Wnt-Notch Crosstalk Tunes Intestinal Crypt Spatial Patterning

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The crypts of the intestinal epithelium are one of the fastest regenerating tissues of the body, with almost complete turnover of 2,000 cells (in humans) every 2 – 6 days. Remarkably, this tissue maintains a consistent mosaic or checkerboard pattern of stem and Paneth cells at its base with tight control over stem niche size. Historically, it was thought that Notch signaling was solely responsible for this patterning, but more recently, it was shown that Wnt signaling cross-talks with Notch signaling through Hes1 which maintains the lateral inhibition mechanism. Additionally, it was shown that Wnt is extremely short range or even "pseudo-juxtacrine" instead of a linear gradient. To investigate the underlying design principles of this cross-talk and secretion mechanism, we formulated an integrated gene circuit combining both the canonical Notch and Wnt signaling pathways considering three secretion mechanisms: mesenchymal (non-transient), paracrine (transient), and juxtacrine (transient). Bifurcation analyses were conducted for two-cell and a multi-cell (n = 30) systems revealing that relative control over the Hes1 promoter (Notch vs Wnt) and the final average Wnt concentration in the system control the size and shape of the bistability region. In multi-cell models, the type of patterning also appeared to change as a function of the parameters. Monte Carlo bifurcation analysis with respect to cross-talk and leaky gene expression parameters suggested that all three secretion mechanisms were equally robust to parameter perturbation in the deterministic regime ($p = 0.621$, Chi-Squared). To determine if the secretion mechanism is significant in the stochastic regime, the ODE models were reformulated as Chemical Langevin Equation models and Epigenetic Landscapes" were constructed via non-parametric kernel density estimation, showing that transitions in the bifurcation plane corresponded to a phase transition like change in the quasi-potential.