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Review

Modelling the dynamics of mammalian gut homeostasis

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ABSTRACT

Homeostatic balance in the intestinal epithelium relies on a fast cellular turnover, which is coordinated by an intricate interplay between biochemical signalling, mechanical forces and organ geometry. We review recent modelling approaches that have been developed to understand different facets of this remarkable homeostatic equilibrium. Existing models offer different, albeit complementary, perspectives on the problem. First, biomechanical models aim to explain the local and global mechanical stresses driving cell renewal as well as tissue shape maintenance. Second, compartmental models provide insights into the conditions necessary to keep a constant flow of cells with well-defined ratios of cell types, and how perturbations can lead to an unbalance of relative compartment sizes. A third family of models address, at the cellular level, the nature and regulation of stem fate choices that are necessary to fuel cellular turnover. We also review how these different approaches are starting to be integrated together across scales, to provide quantitative predictions and new conceptual frameworks to think about the dynamics of cell renewal in complex tissues.

1. Introduction

The intestinal epithelium is one of the fastest-renewing tissue in our bodies, with most cells being replenished within a week. The inner intestinal wall is highly folded into periodic three-dimensional structures, which serve to maximize the surface of exchange, and thus nutrient absorption [1,2]. Epithelial homeostasis of both small and large intestines is insured by populations of proliferating stem cells located in the bottom-most regions of tissue folds, which are small invaginations called crypts [3,4] (Fig. 1). The bulk of cellular loss occurs among differentiated cells, which are located in upper compartments (in small intestine, these are called villi and form evaginations that protrude outwards towards the lumen, while in large intestine, this differentiated cell region is flatter). While different populations of stem cells reside at the bottom-most regions of crypts [3,5], upper crypt regions are populated by fast-dividing cells, which do not remain long-term in these compartments, but instead serve to amplifying cellular outflux, and are termed transit-amplifying cells (TA). Thus, given that cellular division and death occur in spatially distinct compartments, a constant unidirectional flow of cells must occur from the crypts to the villi, similar to a conveyor-belt [2,6,7].

Beyond such "global" homeostatic condition imposing a balance between cell division, flows and death, the relation between the numbers and relative proportions of different cell types along the crypt-villus axis must remain invariant to sustain the functionality of the tissue. The bottom of the crypt, the stem cell region, consists of a salt-and-pepper pattern of stem cells (identified by Lgr5 expression and dividing around once a day [3,6]) and Paneth cells, which are replaced much slower and provide niche signals to stem cells, in addition to other signals being provided by mesenchymal niche populations. TA cells divide even more rapidly (around twice a day), and differentiate into specialized cell types such enterocytes (which have an absorptive function and represent the bulk of differentiated cells), Goblet cells (which have a secretory function) and several other rarer cell types [3]. From a biomechanical perspective, the intestinal epithelium is a columnar monolayer with strong barrier function and cell-cell adhesion. Beyond the epithelium, the intestinal wall displays a layered structure: epithelial cells adhere on a basement membrane and a stroma consisting in particular of collagen and highly contractile fibroblasts [4], which is itself surrounded by layers of circularly or longitudinally oriented smooth muscle undergoing periodic and peristaltic contraction [8].

Given these features, intestinal homeostasis has been a canonical system for biophysical modelling, as it provides a system of intermediate complexity to model. Indeed, although it consists of multiple cell types organized in a complex three-dimensional (3D) architecture, it has a number of stereotypical features (single-layered epithelium, villus-crypt

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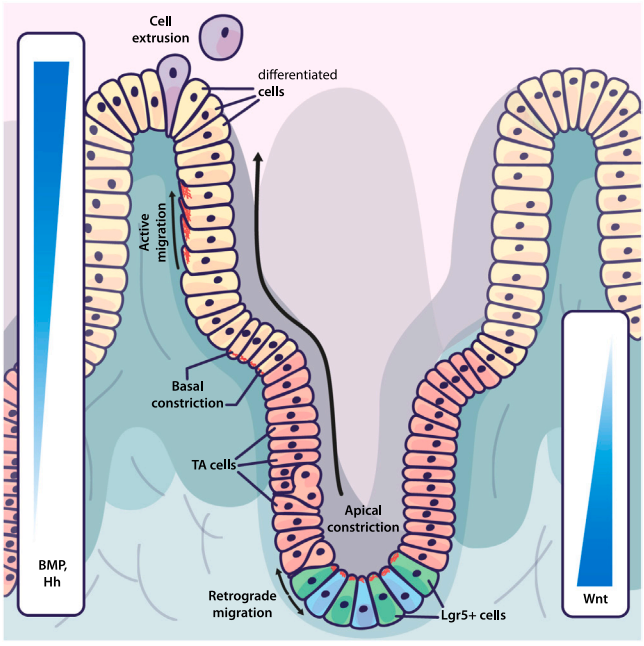


Fig. 1. Schematic of the geometry of crypt and villus in the small intestine, along with the different cell compartments involved in renewal (non-proliferative differentiated cells in yellow, fast-dividing TA cells in red, Lgr5 + stem cells in green, Paneth support cells in blue). Cell extrusion (purple) occurs at the top of villi, while proliferation occurs in crypts, causing a constant movements of cells upwards, a so-called conveyor belt dynamics (arrows). This movement occurs both due to mitotic pressure from crypts as well as active actin-based migration from differentiated cells. Shape maintenance is orchestrated both by apical constriction of cells in the stem cell zone, and basal constrictions of hinge cells at the crypt-villus border. Several signalling gradients contribute to regulate cell fate along the crypt-villus axis.

size, spacing and geometry or relative location of the cell types in relation to this geometry) which can guide modelling approaches.

Historically, modelling efforts have been split in three main categories. The first family of models are biomechanical models, which try to disentangle the puzzle set by the complex combination of mechanical forces acting within the system [1,2,9–11]. The second family are compartment-based models, which consider coarse-grained compartments (stem cells, TA, differentiated) with global population dynamics, in order to establish the generic conditions for the process of renewal/differentiation/loss to be stable in time [12–19]. The third family addresses at a more cellular level how fate choices occur during epithelial renewal, with special emphasis on the stem cell region [7, 20–26]. Clearly, such modelling frameworks are interdependent: Mechanochemical feedbacks, for example, operate in the differentiation processes due to the existence of mechanosensitive regulators of cellular fate [27]. In addition, local cellular dynamics and organ geometry can play a critical role in defining the effective number of stem cells [7,26]. In Fig. 2, we summarize the families of models and their range of applicability. Rather on comparing the performances or advantages/disadvantages of the different modelling strategies, the discussion will be based on their suitability to tackle the phenomena they were designed for. The reason behind this is that the three classes of presented models tackle different (although interlinked) questions. We will start by reviewing these approaches independently, before discussing recent works that have tried to combine some of these concepts, and finish with an outlook of how integrated modelling approaches could improve our understanding of organ homeostasis in general.

2. Mechanical models of intestinal homeostasis

As in many biological settings, phenomena such as cellular movements or changes/maintenance of organ shape must necessarily involve mechanical forces. Accordingly, a number of modelling works in the past decade has been devoted to explore the nature and coordination of physical forces involved in intestinal homeostasis [1,2,10,11], and, in particular, underlying cell migration from crypt to villus as well as maintenance and remodelling of the crypt-villus 3D architecture. In both cases, mechanical models with different levels of details have been considered. Broadly speaking, two classes of mechanical models are i) continuum models, which do not consider individual cells but instead coarse-grained parameters such as tissue density, velocity or material properties, or ii) agent-based models which typically have additional parameters as they consider some more detailed aspect of cellular shapes or interactions, but allow more flexibility in simulating biological tissues. Furthermore, mechanics is not simply involved in shaping cells and tissues, but can also feed back on numerous cellular processes [28], and thus act as a source of information for cell fate choices [29]. Considering how cellular properties can dynamically change with their mechanical environment has started to be tackled theoretically.

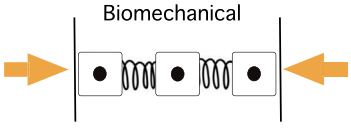
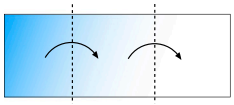
Family of models	Target problem	Features	References
Biomechanical 	· Mechanical forces underlying organ geometry and cellular dynamics	· Based on continuous mechanical and/or discrete agent models · Explicit force balance and rheology · Emerging collective patterns of migration and geometry	[1,2,9--11, 30--66]
Compartmental 	· General conditions for homeostasis	· Based on differential equations/population dynamics · Very general results valid in other tissues · Dynamic stability conditions for the existence of the homeostatic balance	[12--19, 25, 67--86]
Cell based 	· Dynamics of differentiation · Dynamics of stem cell pool	· Based on modelling individual fate choices · Conditions for the robustness of differentiated cell ratios · Determination of the competitive dynamics of the stem cell pool	[7,20--26, 87--100]

Fig. 2. Table describing the different families of models and their target problems.

2.1. Mechanics of cell migration during intestinal homeostasis

As described above, since cell proliferation occurs in crypts and cell loss at the tip of villi, large-scale cellular flows must necessarily occur, although they could have a wide variety of mechanical origins. The most intuitive explanation for cellular flows has been the idea of mitotic pressure from stem and transit-amplifying cells in crypts (Fig. 1) "pushing" cells above towards the villus [30]. Cell division has been shown in a wide-variety of systems to exert significant forces, on the order of *kPa* [31,32], and can therefore be the driving forces of cellular flows, with friction to the basement membrane being the resisting force setting migration velocity. Secondly, cellular extrusion has also been shown to be both mechano-sensitive (i.e. dependent on local tissue stresses) as well as able to create actomyosin-dependent mechanical stresses [33,34], and could therefore also locally create local contraction zones towards the top of the villi (Fig. 1). Thirdly, live-imaging of intestinal migration ex vivo has revealed actin-rich basal protrusions oriented towards the top of villi, typical of active migration forces generated by cells of the villus [10]. Fourth, forces underlying intestinal homeostasis could also have a non-epithelial origin, as crypts and villi are surrounded by different populations of mesenchymal cells (in particular, fibroblasts) which are highly contractile and can also exert significant forces on epithelial tissues [35].

Simple continuum models for epithelial renewal can lead to a number of qualitative predictions which differ for different sources of mechanical stress [36]. For instance, in the "mitotic pressure" model, pressure is expected to be maximal in the crypts and become lower and lower as cells migrate up the villus, as stresses from the crypts are dissipated by friction. On the other hand, in the "active migration" model, each cell in the villus would "add" their own active traction force on the substrate which leads to pressure being highest at the top of villi, where cells are most crowded and compressed due to the migration forces exerted by the cells below them, in analogy to 2D in vitro monolayers [37]. Considering both mitotic pressure and active migration forces then predicts a non-monotonous stress profile, with pressure being highest in the crypts and top villi while being lowest in the central regions [10]. Importantly, this has been tested via different experimental methods: i) local pressure can be expected in simple theoretical models to be correlated with cellular density, and quantitative measurements revealed density to increase both towards the bottom of the crypts and the top of villi; ii) tissue-scale laser ablation tools can be used to infer the local state of stress of tissues, with the recoil velocity being proportional to tissue tension (tension being simply the reverse of pressure in 2D mechanics), and has revealed, not only that the epithelium is globally under tension, but also that tensions in the bottom of villi were larger than on the top. Both of these features are consistent with active migration pulling cells from the crypt to the villus (directly imaged *ex vivo* as actin-rich basal protrusions [10], see Fig. 1) as well as previous reports that cell movements were not fully abolished by inhibition of proliferation [38]. This also was directly tested by traction force microscopy on 2D intestinal organoids [11], which could measure quantitatively the different mechanical forces involved. A key open question from these studies is the nature of the cue that would actively polarize cells towards villi tips. Although a number of signalling gradients along the crypt-villus axis have been reported, the fact that traction forces are also directional away from the crypt in 2D organoids, lacking any non-epithelium tissue or patterned ECM [11], could suggest a self-organized epithelial source for directional cues. This could be addressed theoretically in the future by drawing inspiration from continuum and particle-based models of self-generated chemokine gradients relying on interplays between different cell types in other systems [39].

2.2. Mechanics of crypt-villus shape maintenance during intestinal homeostasis

The stereotypically folded shape of villus and crypts has inspired a large body of theoretical work in the past twenty years. An elastic material growing under confinement (or growing at a differential rate compared to its surrounding) is generically expected to display buckling at a finite length scale, which has been proposed to underlie the morphogenesis of a number of organs [40,41]. During intestinal morphogenesis, both the large-scale looping of the gut and the smaller-scale periodic formation of villi have been modelled using the theory of "morphoelasticity" and experimentally tested via a combination of mechanical measurements (to assess tissue rheology), dissection experiments (to test the hypothesis of tissues as elastic materials) and pharmacological perturbations [42,43]. Although continuum theory is well-suited to describe key global features such as pattern wavelength, numerical simulations are typically required to explore the highly non-linear growth regimes that are relevant experimentally, which may consist either of simulating continuum equations (e.g. via finite element modelling [43]) or with particle-based models (e.g. cells as replicating and adhesive soft particles, [44]).

Crypt formation occurs several days after villus formation and has been shown to depend instead on apical actomyosin localization in crypts driving tissue bending [45,46], a generic process driving a number of developmental processes, as well as the contraction of hinge cells at the crypt-villus boundary [45] (Fig. 1). Interestingly, 3D intestinal organoids consisting only of epithelial cells form crypts with morphologies highly similar to their in vivo counterparts, but do not form villus structures despite containing the same differentiated cell types found in vivo [47]. This is consistent with crypt shape acquisition being mainly dependent on epithelial-derived forces, and villus shape acquisition requiring a mechanical interplay with other tissues. To describe such processes where actomyosin localization at the apical, lateral or basal surfaces of epithelial cells plays a key role in shape acquisition, 3D vertex models are particularly suitable. Indeed, this class of model does not consider cells as individual particles but instead as foams, where surface tensions are the dominant forces. This analogy to foams, or soap bubbles, can be justified by the fact that actomyosin typically forms a thin contractile layer at the surface of cells, and thus can be modelled in first approximation by a simple surface tension [48]. Within these models, cellular volume is typically considered constant and, in consequence, the only three parameters to consider in the theory are the tensions at the basal, lateral and apical sides of cells [49,50]. Notice that this is for a single cell type: considering n cell types multiplies the number of parameters by n, which can quickly become intractable, especially if one additionally considers specific codes of adhesion or tension between two neighbouring cells of different types. Furthermore, compared to particle-based models, 3D vertex models make specific predictions on individual cell shape and geometry, which can be measured experimentally using an expanding number of 3D segmentation tools and used to constrain the theory further [11,51,52]. In particular, combinations of in vivo and in vitro studies with theoretical modelling of 3D cell shape have revealed a pattern of apical localization of actomyosin in crypts and basal localization of actomyosin in villus cells that can quantitatively explain crypt morphogenesis [47]. Furthermore, this has revealed an important role for the lumen fluid pressure in driving crypt morphogenesis in 3D intestinal organoids [47], which is coupled to villus cell differentiation via local upregulation of sodium/glucose cotransporter at their apical surfaces. Indeed, lumen volume deflation decreases epithelial tissue tension and facilitates tissue bending, and dynamical modulations in lumen volume have also been shown in organoids to regulate crypt geometry, stem cell number and fission events [53]. Although the geometry of the gut in vivo is one of an open tube, rather than closed sphere as in organoids, temporal modulations in villus cell density could produce similar effects by changing the stresses applied on crypts [47]. In the next few years, it would be

interesting to integrate these findings into a comprehensive mechanical model of crypt-villus morphogenesis in vivo. In particular, it remains unclear whether the aforementioned mechanisms of crypt morphogenesis remain active throughout life to actively maintain crypt shape, or whether the surrounding tissues and/or ECM adapt to curved crypt shape to provide a stable scaffold. Interestingly, changes in villus shape and size do occur physiologically as a function of nutrition or tissue damage [54], and crypts continuously undergo a process of fusion and fission both in humans and mice [55–57], suggesting that active maintenance of tissue shape would be necessary. Although both crypts and villi undergo fission during development [58], homeostasis imposes strong conditions on how these fusion-fission events must be balanced in healthy tissues. How this occurs mechanistically remains an open question.

2.3. Mechanics of compartmentalisation between different cell types

At a more cellular level, intestinal crypts display strong compartmentalisation. For instance, regions of stem cells, transit-amplifying cells and terminally-differented cells are well-defined spatially. This has been proposed to rely on cell sorting via differential cortical tensions, spatially enforced by gradients of Eph/Ephrin, a classical ligand-receptor pair controlling compartments in a number of biological settings [59]. Furthermore, even within individual compartments, relative cell-cell positions are under tight control: as pointed out above, in the crypts of the small intestine, Lgr5 + stem cells and Paneth cells are intermingled in a salt-and-pepper manner [3]. Given that Lgr5 + and Paneth cells were shown to differentially contribute to apical constriction in intestinal organoid morphogenesis [47], it is also tempting to speculate on potential “anti-sorting” mechanisms, which would favor preferential adhesion to different cell types. On the theoretical side, particle-based or vertex-based models are ideal to address this question as they allow for explicit modelling of individual cell fates and positions [9], although considering multiple fates with a complex code of cell-cell and cell-matrix adhesion properties becomes rapidly intractable and difficult to compare to data due to the large parameter space. However, minimal vertex models considering the formation of interfaces between two different tissues have started to reveal key signatures of differential and heterotypic tension on surface roughness and the geometry of local cell contacts [60,61]. This could provide a theoretical platform that could be used to understand more complex and dynamical situations such as intestinal compartimentalization [11]. In general, dissecting experimentally and theoretically how different fates and signalling gradients endow individual cells with different and complementary mechanical properties (such as migration or adhesion [62]) will be an important topic of research for the next few years. Interestingly, in vitro organ-on-chip approaches mimicking the shape of the intestinal crypt have shown that substrate geometry can be sufficient to guide correct cell type compartmentalisation [63] (e.g., robust localization of Lgr5 + cells in the bottom-most parts of crypts where tissue curvature is maximal). This could provide simplified systems on which to apply and test minimal biophysical theories on the relationship between mechanics, tissue geometry and cell fate [64–66].

3. Hierarchical and compartmental models

The highly dynamical nature of the intestinal epithelium renewal process is particularly striking when considering that cells must also, in the mean time, maintain barrier function, as well as proliferate, differentiate and, collectively, perform all the functional properties attributed to the intestinal epithelium. At the biochemical level, a complex interplay of signaling gradients along the crypt villus axis provide cues leading to either stem cell self-renewal or differentiation into different cell types. Consequently, the different cell types display strong spatial compartimentalization along the crypt-villus axis, setting an interesting puzzle to understand how homeostasis is maintained, which has been addressed by the so-called compartmental models.

Several biochemical cues, with different concentration profiles along the vertical crypt/villus axis, play a key role in organizing the distribution of different cell types, with for instance Wnt showing higher levels at the bottom of the crypt, with roles in intestinal stem cell renewal [5] (see Fig. 1 for a schematic). A classical model for fate identity choices relies on a combinatorial interpretation of Wnt and Notch signals: the Wnt gradient, being short-ranged, maintains stem and Paneth cell fates above a threshold near the bottom of the crypt, while the Notch gradient is both longer-range and displaying strong cell-cell heterogeneity, with high Notch promoting either stem cell and enterocyte fates as a function of position along the Wnt gradient (whereas Notch is low in Paneth and secretory cells) [9]. However, these two pathways are not independent, and recent mathematical modelling has sought to understand how biochemical crosstalk can regulate the proportions and timing of cell fate selection. In addition to these crypt-to-villus signalling gradients, BMP signalling displays an opposite gradient, being higher towards the top of the villus, and provides additional positional information to regulate differentiation into goblet and enterocyte cells [67]. The transcriptional regulator YAP also plays a key role in stem cell fate choices, for example for Paneth cell differentiation and symmetry-breaking in organoids, through an interplay with the Delta/Notch pathway [68]. In the future, the identification of the underlying mechanisms for symmetry breaking events could be addressed from dynamical systems-inspired modelling strategies, accounting for the potential feed back loops between these pathways. Furthermore, several studies in organoid systems have suggested that YAP activation induces differentiation into goblet cells [69,70], although evidences pointing towards the opposite conclusions have been also found [70–72]. As pointed out in [2] such discrepancies could arise from the different roles of YAP either in homeostatis or regeneration, acting respectively as an inducer of differentiation or enhancing the reversal towards de-differentiation. In the future, mathematical models considering the interplay between YAP and other signalling pathways such as Wnt in intestinal renewal [73] could help to resolve this.

Interestingly, and linking to the section above, several of these signalling pathways have been shown in the past decade to be mechanosensitive, with consequences that have been increasingly investigated in intestine [74]. For instance, volumetric compression has been shown to regulate the growth of intestinal organoids through modifications of intracellular crowding and elevated Wnt/β-catenin signaling [75]. At the same time, Wnt/β-catenin signalling is required for the maintenance of the intestinal epithelial stem cell pool [76,77]. Notch activation has also been shown to specifically require local pulling forces in addition to ligand binding [78], which could be particularly relevant in the presence of pulling forces from migrating cells [10,11]. In vitro organoids studies backed by colon samples from patients have also shown that substrate stiffness can regulate intestinal stem cell fate via YAP modulation [69]. Thus, such feedbacks from mechanics to signalling are likely to be key to understand intestinal homeostasis, and further theoretical modelling will be necessary to reach an integrated view of these interactions. Interestingly, findings from other systems might provide inspirations, for instance vertex models on mechano-chemical feedbacks of Notch and mechanics in inner hair cell patterning [79] or spatial models of nuclear deformation and YAP mechano-transduction [66,80]. This could also help to understand departures from homeostasis, such aberrant tumour growth in the intestinal epithelium, especially given reports on the mechanical activation of the β-catenin pathway in response to pressures in the range of those that would be generated by tumours in colon [81].

Due to these graded mechanical and biochemical inputs along the crypt-villus axis, the intestinal epithelium is organized in a strongly hierarchical and compartimentalized manner [19,25,82]. This observation lies at the basis of compartmental models [12–18]. In general, such models assume the existence of two or three compartments: In the case of two compartments, the system is abstracted as being composed of

the stem and differentiated cell regions. In the latter case, the system is abstracted as composed of the stem cell region, the transit amplifying (TA) region and the differentiated cell region. A key question addressed by these models is how to explain theoretically the fairly robust number of differentiated cells both across time and across different crypts, as well as the potential sources underlying the breakdown of such stability in pathological conditions.

To answer this, simple but powerful models have abstracted the global renewal dynamics of compartments based on differential equations akin to the ones found in population dynamics [14,15,19]. In these frameworks, continuity and conservation of flow is assumed as boundary conditions imposed by homeostasis, considering the different proliferation kinetics of the cells in different compartments, and the rates of death and transit to adjacent compartments through differentiation or de-differentiation. Using control theory, modelling efforts have shown that stochastic control loops can maintain stable homeostatic abundances without parameter fine-tuning [83], providing analytical predictions of the variance and mean of the size of the compartments at homeostasis [84]. Still in the framework of control theory, but now in a scenario of crypt morphogenesis, mathematical modelling revealed that the experimentally observed dynamics, consisting on a surge of proliferation of Lgr5 + followed by a sudden burst of asymmetric divisions, can minimize the time spent by the system to reach a mature crypt [85].

Furthermore, modelling efforts have recently aimed at understanding quantitatively the relative extent of each compartment along the crypt-villus axes, as well as sub-compartments dynamics such as the robustness in proportions of secretory and absorptive cells within the differentiated cell compartment. Given that commitment to one of the two differentiated cell fate was found to occur early, this would be expected to occur in a relatively small population of progenitor cells, and thus be highly variable from a population dynamics perspective [18], leading to the undesirable scenario where the distribution of different cell types displays dramatic differences from crypt to crypt. Interestingly, in colonic crypts, mathematical modelling using grid-like cell arrangements has shown that Delta-Notch lateral inhibition at the level of the TA zone is enough to cancel most of the potential noise and keep the cell populations to robust ratios compatible with the observations [18]. Recent approaches using spatial simulations of stem cell and TA compartments have shown that fluctuations in cell proliferation are also minimized if a strong symmetry in proliferative behavior between sister cells is coupled with the partitioning of crypts in compartments of different proliferative potential [86]. Both of these examples underlie the importance of going beyond spatially-averaged compartment models in a number of situations, and consider also the relative spatial arrangements as cells, as well as global organ shape.

4. Models of stem cell fate choices and cellular identity

Agent-based models, which explicitly consider individual cells interacting in space, have been able to introduce a great deal of details into the modelled dynamics [9,44,87,88], by being able to consider cell-generated mechanical forces as well as cell-cell signalling interactions. Particular attention has been given to understand the dynamics and size regulation of the stem cell compartment. Indeed, size regulation can occur via a wide range of models, two extremes being purely asymmetric divisions at the single cell level, or purely symmetric divisions with global and population-level balance [3]. Interestingly, quantitative lineage tracing methods, which irreversibly label a given cell and all of its progeny to follow as a function of time the dynamics of stem cell fate choices, have provided strong support for the latter [20,21,24,25]. Specifically, it was shown that Lgr5 + cells located at the bottom of the crypts neutrally compete with each other, with each cell division being symmetric and expelling another cell out of the crypt towards differentiation [20–23]. This competitive dynamics results in most cellular lineages being lost, with a single stochastically selected cell ultimately winning the long-term competition. Modelling efforts to understand the long-term consequences of stem cell competition dynamics started considering the bottom-most level of a crypt, populated by Lgr5 + cells (Fig. 3B,C). Interestingly, this dynamics could be mapped to a 1D neutral drift, implying that the clonal boundary undergoes a random walk (expansion or regression of the clone via division/differentiation) on a ring [20–22] (Fig. 3C). In spite of its simplicity, this model could explain the key features of the convergence to monoclonality in a quantitative way. It also provided the grounds to understand how stochastic and neutral competition acts as a primary regulatory force shaping stem cell dynamics in other systems - in particular human intestinal crypts. Indeed, although lineage tracing experiments at controlled time points are clearly not possible in humans, it was realized that rare mitochondrial DNA mutations could be used to trace stem cell fate choices - by simply adapting the theory to situations where reconstructed clones can have arisen at any prior time point [89,90] (continuous labelling). This revealed a similar pattern of clonal competition where 5–6 cells compete neutrally in each human colonic crypts, fitting well a one-dimensional neutral drift model [90]. Although this technique requires staining and imaging of crypts, it was recently proposed that methylation patterns (measured by microarrays in single crypts) could also be used as an elegant lineage tracing marker in human crypts [91], with both methods revealing a much slower pattern of neutral competition in human compared to mouse.

Although the first murine studies were performed on fixed samples at different time points, advances in intravital live-imaging have allowed to follow the same cells in given crypts as a function of time [24], revealing that, even if all Lgr5 + cells can participate in the competition and colonize the whole crypt, positional-dependent short-term biases for survival are observed in the small intestine (SI) [24]. Moreover, extension of intravital live-imaging to several months has revealed that these biases are much stronger in the large intestine (LI) [26], with many Lgr5 + cells unable to ever function as long-term stem cells. Theoretical modelling of cell renewal along the crypt-villus axis has shown that cell-cell positional re-arrangements are necessary to avoid that a single cell (the one located at the bottom-most region of the crypt) always wins the competition by deterministically pushing all of the others out (Fig. 3D). Irrespective of the exact nature of these movements, the probability of cells to give rise to long-term lineages decreases in a predictable Gaussian manner as a function of distance to the crypt bottom, with a length scale dependent on the ratio of re-arrangements to proliferation [7] (Fig. 3E). Interestingly, much rarer re-arrangements (termed retrograde movements due to the involvement of active migration) were observed in LI compared to SI, which could explain quantitatively their differences in stem cell numbers [26]. These retrograde movements could be modulated by Wnt levels, and provide a population-level mechanism for stem cell regulation, where the potential of stemness arises as the outcome of collective cellular dynamics and organ geometry [26].

This recently reported role of motility and re-arrangements in regulating the effective number of stem cells suggests that the collective state of the tissue, either jammed/rigid or fluidized, should be taken into account in the future. Rigidity properties of a tissue are naturally linked to mechanical parameters such as cell-cell adhesion, cell contractility or active cell migration [62,92–96]. In consequence, the use of agent-based mechanical models, such as the vertex model which have been extensively looked at rigidity transitions in tissues made of a single, non-proliferative cell type [50,52,97–100], represents a natural next step where the modelling of stem cell regulation, mechanical properties and renewal dynamics may meet for a better understanding of the mechanisms underlying homeostasis in gut epithelium.

5. Concluding remarks

The renewal of the intestinal epithelium is one of the paradigmatic systems to study and model the general question of homeostatic balance [1–4]. Several minimal models (some of them even analytically

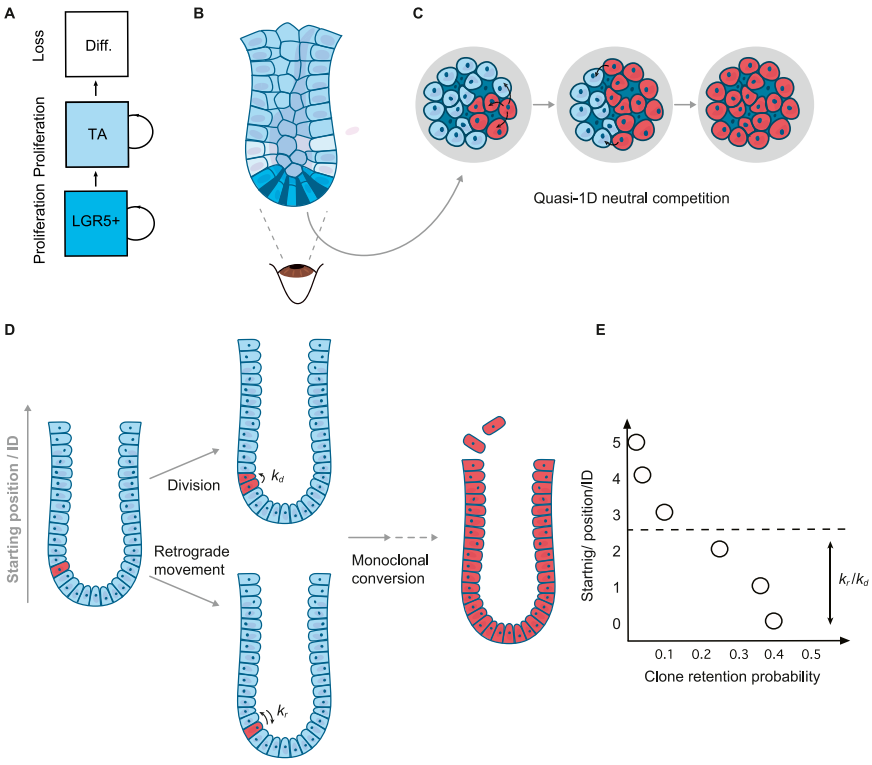


Fig. 3. A/ Schematic representation of the crypt/villus system as a series of compartments containing cells of different identities that can eventually proliferate, differentiate or die at different rates, depending of their identity. Homeostatic equilibrium requires that such rates are balanced —adapted from [15]. B-C/ Schematic representation of Lgr5+ cells (blue cells) proliferative dynamics at the bottom of intestinal crypts, which can be mapped on a one-dimensional clonal competition where each cell has an equal probability of dividing and pushing its closest neighbor out of the crypt. Lineage tracing and mathematical modelling reveals how a randomly selected labelled cell (red) can then progressively take over the entire crypt in a stochastic manner. D/ Model sketch of the stochastic conveyor belt dynamics which can be used to understand how functional stem cell numbers are determined along the crypt-villus axis. k_d is the upward movement rate due to cell division which give an advantage to cells at the lowest positions, while retrograde movements k_r allow for cells to randomly reposition at more favorable positions.E/ The statistics of clone retention as a function of the starting point of the mother cell within the crypt levels displays a Gaussian decay, with length scale proportional to retrograde movement frequency, allowing for a functional definition of stem cell potential.

tractable) have revealed powerful in predicting the mechanical forces or cellular fate choices underlying tissue turnover. In parallel, intravital microscopy techniques as well as novel organoid and organ-on-a-chip models [101], can bring unprecedented insights into the dynamics of this system. Here, we presented three classes of approaches to model the dynamics of renewal of the intestinal epithelium at homeostasis: biomechanical models, compartment models, and cell fate choice models. Such approaches offer complementary perspectives to the problem of homeostatic balance and are not mutually exclusive. A good example of possible links between these approaches is found in the Wnt signalling pathway, which is central for regulating stem and Paneth cell identity, but is also both mechano-sensitive and modulating mechanical properties such as active cell movements. Modelling efforts, therefore, must be aware of this interdependence in order to advance into deeper explanatory frameworks.

Given that most tissues are maintained by specialized populations of stem cells, understanding how signalling and mechanical forces impact on stemness and intestinal turnover is likely to provide generic insights for other systems. The observation that clone retention probability depends on the position the mother cell occupies within the geometry of the organ goes beyond the homeostatic dynamics of the intestinal epithelium [24], and similar phenomena has been reported, for example, in the development of the mammary gland, [7102], adult interfollicular epidermis [103,104] or spermatogenesis [105]. This raises a fundamental question whether stem cell potential is a cell-intrinsic, "inherited" property, or rather an extrinsic, context-dependent state emerging from the collective dynamics and geometry of a tissue and cues from local microenvironments [106–113]. In this context, modelling of intestine renewal is a source of inspiration to understand theoretically how individual stem cells make decisions during homeostasis, which is key to then understand their disregulation in processes such as tumorigenesis [114,115].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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