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Engineered Gene Circuits: From Clocks to Tumors

For synthetic biology applications, intracellular variability is a major obstacle to the fidelity required for “programming” cells. A major theme in our research has been to investigate how determinism can arise from the synchronization of a large number of cells. I will review our basic approach to synchronization within the context of engineered bacteria that can be used to safely produce and deliver therapeutics from within solid tumors. Specifically, we have engineered a clinically relevant bacterium to lyse synchronously at a threshold population density and to release genetically encoded cargo. Following quorum lysis, a small number of surviving bacteria reseed the growing population, thus leading to pulsatile delivery cycles. We have extended this approach to small ecologies, whereby engineered periodic lysis can lead to ecological stability and generate in-teresting drug delivery schemes. Our current work explores how a small number of interacting species behave when constrained to grow on a surface as opposed to a well-mixed culture. It is known that non-hierarchical competitive dynamics, such as cyclical interactions, can sustain biodiversity. We have rationally designed a minimal microbial community with three strains of *E. coli* that cycli-cally interact through (i) the inhibition of protein production, (ii) the digestion of genomic DNA, and (iii) the disruption of the cell membrane. We find that intrinsic differences in these three major mechanisms of bacterial warfare lead to an unbalanced community that is, counterintuitively, dominated by the weakest strain. This work represents our first steps to probe the complexities of small engineered ecologies in environments that begin to approximate solid tumors.