Apical crowding of villi	Gathering together of the tips of villi in the region between adjacent mucosal microfolds that leads to expulsion of fluid from the spaces between the tips
Continuously stirred tank reactor (CSTR)	A theoretical ideal chemical reactor that runs at a steady rate with continuous flow of reactants and product with complete, i.e. perfect mixing, so that the concentration of reactants is uniform within
Mucosal microfolds	Inwardly projecting folds of mucosa that develop spontaneously as a result of relative

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	differences in the mechanical properties and in the axial lengths of the mucosal and muscular components of the small intestine
Newtonian fluid	A fluid in which the shear rates that develop during flow are always proportional to the shear stress applied, so that viscosity remains constant
Phasic contraction	Concerted or coordinated short-lived contraction of groups of smooth muscle following neural or myogenic stimulation, e.g. peristalsis
Pseudoplasticity	The property of a non-Newtonian fluid in which its apparent viscosity decreases with increase in shear rate
Reynolds number	The ratio of the inertial forces within a moving fluid (that generally cause motion to continue) to viscous forces (that can be viewed as frictional and generally cause motion to slow). For flow within a simple tube Reynolds numbers of less than 2,300 are considered to describe a condition in which viscous forces predominate so that flow is laminar, i.e. occurs in an orderly fashion that can be viewed as a series of concentric tubes within the pipe. Conversely, Reynolds numbers >2,300 describe a condition in which inertial forces predominate so that flow in elements of the liquid become unstable and turbulent
Rheometry	Techniques that determine the relationship between the forces that stress materials, or mixtures of materials, and the elastic and fluid deformations that they produce
Shear	Deformation induced in a material when its layers are shifted laterally in relation to each other
Shear rate	In a fluid is given by the rate of change in velocity (velocity gradient) with which one fluid layer passes over an adjacent layer
Strain	Degree of deformation by stretch or compression. Generally determined as a percentage increase or decrease of original length
Strain rate	The rate at which a component is deformed by stretching (positive strain rate) or compression for example during contraction (negative strain rate)
Stress	Force per unit area either parallel or perpendicular to the area to which it is applied
Tonic contraction	Longer lasting contraction resulting from sustained contraction of groups of component smooth muscle cells, chiefly through inhibition of actin–myosin ATPase, that generates ongoing tension (tone) within the wall of the structure in which it operates
Turbulent mixing	A condition in which widespread mixing results from the ongoing appearance of unsteady vortices and areas of folding and kneading on many length scales that interact with one another other
Viscosity	The ratio of the force that is applied to a liquid to the longitudinal movement of the fluid, i.e. shear, that it generates
Viscoelasticity	Time-dependent property of materials that exhibit the characteristics of solid behaviour, i.e. elasticity and of liquid flow, i.e. viscosity when undergoing deformation. The elastic component of digesta is thought to result from interaction of the contained particles

Introduction

The muscular wall of the mammalian small intestine must accomplish a number of tasks by generating movement of the contents. Firstly, it must promote mixing so as to bring food substrates into contact with enzymes secreted from single sites, e.g. the opening of the pancreatic duct and

from distributed sites, e.g. the succus entericus and to transfer the products and other soluble nutrients to the wall of the gut for absorption. Secondly, it must generate flow so as to move the contents sequentially through the various components of the small intestine. Ultimately mixing must allow enzymatic secretions to access both solid and soluble substrates and the products of their actions, along with other soluble nutrients, to access mucosal sites of absorption. Before enzymes and substrates can interact, mixing must take place on a molecular scale by inter-diffusion, but this process is slow over longer distances (France et al. 1993). It is necessary to augment diffusive mixing and the overall rate of digestion if the animal is to be able to process sufficient food for its daily needs and to effectively compete with others for scarce nutrients.

Mixing can be expedited by generating relative movement, i.e. advection, between the fluids containing enzymes and substrates to increase their area of contact thus allowing diffusion to take place over a larger area and enzymes to diffuse a lesser distance before encountering solid or dissolved substrate. The efficiency with which fluids can be mixed increases when the inertial force that is transferred to the contained digesta by contraction in the intestinal wall is great enough to mix them and not rapidly reduced by internal friction as a consequence of their viscosity. The ratio between the inertial force and the frictional, i.e. viscous, forces opposing it in digesta is termed the Reynolds number, a dimensionless number whose magnitude indicates the ease of advective mixing. Hence, turbulent mixing, i.e. widespread randomly orientated advective mixing, cannot be established when the Reynolds number is low, i.e. below 2,300 (Takahashi 2011). However, the forces that are generated within the intestinal lumen by contraction of smooth muscle are low and the digesta sufficiently viscous (Dikeman et al. 2007b) to prevent the establishment of turbulent mixing. Hence the magnitudes of Reynolds numbers for overall flow during segmentation (<0.5) and peristalsis (0.085–0.21) are low in the small intestine (Takahashi 2011) as are those of pendular contractions (Melville et al. 1975). Under such conditions, any increase in the area of contact between secretions and chyme is generally reduced to simple kneading and folding of the interface between them in a coarse manner similar to that seen in the swirling flow of a river.

Whilst our understanding of the electrophysiological events that govern tonic (Lentle et al. 2013b) and phasic (Brookes and Costa 2002; Sarna 2008) contractions in the small intestine has increased over the last hundred years, our understanding of the processes by which these contractile events bring about mixing and propulsion of the gut contents, is still incomplete. However, recent advances in the rheological characterisation of digesta (Shelat et al. 2015), in the study of motility (Dinning et al. 2011b; Huizinga et al. 2014; Janssen and Lentle 2013), in theoretical fluid mechanical modelling (Wang et al. 2009, 2010), in direct modelling of the fluid mechanical consequences of real contractile movements quantified by spatiotemporal maps (de Loubens et al. 2013; Fullard et al. 2014) (see below) in conjunction with an adaptation of dye dilution techniques used by chemical engineers (Levenspiel 1999) for use in ex vivo preparations of gut (Janssen et al. 2007) have allowed verifiable quantitative evaluation. This review summarises these recent advances, explains the associated fluid mechanical and chemical engineering concepts and outlines a number of areas that require further research.

Flow along the intestine

The small intestine is a tubular structure. Early workers assumed that flow within it would be similar to that through a simple cylindrical tube (Latham 1966). Thus, were the flow constant, the contents viscous, and the ratio of inertial (propulsive) to viscous (frictional) forces within the contents (i.e. Reynolds numbers) low, flow would be laminar. In laminar flow within a tube, the bulk of the lumen is occupied by a symmetric concentric series of cylindrical laminae of fluid with the rate of longitudinal flow of the fluid in each lamina inversely proportional to its distance from the axis of the tube with the mean speed of flow proportional to the pressure gradient across the ends of the tube (Steffe 1996).

Whilst laminar flow does occur in the small intestine, its symmetry is modified by the variations in the geometry of the intestinal tube. Hence in regions where the lumen is not fully distended, its shape may be ellipsoidal, the long axis of the ellipse being in line with the plane of the mesenteric attachment (Lentle et al. 2012). Further, lumen fill is not uniform and there are generally regions where the lumen is more or less empty causing the mid-portion of the anterior and posterior walls of the tube lie in contact with each other, so that the cross-sectional profile becomes dumbbell shaped and can act as a potential reservoir. Again the small intestine forms a series of crescentic coils as a result of differences in the lengths of its mesenteric attachments and the confined nature of the peritoneal cavity in which they are contained (Arun 2004). The flow of chyme through the intestine is initiated by a series of propagating or static phasic, i.e. short-lived, contractile events that occur at intervals along its length and locally constrict the lumen. Hence fluid may simply be displaced by static radial (segmentation) or longitudinal (pendular) constriction, or driven ahead of propagating radial (segmentation or peristaltic) constrictions, the latter being termed ‘distributed pumping’ as flow along the lumen can be induced at any point along its long axis. Given this, and the fact that the contained chyme does

not form a continuous column of fluid along the lumen, flow will be inconstant. Thus the pressure generated within the lumen by such contractions, and the consequent flow from higher to lower pressure, will not be sustained or propagated over long distances. Again, propagating constrictions such as those generated by peristalsis will generally be unlikely to generate steady and orderly laminar flow over significant lengths of small intestine.

It is also possible that fluid can be displaced from one segment of the small intestine to another by a generalised change in wall tension, i.e. widespread tonic contraction. Hence, flow will be initiated in a manner similar to the well-known phenomenon in the stomach where a sustained increase in gastric fundal tone causes displacement of gastric chyme into the proximal duodenum (Pallotta et al. 1998). Whilst tonal change may secure the transit of chyme from one segment to another, the rate at which tone changes (Azpiroz and Malagelada 1985) and the corresponding rate of flow are slow. This would again preclude the development of significant turbulence (Dillard et al. 2007) and restrict mixing to advection by folding.

The overall rates of flow of the unabsorbed elements of chyme can be determined using solid and liquid phase markers (Stevens and Hume 2004). However, the inconstant geometry of the small intestinal lumen, the inconstant lumen fill, the irregular spacing and timing of contractile events and the absorption and secretion of significant amounts of water can all confound the accurate assessment of local flow rates.

Quantifying mixing

It is currently not possible to directly visualise the pattern of mixing within the lumen and hence to quantify either the rate at which the area of contact of enzymatic secretions with food substrates increases, or the mean distance through which one substance must diffuse to interact with another, without significantly altering the environment within the lumen. Hence it is necessary to use indirect methods. The traditional indirect method developed by engineers is to infer the rate at which mixing is taking place in a system of pipes from the pattern of elution of a uniformly dyed pulse of fluid that has been injected into and traversed the system (Levenspiel 1999).

Early workers suggested that the small intestine could be viewed as a series of vessels termed continuous flow stirred tank reactors (CSTRs) though which chyme flowed continuously and in which there was instantaneous mixing in the radial and axial dimensions (Penry and Jumars 1987). Chemical engineering principles dictate that, as the number of successive CSTRs along a given length of a tube increases, the rate of mixing per unit length and hence the efficiency of enzymatic digestion will increase. Hence, when a length of small intestine contains a succession of closely packed CSTRs, the rate at which admixture with enzymes and at which consequent enzymatic digestion takes place would be maximised, and the length of intestine necessary to extract and absorb nutrients would be minimised (Penry and Jumars 1987).

If a dye marker is introduced into the fluid flowing into a mixing system that can be viewed as a succession of virtual CSTRs, the temporal pattern of elution of the marker from the system is a characteristic of the number of CSTRs in the sequence (Levenspiel 1999). Thus, for example, if mixing in a segment of intestine was equivalent to a single CSTR then the relative concentration of a pulse dye marker exiting the segment would decline monotonically from an initially high value. Conversely, if mixing was equivalent to that from a number of CSTRs in series, then the profile of the change in the relative concentration of the pulse dye marker exiting the system would be more pulsatile, i.e. parabolic in configuration. Hence it is possible to infer the efficiency of mixing in a system containing an unknown number of functional CSTRs from the elution profile of a dye marker.

Quantifying the properties of chyme and the spatial and temporal disposition of contractions

For the fluid mechanical consequences of contractile activity in the walls of the small intestine to be reliably calculated or modelled, both the physical properties of the contained chyme and the contractile activity in the wall must be quantified. Both are difficult to assess in vivo, but the adaptation of existing methods and the development of a range of novel techniques have allowed this to be done.

Rheometry

The bulk properties of the particulate suspension that is chyme differ from those of the watery fluid in which the particles are suspended (Takahashi and Sakata 2004). The flow that is induced in a watery fluid is directly and linearly proportional to the (shear) force that is exerted on it hence its viscosity, i.e. the frictional (shear) force that opposes fluid flow, is constant (Steffe 1996). However, the flow of a system of particles suspended in a fluid phase, such as is found in chyme, occurs more readily when shear forces are high, than when they are low. Thus the apparent viscosity of chyme is reduced as the shear force that is applied is increased, a condition that is termed pseudoplasticity. This reduction in viscosity is thought to occur as a result of shear forces causing the long axes of particles to become aligned in the direction of flow so that adjacent particles

are less likely to come into contact with each other so that friction is reduced and flow takes place more readily. For this reason it is important to determine the ease with which chyme flows, i.e. its apparent viscosity, under conditions where the shear forces that are exerted on it lie within the physiological range that is generated during contraction, and to determine the extent of (pseudoplastic) variation in apparent viscosity within this range. Hence the apparent viscosity of whole small intestinal chyme has been measured during flow through a tube (tube viscometry). This technique allows the long axes of the particles contained within the fluid to become aligned in the manner described above (Takahashi and Sakata 2004).

However, it is also necessary to determine the apparent viscosity of chyme when such particulate alignment has not been established as this would represent the situation when the shear force is first applied, i.e. at the start of a phasic contraction. The use of a rheometer allows the apparent viscosity of chyme that contains finer particles to be determined at over a range of shear rates that are generated during normal contractile activity. This can be done in a controlled environment between closely spaced parallel plates (Lentle et al. 2002). However, when the chyme contains numbers of particles that are large enough to bridge the gap between such parallel plates, viscosity must be determined between the vanes of a mixer (Dikeman et al. 2007a). The use of the rheometer is also important when digesta contains a sufficient number of particles that they can enmesh to form a network within it, i.e. a gel, when no mixing is taking place, which is dispersed as flow is initiated and the component particles orientate with flow (Bornhorst et al. 2013). In the terminal ileum and large intestine the proportion of solid particles in chyme can become sufficiently high to cause the enmeshing to persist after stress is applied so that the chyme then exhibits some solid-like behaviour, i.e. viscoelasticity. The use of specialised rheometric techniques such as creep rheometry (Lentle et al. 2006) allows such behaviour to be quantified.

Given that secretions are added and water absorbed during the transit of digesta through the intestinal lumen (McDonald et al. 2001) its rheometric properties, i.e. its apparent viscosity and its viscoelasticity, will change and thus must be determined in a series of samples taken at various points along its length. The rheological properties of digesta determined by such techniques, describe the flow of particulate suspensions as a whole and can be related to the microstructure of contained dietary particles (Shelat et al. 2015). When the physical properties of chyme are to be evaluated on a scale that is commensurate with the movements of small mucosal structures such as villi, then the motions of the fluid and particulate components must be separately evaluated in situ. Again this must be done at a series of locations around these structures using micro-rheometric techniques. The latter techniques infer local viscosity and viscoelasticity from the Brownian movement of micro or nano-sized particles distributed within the system (Lim et al. 2013b).

Spatiotemporal mapping

Electrophysiological studies have provided a wealth of detail regarding the timing of intestinal contractions by mapping the spread of the slow wave (Lammers 2005), the regular electrical pacing wave that occurs throughout the intestine, as well as the direction of travel of the action potentials that signify muscle contraction, i.e. spike patches (Lammers and Slack 2001). However, such parameters cannot quantify the movements of the intestinal wall that they induce, i.e. the architecture of wall movement during the contractile process.

The principal means by which the diverse movements of the intestinal wall have been quantified is by spatiotemporal mapping of the surface of the intestine (Benard et al. 1997; Hennig et al. 1999; Janssen and Lentle 2013). The quantitative data obtained from spatiotemporal maps can then be directly incorporated into 'real time' models (de Loubens et al. 2013; Macagno and Christensen 1981) and their validity tested against the outcome of dye marker studies (de Loubens et al. 2014; Janssen et al. 2007).

Spatiotemporal mapping is able to quantify, frame by frame, movements of all visible parts of the intestinal wall along a length of intestine in a succession of video images. Hence, for example, the radial dimensions of the small intestine at a particular site can be determined by counting pixels between the upper and lower boundaries of the intestinal image at that site and compared with the dimensions at the same site in the subsequent video frame, i.e. over time (Janssen et al. 2007). Similarly, changes in longitudinal dimensions between particular marks on the surface, e.g. points on a vascular tree, can be determined by counting pixels between these distinctive structural features in successive frames. Given that the frames are taken at specific time intervals, this information can be translated, time interval by time interval, into a graph of radius or rate of a change in relative length at a succession of points along the intestine. Hence the diameter or relative distance between distinctive points on the wall of the small intestine for specific pixels that correspond to a set location and time (strain rate) are coded as a colour or shade of grey. This process, conducted over the time period of the experiment, produces a spatiotemporal map (Figs. 1, 2) on which the dimensions, durations, form and speed of propagation of contractile or expansile events are quantified (Janssen and Lentle 2013). These maps not only afford a temporal sequence of changes in the shape, length, and morphology of the leading and following edges of contractions, and of

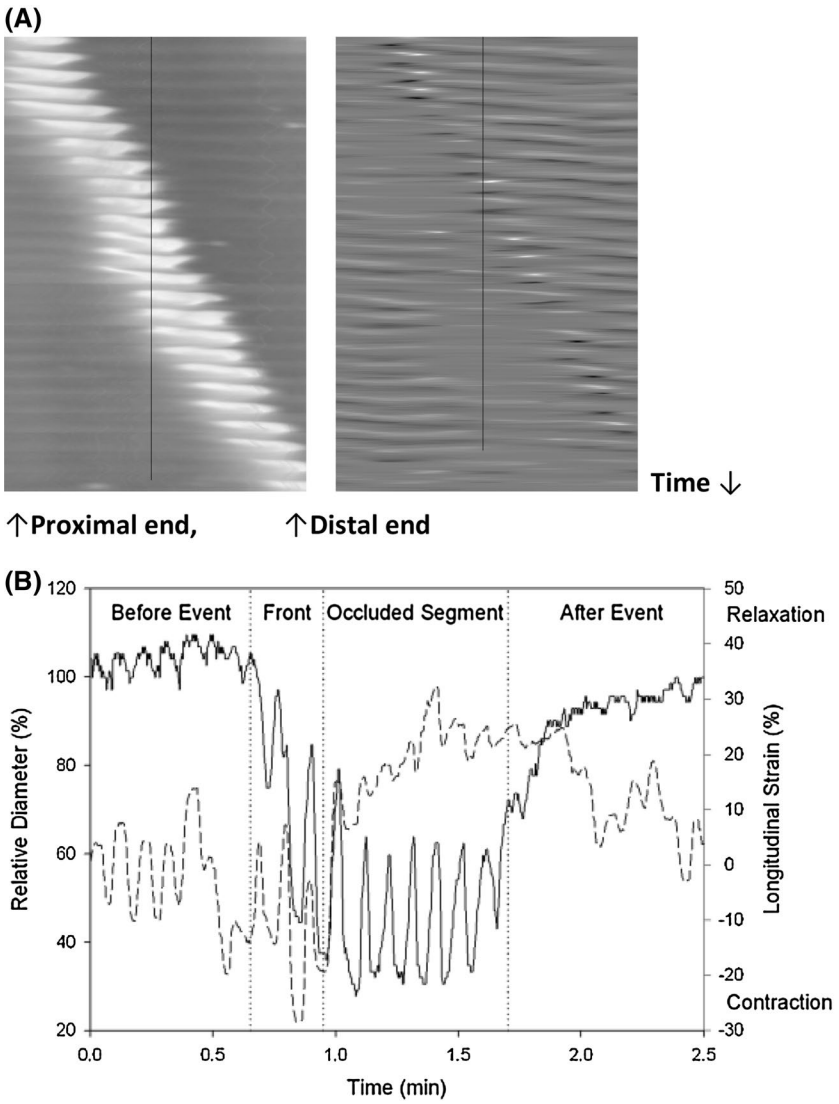

Fig. 1 Spatiotemporal maps showing coordination between circular and longitudinal muscle contraction during peristalsis in the small intestine (modified from Lentle et al. 2008). **a** Spatiotemporal maps of circular (D map) (*right*) and longitudinal (L map) (*left*) contraction during a peristaltic event. The *white areas* indicate contraction, the dark areas relaxation. The *two black vertical lines* mark the same set point on the length of intestine for the purposes of comparison. Contraction of the longitudinal muscle can be seen to travel in the leading edge of the region of circular muscle as it transits along the length of the intestine. Note the variation in length of contraction, the commencement and termination of contraction and duration in successive contractile bands. **b** Coordination between D (*solid line*) and L (*dashed*) maps during a peristaltic event. Values for percentage change in diameter (*solid line*) and percentage change in longitudinal strain (*dotted line*) were taken from the *two black vertical lines* drawn on the map **a**. Contractions are seen to be in phase and the D map amplitude is comparatively large during the peristaltic event

the duration, frequency and speed of propagation of each macroscopic contractile event, but also of the component micro-contractions that result from sequential activation of component groups of muscle cells during a particular type of contraction. This allows for the detailed analysis of the spontaneous variation in each parameter and the importation of the data into computer models to simulate flow and mixing outcomes of real sequences of contractile events in real time (de Loubens et al. 2013). Further, as noted hitherto, the fidelity of such models can be validated by comparing mixing outcomes of the model with those obtained following the transit of a pulse of dye marker through the length of small intestine over the time period during which the spatiotemporal mapping was conducted (de Loubens et al. 2014).

Spatiotemporal mapping, like all physiological methods, has as number of limitations, notably in regard to its use with ex vivo preparations of the intestine. The excision of a segment of small intestine that is necessary for such preparations, severs the descending inhibitory neural pathways at the proximal end of the segment and ascending excitatory neural pathways at the distal end of the segments as well as all extrinsic nerve supplies. Hence the frequency of intrinsically mediated events may be heightened at the proximal end of the preparation whilst extrinsically mediated contractile events are eliminated (Bornstein et al. 2002).

Quantification of longitudinal shortening during contractions, i.e. percentage strain between markers that have been applied to the intestinal wall (Lammers 2005), can be useful in calculating the movement that it imparts to chyme within the lumen, i.e. the distance that deformation from shear propagates into the lumen contents from the wall of the intestine (Fullard et al. 2014), but provides no information regarding the sites at which the underlying contractions occur. However, L maps of the rate of longitudinal shortening, i.e. strain rate, allow regions where smooth

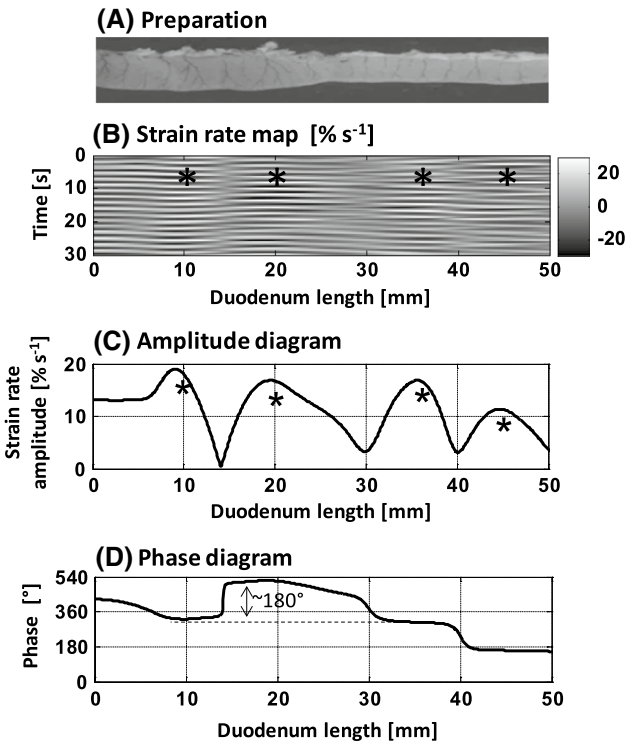

Fig. 2 Spatio-temporal organisation of pendular activity in the proximal duodenum of the rat (adapted from Lentle et al. 2012). **a** Shows the length of proximal duodenum with the pylorus positioned on the *left* and the pancreatic duct to the *right*. The strain rate map **b** shows variation in phasic pendular activity over 4 spatial domains. Hence the *light regions* of negative strain rate indicate a lengthwise contraction and the *dark areas* positive strain rate indicate stretching. The areas of alternate contraction and stretching do not propagate but remain at around the same point along the length of the duodenum which is termed a domain (marked with *asterisk*). **c** Shows the variation in the amplitude of strain rate at various points along the length of the duodenum. The position of the maximum variation in amplitude (marked *asterisk*) varies within each domain. **d** Shows the variation between successive domains in the timing of the peaks and troughs (phase angle) (generally about 180°)

muscle is contracting (regions of positive strain rate) to be distinguished from regions where the muscle is relaxed and consequently undergoing stretching (negative strain rate).

The data from a given L map only track change in strain rate through time along a chosen axially orientated line of interest (LOI) in the video frame and are restricted in this respect. However, the video data can be repeatedly reanalysed with the LOI repositioned at various positions across the width of the intestine. This allows a two-dimensional profile of strain rate to be built up across the entire width of the segment.

High-resolution fiberoptic manometry

The local changes in pressure within the intestinal lumen that accompany phasic contraction can be quantified by manometry (Bampton et al. 2001) both in vivo and in segments maintained ex vivo (Arkwright et al. 2009), but sensu strictu this technique cannot directly determine the causative pattern of muscular action. The modern fibre-optic, high-resolution, manometric techniques employ closely longitudinally arrayed sensors that avoid aliasing (Dinning et al. 2013). This allows for more detailed evaluation of intraluminal pressure generated by individual contractions. Recent work showing that individual colonic contractile events identified on D maps can be correlated with discrete propagating changes in pressure (Dinning et al. 2011a) speaks for the sensitivity of the method. Hence the data that is produced could also be used in models to predict luminal flow. The technique suffers from a similar problem to that of a spatiotemporal L map taken along a single line of interest in that the device only provides pressure data from each sensor in the longitudinal array of sensors at a single point within the circular cross section of the lumen. However, combination of this data with spatiotemporal D mapping allows useful maps to be produced (Dinning et al. 2011a). To date the bulk of published work has been conducted on the pattern of lumen pressures in the colon.

Results from these and other methods

The physical properties of small intestinal chyme

Small intestinal digesta comprises a viscous (Dikeman et al. 2007a) and shear thinning, i.e. pseudoplastic (Lentle and Janssen 2008; Lentle et al. 2002) particulate suspension that may behave as a weak gel (Bornhorst et al. 2013; Lentle et al. 2005). As discussed hitherto, the tendency to form a weak gel occurs when there is a sufficient volume of particles within the fluid component of chyme to interact and form a matrix when it is static but which weakens or dissipates during flow.

The thinning of digesta a high shear rates, i.e., pseudoplasticity, may promote slip at the wall. Thus, chyme that is situated at the periphery of the lumen in close proximity to the moving wall will be exposed to greater shear and become correspondingly less viscous, flow more readily and be more readily mixed (Lentle and Janssen 2008) than is the material that occupies the central lumen which is not exposed to such to levels of shear. However, the extent to which shear thinning takes place depends upon the duration and extent of movement between the wall and the contents as well as the composition of the chyme. When the movement is small and the proportion of particles is too low to form a gel, flow will take place only briefly and particle alignment will not develop. Hence apparent viscosity will be to all intents unchanged so that flow is in constant proportion to the force applied. Conversely, when the

movement is small and the proportion of particles is high, the gel structure may persist for the duration of the contraction so there is no flow, only elastic distortion and recovery.

Mixing and the form and distance of propagation of small intestinal contractions

The process of intestinal mixing is time dependent in that the rates at which particular types of phasic contractile events occur varies between the fed and the fasting state (Sarna 1985). It also varies with the nutrient composition of the meal (Siegle and Ehrlein 1988). During the post-prandial period, the number of propulsive contractions, i.e. peristalses, are reduced whilst the number of stationary and propagating segmentative and pendular contractions are increased (Husebye 1999; Sarna et al. 1983). The timing and action of the latter types of contraction would seem to indicate that they are better suited to the induction of mixing than to the propulsion of the lumen contents. As was noted by Huizinga et al. (2006), were peristalsis to proceed in an uninterrupted fashion then 'the small intestine would be empty in minutes not in hours as required for absorption'.

The small intestine exhibits an array of phasic contractile activities that differ in form, i.e. the relative contributions of circular and longitudinal muscle contraction to the particular activity (Stevens et al. 2000) and in their rates of propagation (Sarna 1985). Hence phasic contractions may occur independently in each of the two muscular layers or become coordinated to produce peristaltic movements (Stevens et al. 2000). Two types of rapidly propagating 'ultrapropulsive' contractions (giant migrating and retrograde giant contractions), which are under extrinsic neural control (Husebye 1999) are reported along with various types of static or more slowly propagating rhythmic phasic contractions (Sarna 1985) whose timing may be governed by the frequency of the slow wave (Huizinga and Lammers 2009; Lammers 2005; Lammers et al. 2002) or by local distension (Donnelly et al. 2001).

Pendular activity, a complex swaying activity of the intestine (Bayliss and Starling 1899; Cannon 1902, 1912) occurs both during the post-prandial period and the inter-meal interval. It was originally thought (Bayliss and Starling 1899), and latterly shown, to result from short-lived radially asymmetric contraction of limited lengthwise domains of the longitudinal musculature at the slow wave frequency (Lentle et al. 2012). The fact that it is not extinguished by neural blocking agents such as tetradotoxin (Lentle et al. 2012) suggests it is myogenic in origin.

Segmentation, a pattern of short-lived cyclic radial constrictions in successive limited lengthwise domains, that are each out of phase with their neighbours (Cannon 1902, 1912), is reported as the dominant form of contractile activity during the post-prandial period (Schemann and Ehrlein 1986) and thus may be particularly important in securing mixing. Whilst similar short-lived standing and propagating cyclic radial constrictions have been shown in ex vivo preparations (Gwynne et al. 2004) they do not occur in extensive alternating arrays. It has been generally considered that segmentation activity results from the isolated contraction of radial musculature (Cannon 1912) and is myogenic in origin (Huizinga et al. 2014). However, recent in vivo spatiotemporal mapping studies in the laparotomised post-prandial pig showed that non-propagating arrays of segmentation contraction in the terminal ileum consisted of alternating zones of radial and longitudinal constriction (Janssen et al. 2014). Further that the administration of remifentanyl, a pharmacologic agent that is known to suppress inhibitory inputs from the ENS (Galligan and Vanner 2005), caused this pattern of segmentation to propagate.

When static pendular and segmentation contractions of short duration occur in sites where the proportion of solids in digesta is high, e.g. in the terminal ileum, as was noted hitherto, the viscoelastic properties of chyme may oppose its displacement (Lentle et al. 2006; Lentle and Janssen 2008) and reduce the efficiency of mixing. Correspondingly, whilst pendular and segmentation contractions make up the bulk of post-prandial contractile activity in the upper small intestine (Husebye 1999; Sarna et al. 1983), more sustained events such as peristalses, though relatively infrequent, may contribute significantly to the mixing of viscoelastic chyme. This is not to say that mixing would be enhanced by the propulsion of one mass of chyme into another, given that the propagation of post-prandial contractile events are coordinated by slow wave activity (Huizinga and Lammers 2009; Lammers 2005; Lammers et al. 2002), such events are unlikely.

The propulsive nature of peristaltic contractions may be viewed as a disadvantage in sofar as maximising mixing and absorptive efficiency in a given length of intestine. However, whilst all peristaltic contractions propagate, the distance of this propagation varies (Huizinga et al. 2006) and is relatively short during the post-prandial period. Huizinga et al. (2006) suggest that limitation in the distance over which peristalsis propagates may allow for nutrient absorption. Limitations in distance of propagation would not solve the dilemma of transit versus absorption unless some means of reversing the distal transit was to operate, e.g. reverse peristalsis. Logic would dictate that retrograde small intestinal peristalses (RPs) would impart maximal efficiency were they to occur on a one to one basis with similar distally propagating events during the post-prandial period. However, reverse small intestinal peristalses (RPs) are relatively infrequent (Bayliss and Starling 1899; Cannon 1898, 1902) particularly in the proximal intestine

(Ahluwalia et al. 1994; Kerrigan et al. 1991). Again, whilst the number of RPs increase post-prandially (Björnsson and Abrahamsson 1995), they seem to occur chiefly in concert with a similar distally propagating events, the two originating at a single site with pacemaker activity (Castedal et al. 1998; Seerden et al. 2005).

Peristaltic contractions each consist of a zone of lumen distension travelling in advance of a zone in which the lumen is constricted (Benard et al. 1997). There has been considerable discussion as to the cause of the distension (Wood and Perkins 1970) notably, whether it results from distension of a relaxed foregoing band of radial smooth muscle by chyme that accumulates in advance of the propagating constriction, or from active contraction of foregoing longitudinal musculature with corresponding widening of lumen diameter (Stevens et al. 2000). Recent spatiotemporal mapping results indicate the latter (Lentle et al. 2007) (Fig. 2). At either event, modelling studies that incorporated physiological flow rates, contraction profiles and viscosity of chyme with flow conditions characterised by low Reynolds numbers, showed that a region of augmented lumen volume travelling in advance of a peristaltic wave of constriction would have little effect on local fluid dynamics or on mixing (Love et al. 2012).

The radially constricted segment of each peristaltic event appears to consist of a succession of rapidly propagating radial constrictions, i.e. contractile bands (Fig. 1a), with each band progressing slightly further than the previous in the direction of propagation (Fig. 2). The individual bands are thought to result from propagation within electro-physiologically conjoined groups of smooth muscle cells, i.e. 'spike patches'(Lammers 2000), the direction and extent of their propagation sometimes differing from those of slow waves (Lammers and Slack 2001).

It is noteworthy that the slow modulation of tone and the resulting change in wall compliance and lumen volume, may also alter the extent to which peristaltic and other phasic contractions and permanent mucosal folds, e.g. plicae circulares (Junqueira and Carneiro 2005) can occlude the lumen. Hence muscarinic (Lin 2006) and nitrergic (Tonini et al. 2002) modulation of circular or longitudinal muscle tone may widely influence the relative diameter or the length of the lumen (Lentle et al. 2013b). More widespread alterations in tone are thought to underlie the action of the jejunal and ileal 'brakes' that slow the passage of chyme though the jejunum (Lin and Wang 1996) and ileum (Cserni et al. 2005). Similarly, widespread modulation of tone in the wall of the distal small intestine, concomitant with the operation of the ileocaecal (Cserni et al. 2005) or ileo-colic (Malbert 2005) sphincters, can alter the volume of the distal lumen (Hurst 1931) and cause both particulate (Khosla et al. 1989; Wilding et al. 1991) and liquid (Spiller et al. 1987) phases of chyme to accumulate in the terminal ileum.

Mixing and the velocity of small intestinal contraction

Successions of propagating phasic contractions of smooth muscle, such as in peristalsis and propagating segmentation, are undoubtedly able to induce flow. However, the slow overall speed with which smooth muscle contracts (shortening velocity of around 2 % per unit length s^{-1}) (Gordon and Siegman 1971) and the overall rates at which peristalses (between 0.5 and 4.3 cm min^{-1}) (Kellow et al. 1986) and segmental contractions (1–2 cm min^{-1}) (Grivel and Ruckebusch 1972) propagate along the small intestinal walls are such that overall shear rates will be low. Hence the flow that is induced in the contents of the lumen is correspondingly reduced, especially in situations where chyme contains more particles and less fluid and is proportionately more viscous and viscoelastic, e.g. in the distal ileum (Lentle and Janssen 2008; McDonald et al. 2001).

It is noteworthy that the overall rates of propagation of peristalses (Lammers et al. 2002) and other small intestinal contractions that occur during the post-prandial period generally lie below that of the electrical slow wave (9 mm s^{-1}) (Angeli et al. 2013) perhaps from ICCs or myocytes in successive spike patches failing to respond to a single advancing slow wave and responding to every second or third (Lentle et al. 2008; Pescatori et al. 1980).

Whilst the velocity of smooth muscle contraction within a spike patch is significantly higher (85 mm s^{-1}) (Lammers 2000) than the overall rates of propagation, it is only greater by one order of magnitude. For Reynolds numbers to be augmented to a level that is conducive to the generation turbulent mixing it would need to greater by several orders magnitude (Lentle et al. 2002). It is nevertheless conceivable that the higher velocities of propagation within spike patches could augment non-turbulent mixing, but a number of factors render it unlikely. Firstly, the directions of propagation of spike patch contractions vary spontaneously (Lammers and Slack 2001) and are not necessarily aligned with the overall direction in which the contractile event is propagating so that this rate would not be sustained in that direction. Secondly, the velocity with which smooth muscle contracts within the muscular coat of the small intestine is not efficiently transmitted through the mucosa. Recent work shows that there is redundancy of the mucosa (Egorov et al. 2002) and laxity of the submucosa (Lentle et al. 2013a) such that the muscular coat can move independently of the mucosa over short distances. Thirdly, the action of short-lived events such as conduction within a spike patch is particularly likely to be compromised by the viscoelastic nature of the digesta.

In sum it appears that the overall velocities at which phasic contractions can propagate lead to Reynolds numbers that are incompatible with the generation of turbulent mixing (Lentle et al. 2002; Takahashi 2011) and are only sufficient to generate localised stretching and folding of chyme, chiefly in the layers that are adjacent to the intestinal wall.

Mixing from inconstancy of small intestinal contractions

Work with a number of simple hydrodynamic models suggests that cyclic longitudinal contractions are likely to generate regular patterns of circular flow termed streamline cells (Melville et al. 1975). Were such symmetrical streamline cells to occur in vivo they would cause little ongoing mixing, the lumen contents being repeatedly transposed from the lumen to the wall and back again. However, ongoing variation in the site and in the form of these flow cells resulting from spontaneous variation in the site and character of contractions in the wall of the intestine would be likely to augment the rate of mixing in comparison to that from repeated symmetric transposition. Similarly, variation in the pattern of folding and kneading from inconstancy of spontaneous contractions generate will also augment mixing. Fluid dynamic models that do not incorporate such variation may therefore underestimate the extent of non-turbulent mixing. (Lentle et al. 2002; Takahashi 2011).

A number of physiological phenomena that may contribute to the inconstancy of peristalsis are evident on spatiotemporal mapping (Fig. 1). The contraction and relaxation of smooth muscle are known governed by separate processes, the tightly regulated action of myosin light chain kinase, i.e. onset governing the former, and myosin light chain phosphatase, i.e. 'off-set' governing the latter (Makhlouf and Murthy 2006). A body of research has shown that two process may be regulated independently (Makhlouf and Murthy 2006). Hence spatiotemporal mapping of ex vivo segments of ileum (Fig. 1) indicates that the contours of the leading and following edges of an annular constriction that are generated during a phasic contractile event are not symmetrical (Sarna 2008; Schulze-Delrieu 1999) so that the folding and kneading actions generated at the leading and trailing edges are correspondingly varied. Again dyssynergia in the onset, duration and offset of the component longitudinal and circular contractions of a peristaltic event (Fig. 1) may further contribute to asymmetry at the leading and trailing edges (Lentle et al. 2007). Further, there is inherent asynchrony on a smaller scale in the sequence in which component smooth muscle cells are activated at the front of a given wave of contraction. Hence, for example, spatiotemporal maps show an ongoing inconstancy between the territories of adjacent waves of phasic contraction in the rat duodenum (Fig. 2) (Lentle et al. 2012) that likely results from slight differences in the directions and areas through which the muscle contractions propagate, i.e. spike patches (Lammers and Slack 2001).

It is noteworthy that the physical properties of the lumen contents may accentuate any asymmetry generated by the contractile process. Hence, provided that there is a sufficient variation in shear rate, the pseudoplastic properties of small intestinal chyme (Lentle et al. 2002, 2005) may cause the apparent viscosity to be lower and ease of flow to be correspondingly greater in the faster contracting leading edge than in the more slowly relaxing following edge of a peristaltic contraction.

Quantification of mixing by dye elution and modelling

It is important to recognise that, owing to the difficulties in visualising the lumen contents in a living length of gut (with the exception of a few low-resolution dynamic barium X-ray contrast studies) (Rao et al. 1996; Schemann and Ehrlein 1986), there are few experimental preparations that allow fine-scale mixing within the small intestine to be directly visualised and quantified (Schulze and Clark 2008). The bulk of the evidence regarding mixing is therefore indirect and in many cases does not entirely recapitulate conditions within the living intestine. Hence, for example, the use of viscous pseudoplastic solutions, e.g. 1 % guar gum (Janssen et al. 2007) rather than real chyme, in ex vivo preparations is necessary to avoid settling out of particulate matter, but can only recapitulate mean viscosity and will not provide a full picture of the fluid dynamic effects of particulate matter.

Again the bulk of our current understanding is derived from two-dimensional modelling of flow characteristics using various mathematical techniques and from dye dilution studies. The use of three-dimensional models would be preferable but, as was discussed in the methods section, the modern techniques have inherent shortcomings in the acquisition of three-dimensional data. Whilst the results from many two-dimensional models have been published, a number have incorporated parameters that are not based on real contractile data, a particular example being the use of symmetric geometric functions to describe the occlusive profile of peristaltic constriction (Burns and Parkes 1967; Latham 1966). We limit our current discussion to those models that have incorporated real physiological data. Currently, these are limited in scope, both in regard to the segments of the small intestine from which the data is gathered, and the types of contraction that are taking place. It is noteworthy that, to date, no studies have determined the pattern of dye elution from lengths of the small intestine that are undergoing segmentation.

Models based on 'real time' contractile data obtained from ex vivo segments of rat duodenum maintained in

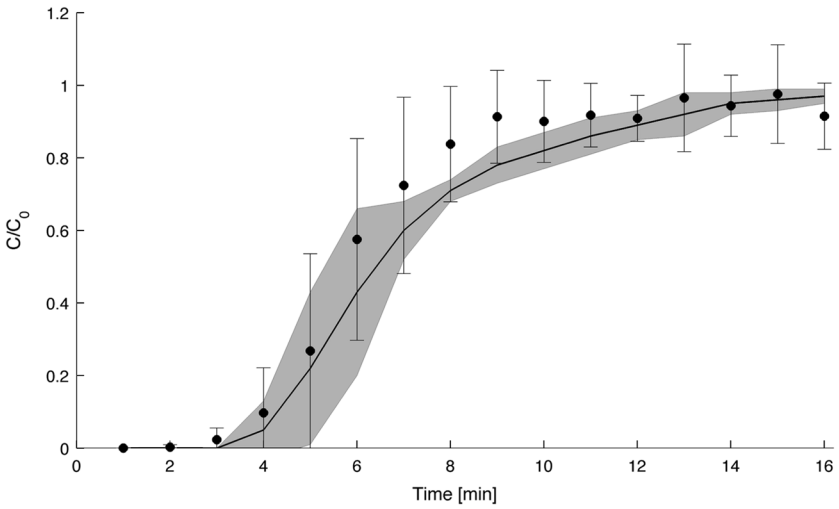

Fig. 3 Comparisons of residence time distribution of a dye step perfused into a living ex vivo preparation of proximal duodenum of the rat with the response (*F* curve) predicted by incorporating real-time contractile data into a Lattice Boltzmann model (From De Loubens et al. 2014). Sequences of real longitudinal contractile activity were incorporated into a model that simulated the residence time distribution of the dye marker (*F* curves) after changing from a perfusate that contained no dye marker to one which did (stepped dye input) at time zero (*plain line* mean value for 5 rats, limits of the shaded envelope ± SD). The data obtained from the actual dye perfusion experiment (*plain circles*, *error bars* ± SD) lay within the SD of the output from the model for times up to 7 min after the step, but lay outside the SD of the model at times between 7 and 11 min after step. This discrepancy could be attributed to the absence of phenomena such as mucosal microfolds in the model, that increased mixing at the wall in the real experiment

an organ bath and perfused with saline (de Loubens et al. 2014), indicate that the static, i.e. non-propagating, pendular contractions do not generate high levels of mixing over a short length of small intestine. Similar results were obtained for perfusion with liquids of a range of differing viscosities, i.e. with water (1 mPa s) and with simulated viscosities close to those of small intestinal chyme (10 and 100 mPa s) with consequent low Reynolds numbers (*Re* 0.5–15). However, the effects of pseudoplasticity were not studied (de Loubens et al. 2014). Importantly, the elution profiles of a dye step tracer (de Loubens et al. 2014), which was instilled during the same periods of continuing pendular contraction that were used for the models, were broadly similar to those predicted by the model. Moreover, the widespread lengthwise dispersal of dye along the whole length of the mounted segment of duodenum was similar to that reported with particles of Indian ink during peristaltic activity in the segments of duodenum and ileum of the guinea pig maintained ex vivo (Schulze and Clark 2008). Again, the widespread lengthwise dispersal was similar to that of dye step perfused through a length of possum ileum that was undergoing a mixture of pendular and peristaltic activity (Janssen et al. 2007). It is therefore evident that significant lengthwise as well as radial mixing occurs in the small intestine regardless of the type of contraction. This is not to say that lengthwise mixing within the intestinal lumen is wholly due to the generation of folding and kneading of the lumen contents by simple shear. The levels of longitudinal mixing indicated by the elution profile of the dye tracer from the rat duodenum were somewhat greater than those predicted by the computer simulations based on real-time contraction data (de Loubens et al. 2014). This difference suggests that mixing may be augmented at the wall, i.e. peripherally, by some means other than simple shear generated by contraction (de Loubens et al. 2014) (Fig. 3). The finding fits in with those of a number of other modelling studies showing that mixing is augmented in the peripheral, i.e. epi-mucosal region, when villous movement is incorporated (de Loubens et al. 2013; Wang et al. 2007). However, it is noteworthy that the model published by Wang et al. (Wang et al. 2009) incorporated spontaneous movements of villi which, though previously reported, (Womack et al. 1987) have not been fully quantified in vivo.

Mixing within the central lumen

Models of the propagation of a real peristaltic contraction profile through a simple flexible tube, (Jeffrey et al. 2003; Love et al. 2012) (Fig. 4) based on that in a superperfused ileum maintained ex vivo (Schulze-Delrieu 1999), showed that mixing by folding and kneading, as indicated by disturbance of the horizontal vector of velocity, occurred both in the rear and in advance of the propagating constriction. The relative areas of these disturbances changed with the simulated viscosity of the lumen contents, that at the

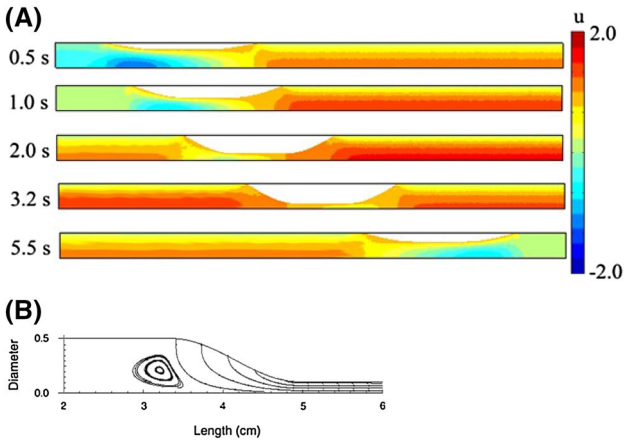

Fig. 4 Showing the output of a finite element matrix model modelling the flow induced by peristalsis. Shows the effect of peristalsis on the horizontal velocity profiles (cm s^{-1}) (colour scale to left marked 'U') of a pseudoplastic fluid flowing through a simple tube (adapted from Love et al. 2012). The sites at the front and rear of the constriction areas where the speed of horizontal flow is reversed, i.e. becomes negative indicate sites of vortex formation or folding. These areas increase in size with degree of wall occlusion, and decrease with increase in slip at the wall but vary little with level of pseudoplasticity. Flow line contours of a vortex formed in the rear of peristaltic constriction from a similar model published by Jeffrey et al. (2003). The profiles of lumen constriction in this and the work by Love et al. (2012) were based on real physiological data

leading edge of peristalsis increasing, and that at the following edge decreasing, when the viscosity of the contents was increased (Love et al. 2012). A similar effect was observed when the level of shear thinning that developed in the lumen contents during the passage of the peristalsis, i.e. pseudoplasticity, was increased (Love et al. 2012). However, there was a general reduction in the areas of mixing when the passage of the chyme across the surface of the mucosa was 'lubricated' for example by a significant layer of mucin (Love et al. 2012).

These models (Jeffrey et al. 2003; Love et al. 2012) (Fig. 4), recapitulated the rates at which the walls moved radially inward, the rates at which contraction advanced along the long axis of intestine within the occluding segment and the profiles of the indentations of real peristaltic events in the ex vivo guinea pig ileum (Jeffrey et al. 2003). Nevertheless, it is likely that the profiles of the leading and tailing edges of the constriction would also vary with the nature of the material in the lumen (Larson and Schulze 2002), with the volume of the bolus (Schulze-Delrieu 1999) and with the underlying tone of the wall, as occurs in the gastric antrum (Gregersen et al. 2006). Similarly the degree of occlusion within the constricting segment may vary with the level of tone, i.e. with the functional diameter of the intestine (Lentle et al. 2013b).

In considering mixing within the central, i.e. peri-axial, region of the lumen it is important to remember that the dispersion of enzymes within the matrices of the solid particles that are contained in chyme will not be enhanced by folding or kneading of the lumen contents (Kong and Singh 2009a, b; Mandalari et al. 2008). Rather, that digestion within particulate matter will be limited by the rates at which water and enzymes can diffuse into and through their solid matrices (Mandalari et al. 2008). These limitations apply to a significant quantity of substrates within a given volume of chyme. Hence, whilst the proportion of solids exiting the stomach varies considerably, significant quantities of solid matter are reported to enter the duodenum in post-prandial chyme (Meyer et al. 1986). Again the relative proportion of solid matter in digesta increases as water is progressively absorbed as digesta traverses the small intestine, rising to around 12 % in the terminal ileum (v/v) (McRorie et al. 2000). Correspondingly, expending the large amount of energy that is necessary to establish localised turbulent mixing would have little effect in augmenting the rate of digestion of a significant proportion of the substrate.

Peripheral mixing and villous crowding

A number of contractions that induce only limited mixing within the central lumen may generate significant peripheral mixing. In the case of peristalsis this may result from the closely situated regions of contraction of longitudinal and circular smooth muscle in the advancing front of the contraction (Lentle et al. 2007). Again, models based on real-time sequences of pendular contractions in the duodenum show they induce mainly peripheral (de Loubens et al. 2013) and little mixing within the central lumen, and thus may be principally concerned with augmenting nutrient absorption at or near the mucosa (de Loubens et al. 2013).

It is possible that, during pendular contractions, peripheral mixing is also augmented by the arrays of villi that cover the intestinal mucosa. Given the low rates at which chyme flows through the lumen (Bueno et al. 1975; Grovum and Williams 1973) and the low levels of shear that are generated during the various contractile movements (Fullard et al. 2014; Jeffrey et al. 2003) it is highly unlikely that mixing could be augmented by vorticeal movements of fluid generated in the lee of projecting rigid villi or by the generation of flow streams along their leading and trailing edges (Lim 2014). This was confirmed by three-dimensional simulations that incorporated data obtained from particle image velocimetry of microbeads in an ex vivo preparation of ileal villi, perfused at physiological flow rates, showing that, whilst movement of fluid along the long axes of villi was generated, the speed was so slow that

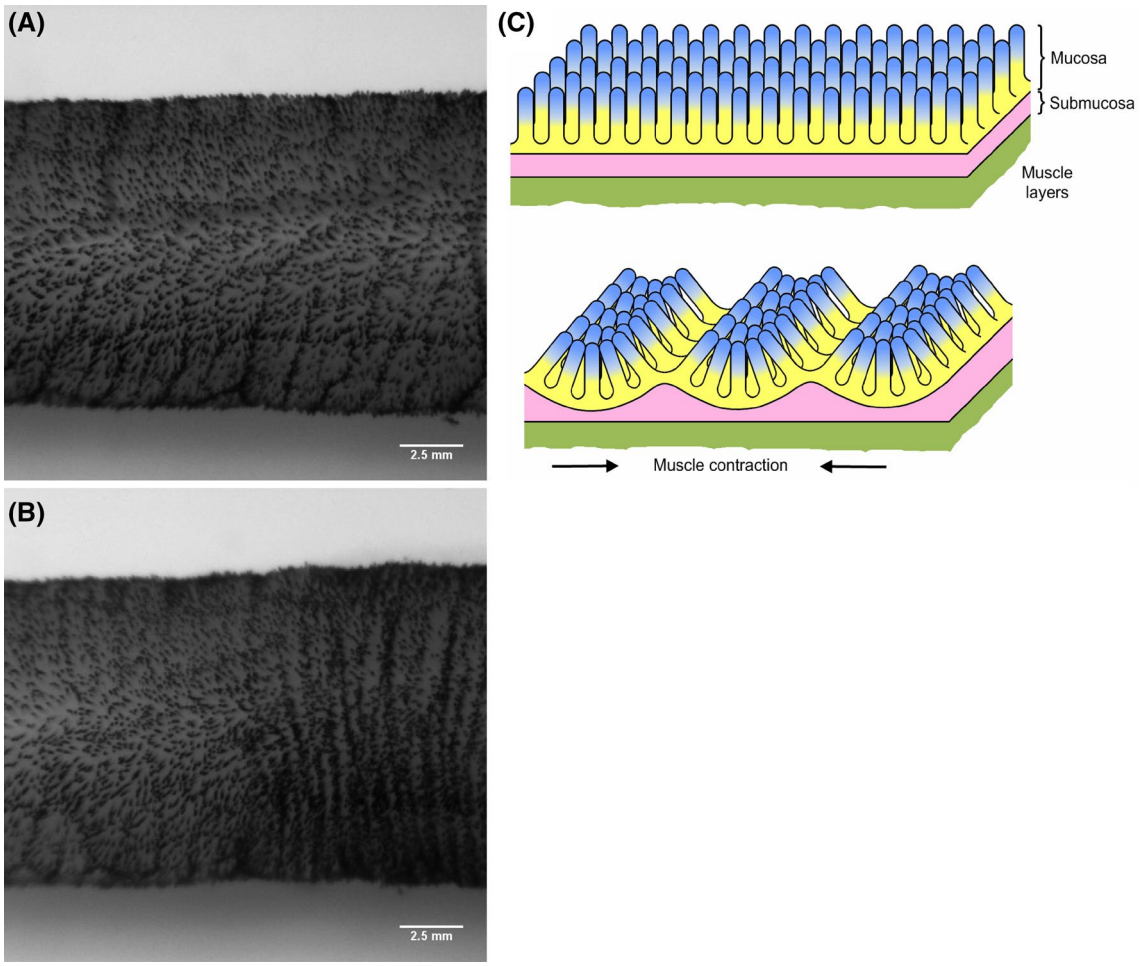

Fig. 5 Showing the manner in which mucosal folding and apical crowding originate (from Lentle et al. 2013a, b). **a** Section of ileal intestinal mucosa from the possum during relaxed phase of pendular activity showing areas of permanent radially disposed villous crowding, **b** the same site during contractile phase of pendular activity showing development of additional areas of temporary villous crowding due to contraction induced mucosal microfolding. **c** Schematic showing development of alternate areas of apical crowding and thinning from microfolds in the underlying mucosa

it would have little if any effect in augmenting the mixing of nutrients at rates above that from simple diffusion (Lim 2014).

A number of early workers suggested that villus motility, i.e. the waving and bending (Hambleton 1914; King and Arnold 1922; Womack et al. 1987) movements seen in vivo, could locally augment mixing and increase the rate at which nutrients were absorbed, but they did not quantify either the velocity or amplitude of these movements. Such motility was not evident in the ex vivo preparations that were used in the work described above. However, were they present in vivo and of sufficient amplitude and velocity, randomly orientated movements of individual villi would be unlikely to generally augment the flow of chyme between villi unless they were coordinated across an area of villous mucosa, i.e. 'patterned motions of groups of villi' (Wang et al. 2010) would be needed. Again, given the recent reports that terminal ileal villi of the possum are inflexible at physiological shear rates (Lim et al. 2014) it seems likely that the amplitude of any such villous movement would be limited.

It is possible that passive movements of villi, generated by motion of the underlying intestinal wall to which they are attached, could augment peripheral mixing. Recent work shows that the strength of the mucosal layer of the intestine on axial stretching was lower than that of the muscular layer whilst its flexibility was higher. Further, that in spite of the differing mechanical properties of the two layers, the mucosa was the last to rupture on stretch testing of specimens of the whole intestine to destruction (Egorov et al. 2002). Hence that there is a laxity of the tissue between the two layers, i.e. a discrepancy between the axial length of mucosa and that of the smooth muscle layer, presumably from repeated folding of the former.

This behaviour could allow relative movement between the two tissue layers, during contraction and relaxation of the pars muscularis. Theoretical work has shown that the inner walls of cylinders similarly fabricated with two layers of differing mechanical properties, are inherently mechanically unstable and prone to infolding (Moulton and Goriely 2011; Yang et al. 2007). Hence the pushing up of the 'redundant' mucosa into the inwardly projecting radially orientated successions of microfolds that are observed during longitudinal contraction (Fig. 5), or into longitudinally orientated microfolds during radial muscle contraction (Lentle et al. 2013a) is likely to result from mechanical instability. Regardless of its origin, such cyclic folding could induce flow around the tips of the attached villi. Hence fluid would be displaced where the apices of villi become crowded together in the troughs between adjacent microfolds, and drawn between them where they become separated on the crests (apices) of microfolds (Lentle et al. 2013a). Simulations that recapitulated such cyclic apical crowding confirmed that it caused fluid to be expelled from intervillous spaces whilst apical thinning caused fluid to be drawn back into these spaces (Lim 2014). Again real-time models that incorporated spatiotemporal data from these ex vivo preparations showed that, whilst the processes of villous crowding and thinning improved mixing in the peripheral space, they had little effect on mixing around the central axis of the lumen (Lentle et al. 2013a).

Such peripheral space mixing depends on the inflexibility of the shafts of villi (Lim et al. 2014) allowing any changes in the orientations of the bases of villi from folding of the underlying mucosa to be transmitted to their apices. However, the extent to which the shafts of the villi are approximated or separated may be further increased by the hinging of villi at their bases and by translational movements of villi across the underlying wall. It is known that villi can hinge and move relative to the mucosa (Lim 2014). The laxity that allows such movement likely results from the radial dispersion of the collagen fibres, that traverse the long axis of each villus, at their bases, (Hosoyamada and Sakai 2005, 2007). It is not known whether the flexibility of villi, or their capacity to hinge, vary with site or with species.

The effects of secreted mucins on mixing

The mucosal surface of the small intestine is coated with varying thicknesses (Atuma et al. 2001) and types (Robbe et al. 2003) of mobile mucin which may impair the mixing and absorption of nutrients. As noted hitherto, models predict that the transmission of shear to generate folding of chyme during peristaltic events will be significantly reduced when the flow of chyme is lubricated by mucins (Bongaerts et al. 2007). Similarly it is conceivable that the movements of the villous tips may be impeded by the accumulation of mucins within the intervillus spaces, although such an effect has not been demonstrated.

Experiments that assess the absorption of drugs such as paracetamol from the lumen of the small intestine, show that rate at which paracetamol is absorbed by the mucosa can be predicted from models in which the area of the absorbing surface is equivalent to that of a simple cylinder, rather than an area augmented by folding of the mucosa over the villi, and which incorporates a delay factor. The latter was postulated to result from the interposition of an 'unstirred water layer' between the lumen and the absorbing mucosa around the tips of villi that inhibited the transit of nutrients by advection and restricted it to diffusion (Barry and Diamond 1984; Levitt et al. 1992). Although the delay that led to the idea of an 'unstirred water layer' could result from a variety of phenomena, either dynamic or structural, it was generally thought to result from a contiguous layer of mucin overlying the villous mucosa (Levitt et al. 1988; Thomson and Dietschy 1984). Hence, the structure of mucin allowed diffusion in the spaces between component carbohydrate chains but prevented convective movement of fluids. Such a phenomenon seems likely in the gastric and proximal duodenal mucosa where a contiguous layer of mucin with low permeability to protons provides protection of the underlying mucosa from acidic chyme from the stomach (Tanaka et al. 1997). However, recent work by our group, mapping the distribution of mucin around the tips of living villi from the distal ileum of the possum by analysing the patterns of Brownian movement of microbeads in the lumen space that surrounds them, has shown that in this species at least the mucin layer is discontinuous, and comprises a suspension of discreet masses of mucin, each with a volume of similar order of magnitude to that of an expanded goblet cell mucin granule (Lim et al. 2013a). This finding fits in with other recent reports that the spatial organisation of mucin varies between segments (Ermund et al. 2013) and that the mucin layer in the distal small intestine may be penetrated by beads that are greater than two microns in diameter (Ensign-Hodges et al. 2013; Ermund et al. 2013). Such 'granular' dispersal of mucin masses indicates that, in the terminal ileum at least, they do not 'anneal' (Lin and Metters 2006; Verdugo 1990) to each other or accumulate, either around or between adjacent villi. Indeed, the expulsion of the Newtonian fluid in which the mucin masses are suspended, from the perivillous spaces during cyclic apical crowding (Lentle et al. 2013a) may eject the discrete masses of mucin secreted by individual goblet cells and reduce the time available for adjacent mucin masses to anneal 'on site' by the inter-diffusion of component carbohydrate chains (de Gennes 1971). Given that the rate of annealing, i.e. the time to fusion of individual mucin masses, is around 40 s for tracheal mucin

(Puchelle et al. 1986) and that the frequency of pendular contractions is around 5 cpm (Lentle et al. 2012) it seems likely that mucin masses will be ejected from the perivillous layer of the lumen before significant annealing has taken place.

This 'granular' disposition of mucin in the perivillous layer fits in with experimental findings that smaller molecular weight probes appear to take longer to transit the 'unstirred water layer' than do probes of larger molecular weight (Pohl et al. 1998). This effect had been previously attributed to the dynamics of solvent drag at the mucosal surface, the transit of smaller sized molecules toward the mucosa being impeded to a greater extent than that of larger molecules as a result of their higher rates of diffusion towards the lumen in the face of rapid water absorption (Pappenheimer 2001; Pohl et al. 1998). However, a similar effect may be produced by size exclusion chromatography, i.e. the tendency for smaller molecules to diffuse more rapidly into discrete masses of mucin than do larger molecules. Such a mechanism does not require the mucin layer to be contiguous and fits in with other findings, notably with the penetration of mucin by bacteria and by macromolecules such as those of alkaline phosphatase (Bates et al. 2007), sIgA2 (He et al. 2007), antimicrobial peptides and microbial products, e.g. LPS (Backhed et al. 2004). Further it fits with the granular characteristics of the outer mucin layer seen on immunochemical staining (Johansson et al. 2008).

Is the contractile response adjusted according to the physical properties of the lumen contents?

Having reviewed what is known regarding the flow and mixing of intestinal contents it remains to examine whether the contractile response is adjusted according to their physical state. Hence, either the predominant type of contraction or the characteristics of a particular type of contraction could be modified. There is considerable evidence of the former response, notably in regard to the incidence of peristaltic and MMC activity during the post-prandial period and inter-meal interval (Sarna et al. 1983) and in regard to the chemical characteristics of the contents (Gwynne et al. 2004). Whilst it has long been known that elevation of lumen pressure will stimulate peristalsis in segments of small intestine that are maintained in an organ bath (Trendelenburg 1917) it seems that considerable increments in pressure or volume are needed to initiate this reflex (Gregersen et al. 1992). With regard to the modification of individual contractions, there is evidence for the existence of stretch- and tension-sensitive receptors that influence contractile activity in longitudinal and circular musculature (Spencer et al. 2002, 2003). What is not clear is whether the sequence and duration of contraction in circular and longitudinal muscle can be altered according to the pattern in which consecutive mechano-receptors are activated by the transit of lumen contents, i.e. their ease of flow. Evidence suggests that there is consistent concerted firing of the two layers during peristalsis (Spencer et al. 2003), moreover recent evidence suggests that the firing sequence in the myogenically, i.e. slow wave induced, segmentative contractions may be more variable as it appears to result from interaction of discharges from ICC-MP and ICC-DMP (Huizinga et al. 2014). Networks of interstitial cells in the deep muscular plexus are known to be mechano-sensitive (Won et al. 2005) perhaps via forces applied to peg and socket junctions (Thuneberg and Peters 2001) and could for example respond to every second or third slow wave when under such stress (Lentle et al. 2008; Pescatori et al. 1980). However, more recent work showing that radial and longitudinal contractions of slow wave frequency in the distal ileum of the pig in vivo are abolished by intraluminal lignocaine indicates that neurogenic stimuli may act in a 'permissive' manner and limit the onset and local propagation of myogenic types of contraction (Janssen et al. 2014).

Conclusions and future directions

A range of recent evidence suggests that the small intestine does not function to optimise mixing within a minimal length of small intestine or within a minimum time as was proposed by Penry and Jumars (Jumars 2000; Penry and Jumars 1987). Rather, it appears that post-prandial contractile activity disperses chyme along the length of the small intestine and facilitates mixing within the bulk of the luminal space by kneading and folding. The resulting, relatively slow, rate of mixing within the bulk of the lumen allows for the more tardy rate of enzymatic diffusion into, and digestion of, nutrients within particulate matter.

The establishment of mixing throughout the lumen of the small intestine also maximises the surface area of mucosa that is available for absorption at a given time. Further, a series of subsidiary process that specifically augment peripheral mixing, may increase the efficiency of transit of enzymatic products from the lumen to the mucosa.

Whilst optimisation of mixing and digestive efficiency per unit length of small intestine (Penry and Jumars 1987) may be important in some species (Sibley and Calow 1986) different considerations may predominate in others. Hence, more work is needed in comparing mixing and digestive efficiency in animals of differing dietary habit. Thus, for example, comparing motility, mixing and digestive efficiency in animals that habitually consume food items with little nutrient content that would require high-throughput rates in order to achieve the daily nutrient requirements

(Sibly and Calow 1986) with that in those that consistently consume foods of high nutrient density. Similarly in animals that take large quantities of nutrient-rich foods in a short time, i.e. meals (Slater and Lester 1982) compared with those that eat more or less continuously. Given that gastric and small intestinal chyme are generally more viscous after a meal than between meals (Dikeman et al. 2007b; Takahashi and Sakata 2004), it is likely that chyme is less readily mixed and residence time is correspondingly prolonged post-prandially to ensure efficient digestion, and shortened during inter-meal meals when the chyme exiting the foregut contains less nutrients and is less viscous.

It is important to note that this review has considered mixing in a general sense that would apply to admixture of chyme with enzymes whose production is dispersed along the length of the small intestine but has not considered mixing with secretions that enter the lumen at a single point, e.g. the opening of the pancreatic duct, as currently there appears to be no quantitative work in this regard. Similarly we have not discussed mixing and diffusion into the oil–water interface of dietary fat. Further, it is important to note that the outcomes of a number of the models are limited in that they are based on two dimensions rather than three.

More quantitative work is needed to investigate the manner in which the different hierarchical systems that control contractile activity in the small intestine influence throughput and mixing. Hence in quantifying the manner in which elements of the enteric nervous and the myenteric systems adjust local throughput and mixing in response to local changes in the physical properties of digesta and nutrient conditions within the lumen (Bornstein et al. 2002). In particular, the extent to which they alter the form and frequencies of various types of contraction or adjust intestinal tone and capacity. Similarly, how elements of the centrally linked, autonomic nervous system can modify mixing and transit for example by adjusting the predominant patterns of contractile activity or tone after the consumption of meals (Costa and Furness 1982).

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