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Optimality in the Development of Intestinal Crypts

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Intestinal crypts in mammals are comprised of long-lived stem cells and shorter-lived progenies, maintained under tight proportions during adult life. Here we ask what are the design principles that govern the dynamics of these proportions during crypt morphogenesis. We use optimal control theory to show that a stem cell proliferation strategy known as a 'bang-bang' control minimizes the time to obtain a mature crypt. This strategy consists of a surge of symmetric stem cell divisions, establishing the entire stem cell pool first, followed by a sharp transition to strictly asymmetric stem cell divisions, producing non-stem cells with a delay. We validate these predictions using lineage tracing and single molecule fluorescent in-situ hybridization of intestinal crypts in newborn mice and find that small crypts are entirely composed of Lgr5 stem cells, which become a minority as crypts further grow. Our approach can be used to uncover similar design principles in other developmental systems.