# Towards Anatomic Scale Agent-Based Modeling with a Spatially Explicit General-Purpose Model of Enteric Tissue (SEGMEnT_HPC)

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## Background and Motivation

- Dynamic representation of mechanistic knowledge
- System level phenotype reproduction (tissue patterning)
- Able to model "healthy state" at baseline
- Disease phenotypes represent some divergence from baseline healthy state



**Spatially Explicit:** signaling interactions modulate epithelial architecture
**General-purpose Model:** Not a disease-Specific Model; Disease states arise from Perturbations in the signaling network
**Enteric Tissue:** the Gut

## Previous Studies on Pouch Metaplasia
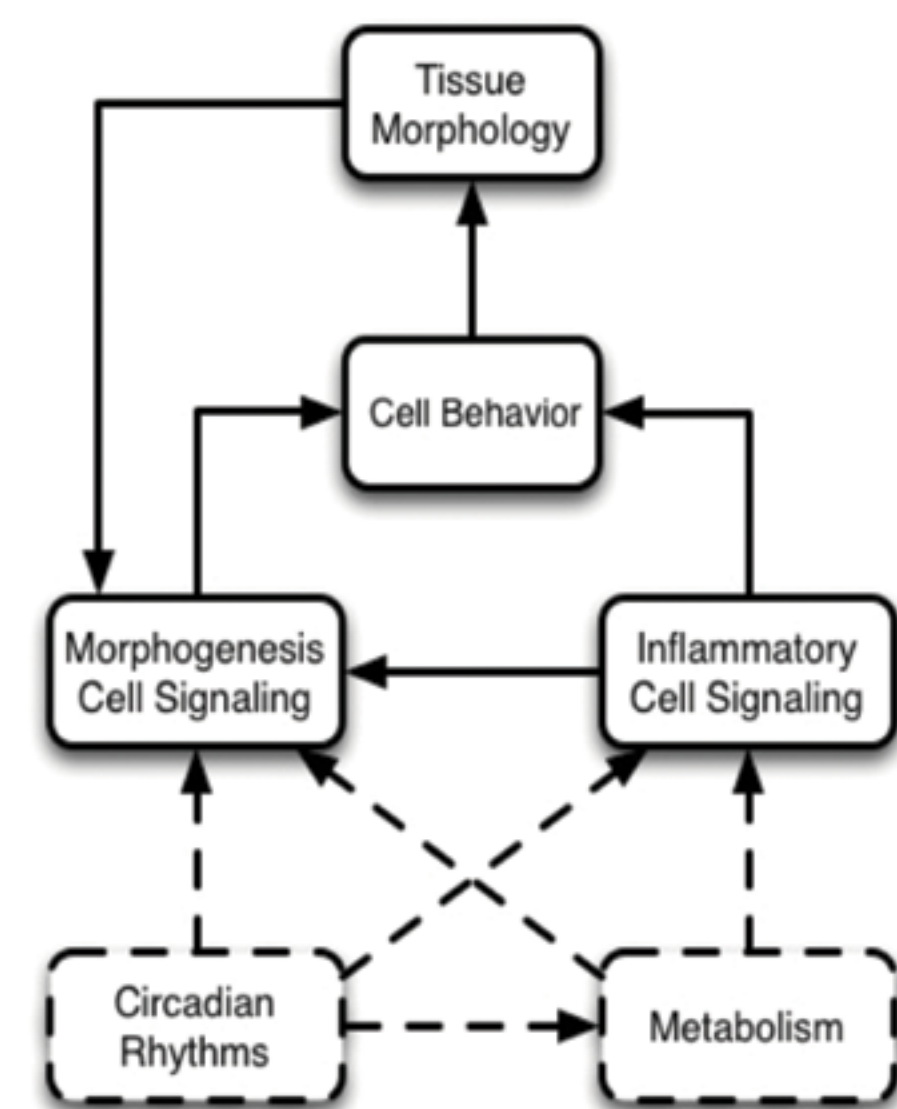
**Colonic Metaplasia of the Small Intestine**
As noted above, simulation experiments were performed implementing the hypothesis that colonic metaplasia of the ileal pouch was induced by chronic low-level inflammatory stimuli from fecal stasis. The figure on the left displays crypt and villus GEC populations when the system is exposed to chronic low-level TLR signaling (an abstraction of fecal stasis). This up-regulation leads to an increased rate of apoptosis, shortening the villus, as well as an inhibition of the Hh pathway, which leads to an increase in the size of the proliferative compartment. Figure B in the center displays output from SEGMEnT when simulating conditions leading to colonic metaplasia. Crypt hyperplasia and villus atrophy are clearly evident, along with a villus to crypt height ratio that closely matches the alterations seen in colonic metaplasia, suggesting the plausibility of this mechanism as the driver for colonic metaplasia. These features are more apparent when comparing to the ileal system in a baseline healthy state (Panel C). On the far right, a diagram of the signaling network implemented in SEGMENT_HPC is shown.
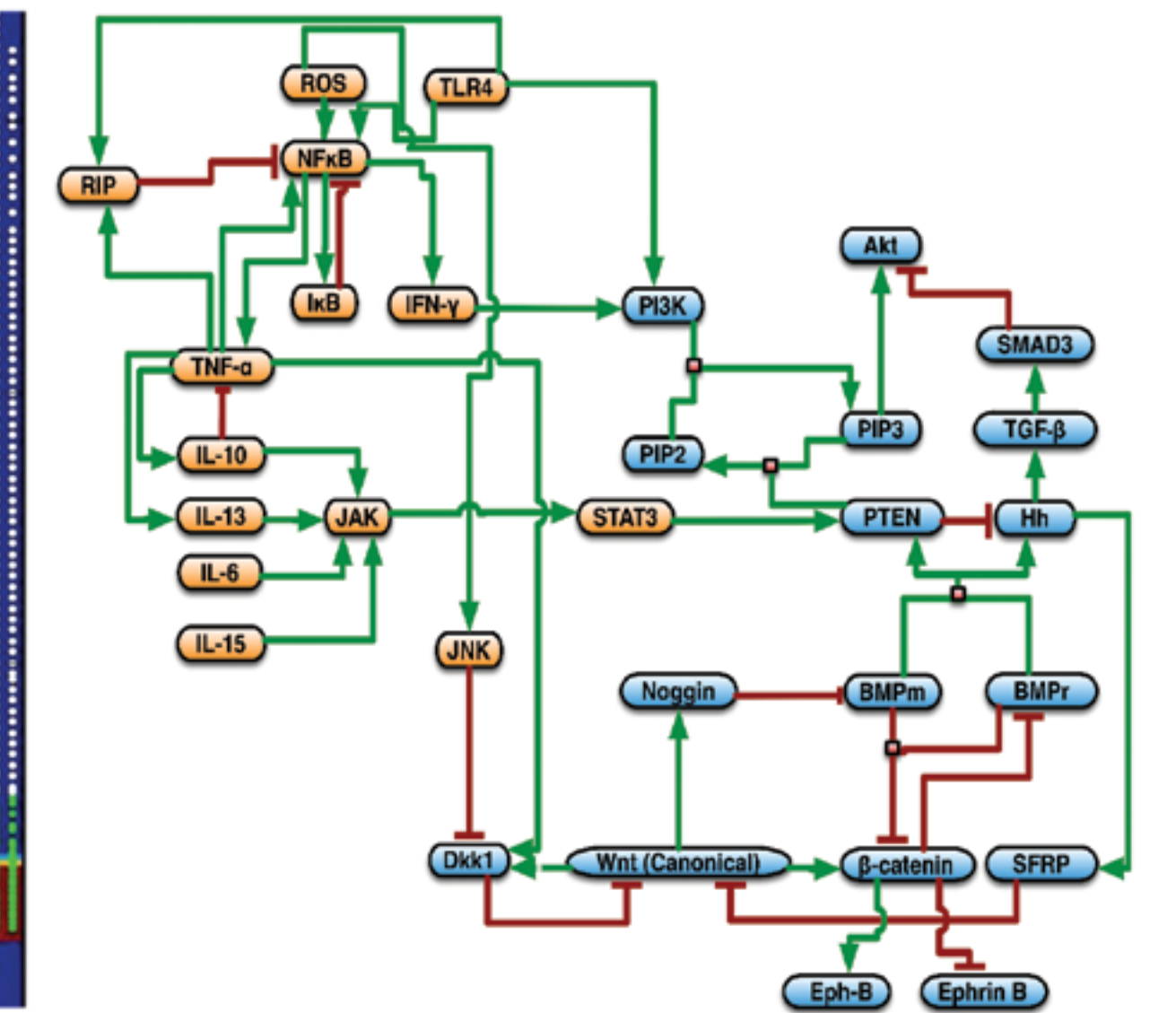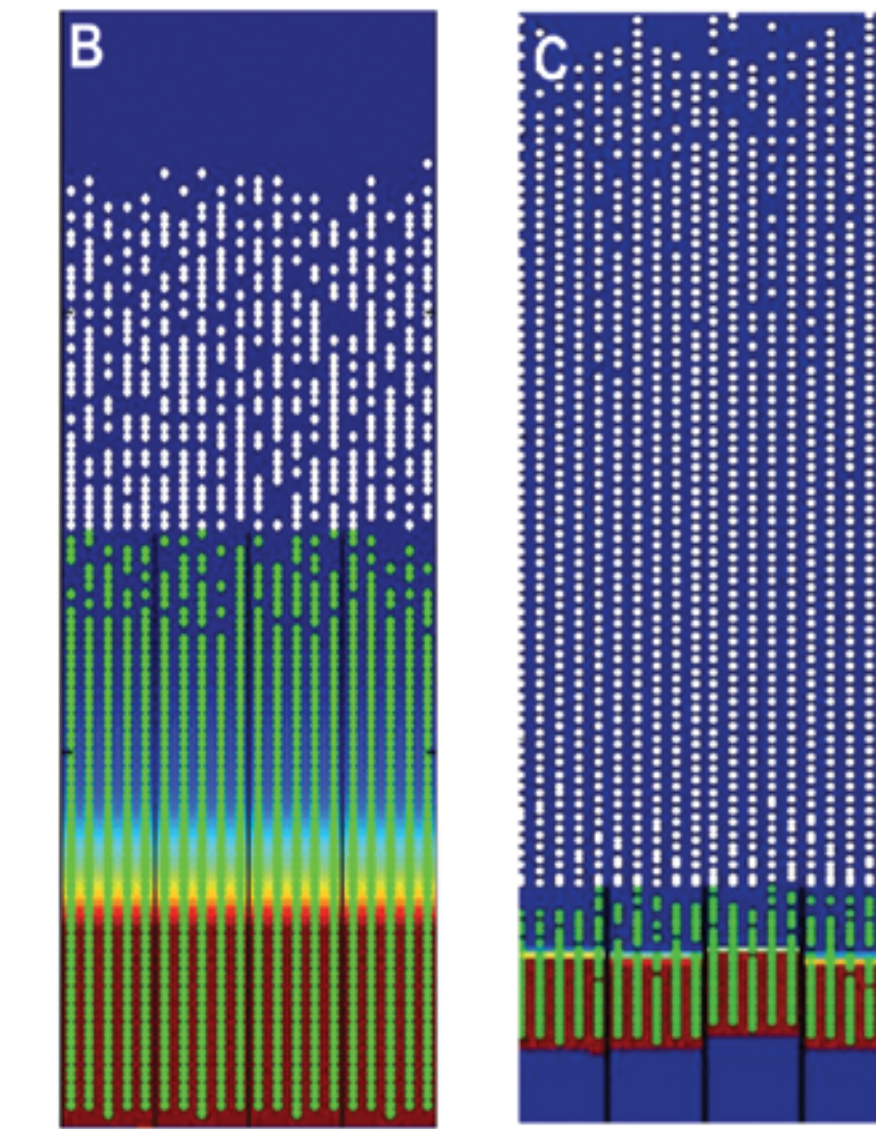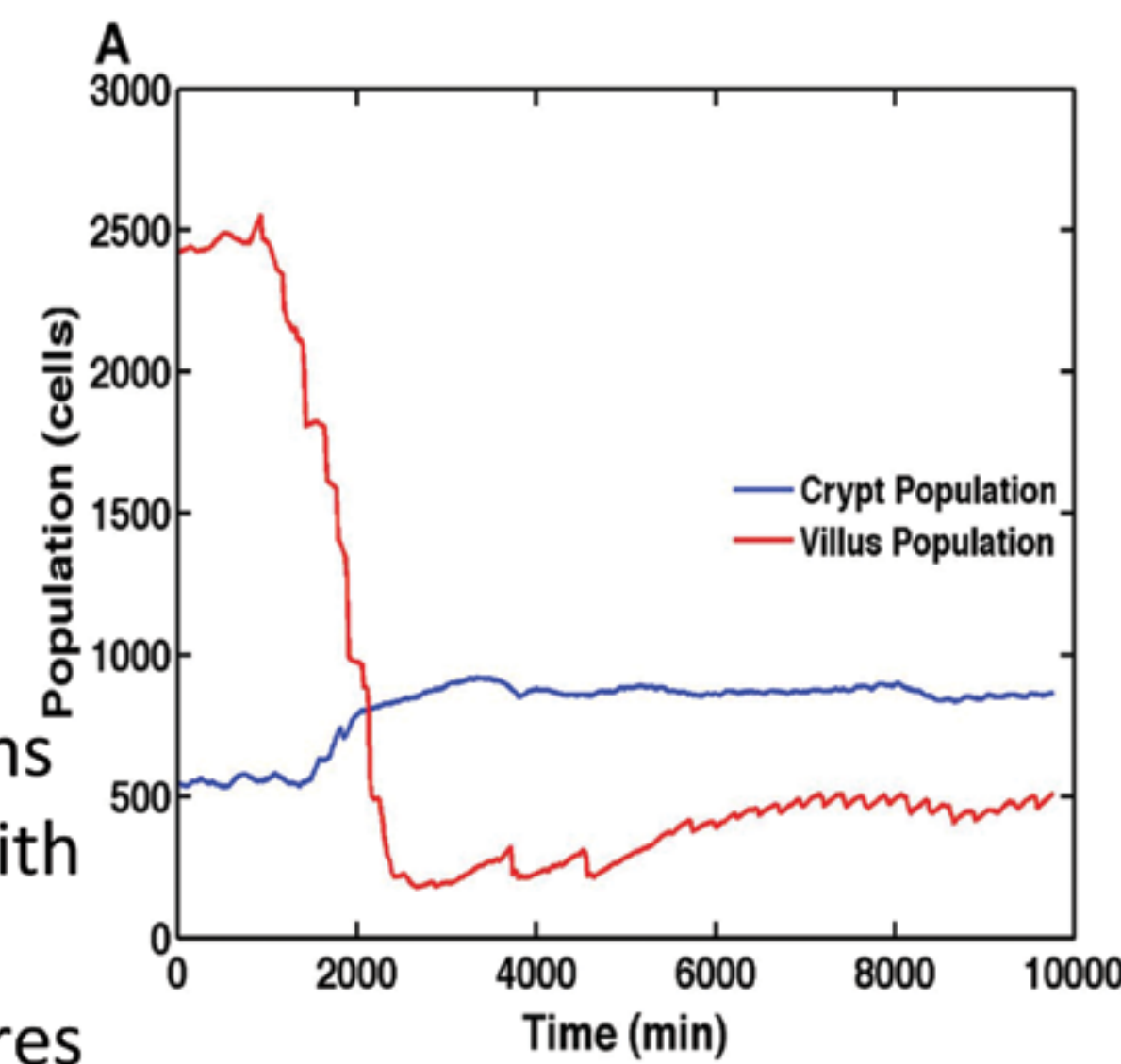


## Methods and Computational Model

**SEGMEnT_HPC** is an **Agent Based Model** that utilizes the actions and interactions of autonomous computational agents in order to study their behavior at a system level.

- **Gut Epithelial Cells (GECs)** function as the primary agents.
- **GECs** incorporate variables and rules corresponding to known molecules and pathways involved in differentiation and inflammation.
- **GECs** execute their rules to simulate signaling events to generate population-level system dynamics/tissue phenotypes

As Illustrated to the right, large tissue surfaces are discretized over a square grid. Equally sized sections of tissue are then distributed over an array of processors. SEGMEnT_HPC's master scheduler ensures that all of the processors stay synchronized as data regularly needs to be passed between neighboring processors. Transferred data includes differentiating cells migrating from crypt to villus as well a numerous chemokines, which undergo diffusion according to a first order discrete diffusion approximation on each time step of the simulation.
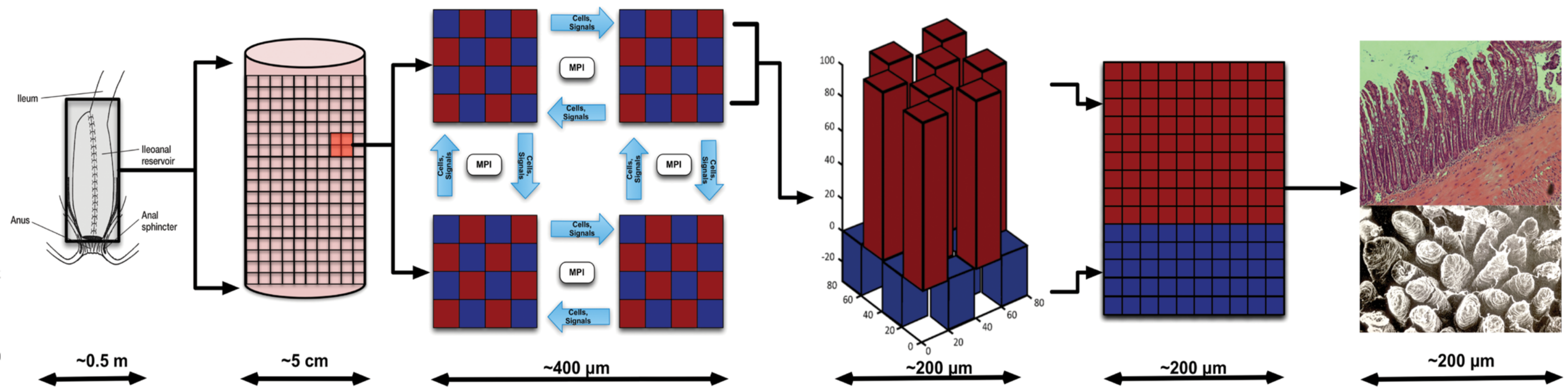


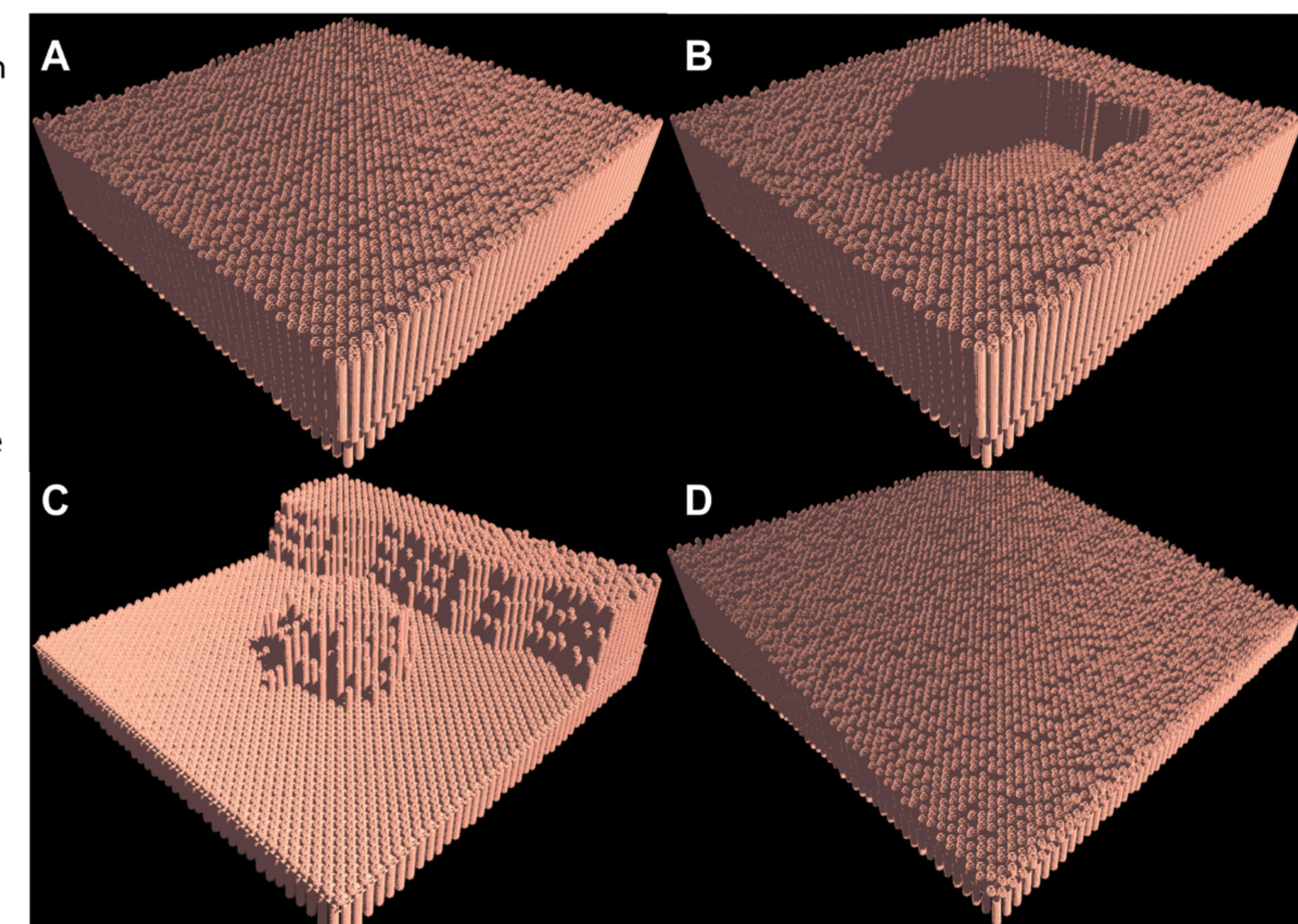## Scaling Studies: Towards Anatomic Scale
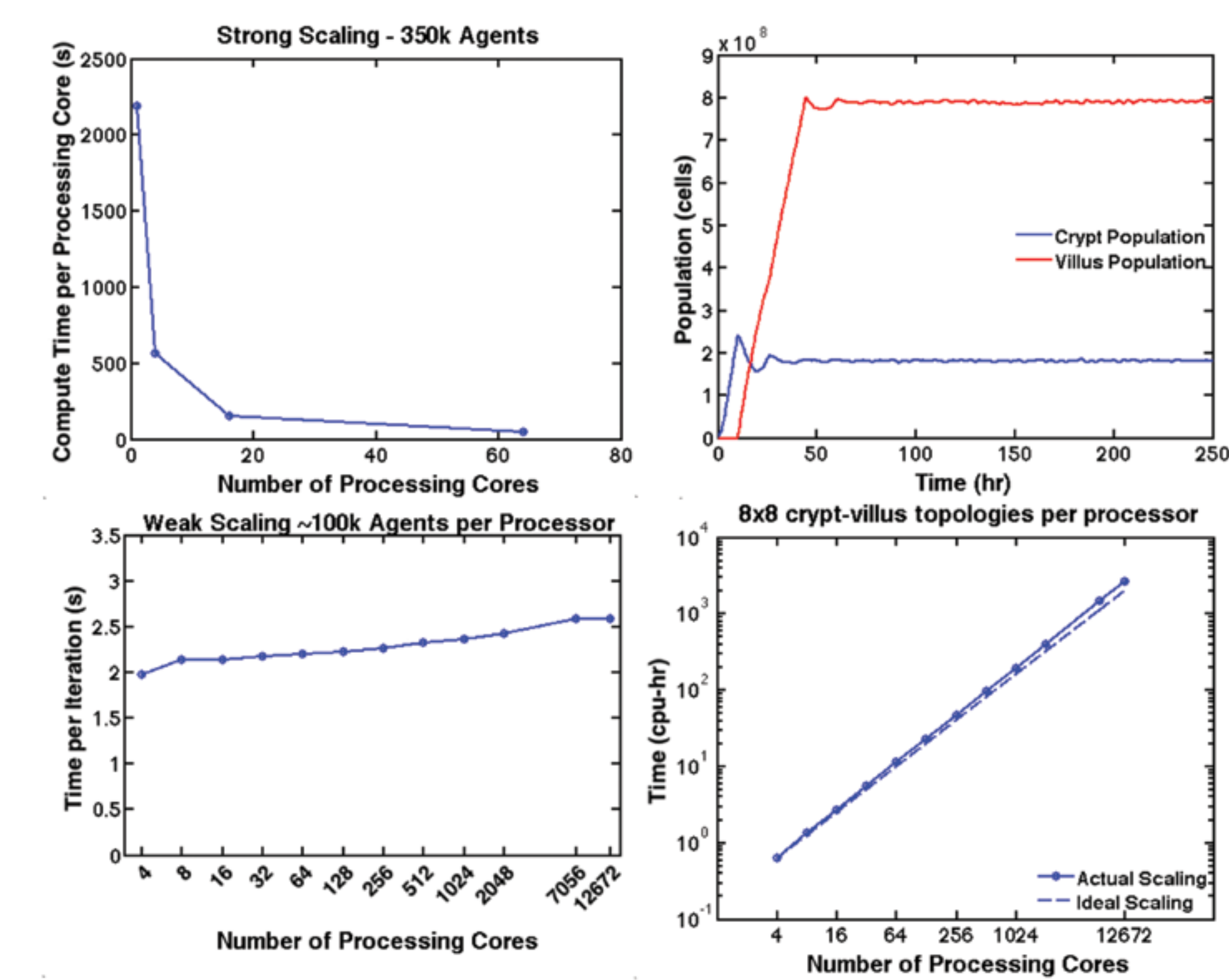


Scaling studies were performed on the Midway High Performance Computing Cluster at the University of Chicago Research Computing Center, and the Beagle supercomputer at the Computation Institute – University of Chicago. On the left, we show the strong (top) and weak (bottom) scaling curves for SEGMEnT_HPC. On the right we present a stable simulation of over 1 billion cells (top) and a demonstration of how SEGMEnT_HPC scales when simulating increasing areas of epithelial tissue (bottom).

## Results

Panel A displays a healthy section of ileal tissue. Crypts and villi are normal sized and the system exists in homeostasis. Panel B displays an ulceration resulting from excess TLR stimulation in otherwise healthy tissue. Panel C displays a section of tissue exhibiting a protective inflammatory response against low-grade inflammation, leading to a small island of metaplasia reversal near the metaplastic boundary.

Panel D shows a larger area of tissue representing a cutout (due to rendering limitations) of a ~1/4 scale ileal pouch unfolded into a flat grid. The degree of metaplasia becomes progressively worse as it nears the terminus of the pouch. The inflammatory stimuli in this case is represented by a flowing liquid (stool) that fills up the pouch and periodically empties. This results in a heterogeneous application of inflammatory stimuli, with a greater inflammatory response exhibited by tissue which is in direct contact with stool for the longest period of time.

Future research directions include extending the scale of SEGMEnT such that it represents truly anatomic scale tissues, implementing a more complex immune response, and peta-scale validation experiments to further parameterize the above ( and possibly other) signaling and metabolic networks.