Serotonin distribution in the colon: insights from computational biology

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Approximately 95% of serotonin is produced in the intestines by enterochromaffin cells where it has been shown to modulate muscular contraction pattern and contraction force (Erspamer, 1954; Bulbring & Crema, 1959). Intestinal muscle contraction also causes increased release of serotonin into the intestinal tissue (Bulbring & Crema, 1959). Perturbation of intestinal muscle contraction underlies pathologies where changes in total digestion time, gastrointestinal emptying and gastrointestinal motility are observed (Chey *et al.*, 2001). Similarly, studies in patients with Irritable Bowel Syndrome or with chronic constipation have found altered intestinal serotonin concentrations by direct measurement of serotonin in the mucosa (Coates *et al.*, 2004; Faure *et al.*, 2010; Costedio *et al.*, 2010).

Enterochromaffin cells are found in the epithelial cell layer of the gastrointestinal mucosa, where they release serotonin into both the lumenal colonic mucus and the mucosa mesentery. These pools of serotonin remain separated by the epithelial border (Gershon & Tamir, 1981). The mucosal serotonin pool is detected by receptors on nerve terminals originating from deeper colonic tissue layers. The response of intestinal muscle to fluctuations in mucosal serotonin concentration patterns is thought to be achieved *via* these mucosal terminals by neural signalling.

Serotonin concentration fluctuations are studied in relation to muscle contraction using *ex vivo* human and animal colonic samples. Amperometry detects lumenal serotonin concentrations by hovering the probe directly over the colonic mucosa and measuring serotonin oxidation frequency relative to muscle contraction pattern and force. However, it has proved difficult to identify the complex relationship between these factors. Rather than manually compare serotonin release data to intestinal muscle contraction data, this project collates the data in a three-dimensional computational model of the intestines. This allows potential interactions between serotonin and muscle contraction to be explored and possible interactions to be applied consistently to inform hypothesis development.

Our model replicates a transverse segment of human colon *ex vivo* study containing a buffer solution in the lumenal space. All parameters applied to the model are experimentally determined, and are physiologically present. We have found that the addition of involutions in the mucosal epithelium, termed crypts, results in the formation of distinct serotonin concentration patterns in the mucosal pool with respect to the mucus and buffer pool concentrations ($P < 0.5$, Man-Whitney-Wilcoxon test comparing coefficients of variation and means). The mucus sitting in the crypts acts as a well of serotonin, stabilising serotonin release from the mucus into the lumenal buffer solution. As a result, mucus and lumenal serotonin concentrations remain comparatively steady during muscle contraction, where serotonin concentrations in the mucosa change rapidly. The steady lumenal concentration pattern identified by our model reflects the results of *ex vivo* studies. If this serotonin concentration were also found within the mucosal tissue, it would desensitise the serotonin receptors expressed by the nerve terminals projecting into this tissue. The rapid fluctuations of serotonin concentration simulated by our model may provide an explanation for the lack of neural serotonin desensitisation observed physiologically.

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