Examining the pathogenesis of pouchitis using a multiscale model of the intestinal mucosa: Spatially Explicit General-purpose Model of Enteric Tissue (SEGMEnT_HPC)

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Introduction: Inflammation of the illeal pouch following remedial surgery for ulcerative colitis, a condition termed pouchitis, is a significant source of morbidity in patients with inflammatory bowel disease with reported long-term incidence rates of up to 95%[1]. The pathogenesis of pouchitis is believed to involve the intersection of dysregulated intestinal inflammation, abnormal mucosal tissue response, and alterations in gut microflora due to stasis resulting from the anatomic configuration of the illeal pouch. Thus the pathogenesis of pouchitis is a multiscale process that extends from microscale molecular signaling to tissue scale cellular patterning to anatomic-scale dynamics of the flow of intestinal contents. We have previously developed the Spatially Explicit General-purpose Model of Enteric Tissue (SEGMEnT)[2] to dynamically represent existing knowledge of the behavior of enteric epithelial tissue as influenced by inflammation with the ability to generate a variety of pathophysiological processes. Given that the progression of pouchitis and the spatial distribution of the stimuli that drive it are not homogenous throughout the entirety of the pouch, and as such anatomic scale simulations are required in order to plausibly simulate the complicated interplay of ileal and rectal (colonic) tissue with a dynamic microbiome, we have implemented a parallelized version of SEGMEnT, SEGMEnT_HPC, with the ability to generate anatomic-scale simulations of intestinal epithelial tissue patterning and response to inflammation.

Methods: SEGMEnT_HPC is an agent-based model implemented in C++. It incorporates gut epithelial cells (GECs), inflammatory cells (macrophages and neutrophils), and their effects on the extracellular matrix with consequent changes in crypt-villus morphology. Simulations of knockouts of GEC morphogenesis pathways were performed to validate their effects on crypt-villus architecture. Parameter sweeps of inflammatory responsiveness were performed to characterize the dynamic range of metaplastic transformation. Inflammatory stimuli are represented by the fecal microbiome, a flowing liquid with a dynamic inflammatory potential.

Results: In addition to reproducing baseline healthy ileal mucosal dynamics and reproducing a series of morphogen suppression experiments, SEGMEnT_HPC simulations suggested a putative role for Phosphotase and tensin homolog/phosphoinositide 3-kinase as a key point of crosstalk between inflammation and morphogenesis and confirmed chronic inflammation due to fecal stasis as a plausible driver for colonic metaplasia in the ileal pouch.

Conclusion: SEGMEnT_HPC can serve as an integrating platform for the study of inflammation in gastrointestinal disease. We hypothesize that the clinical setting of pouchitis involves the effect of fecal stasis and alterations in the resident microbiome on stimulating the inflammatory dynamics of the pouch and rectal cuff, and therefore we believe SEGMEnT_HPC will be a vital adjunct in our future exploration of this and other complex, multi-factorial processes.

[1] Simchuk, Erik J., and Richard C. Thirlby. "Risk factors and true incidence of pouchitis in patients after ileal pouch–anal anastomoses." *World journal of surgery* 24, no. 7 (2000): 851-856.

[2] Cockrell, Chase, Scott Christley, and Gary An. "Investigation of Inflammation and Tissue Patterning in the Gut Using a Spatially Explicit General-Purpose Model of Enteric Tissue (SEGMEnT)." *PLoS computational biology* 10, no. 3 (2014): e1003507.