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Synthetic communities, the sum of parts

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Working title: The Sum of its Parts

Cooperation between cells is one of evolution's fundamental innovations. Cooperation allows cells to specialize: different members of a consortium assume different responsibilities, increasing overall productivity and allowing for more complex behavior than is possible with a single cell or a monoculture{Wintermute2010}. These features of natural systems have attracted the attention of synthetic biologists, who have made the engineering of cooperation between cells a long-standing goal. On page {} of this issue, Chen et al.{Chen2015} report on the creation of a synthetic consortium of cooperating *E. coli*; the design principles they demonstrate have important implications for the construction of multicellular synthetic systems.

Mutual, obligatory cooperation between cells is widespread in nature. The developmental programme of a complex multicellular organism leads to a bewildering array of specialized, cooperating cell types; but even unicellular prokaryotes are found primarily in consortia such as biofilms, whose community structure provides for both sharing of metabolites and resistance to environmental perturbations{Brenner2008}. Specialization is key to productive cooperation because it allows for spatial segregation of function{Wintermute2010}: for example, one species in a biofilm might be responsible for adhesion, while the other synthesizes an expensive metabolic product.

As the field of synthetic biology begins to address problems that span from bioremediation to manufacturing, energy to human health and medicine{Slusarczyk2012}, engineered multicellular behavior is emerging as an important tool for building advanced synthetic systems that robustly perform complex behaviors. Recent work{Bacchus2013} has ranged from density-dependent population control to spatial patterning to entrainment of spatially separate oscillating populations. However, most previous reports describe a single isogenic strain of cells or two distinct populations of cells with distinct behaviors such as "senders" and "receivers," each running their own complete, independent genetic program

Chen et al. {Chen2015} take a different approach. The authors' goal remains synchronous population-wide oscillations; but instead of synchronizing a set of independent oscillators, the authors implement a single dual-feedback oscillator spanning two non-isogenic populations of *E. coli*, an "activator" strain and a "repressor" strain. The two strains communicate with a pair of orthogonal intercellular signaling molecules, and when they are cultured together the two populations begin to oscillate in synchrony. The oscillatory behavior of the consortium is mutually obligatory: the two populations together display an emergent behavior that neither constituent is capable of alone.

This "division of labor" approach has broad implications for the design of synthetic multicellular systems. First, observations of natural systems strongly suggest that such consortia are robust to various perturbations{Brenner2008}, and Chen et al.'s experimental results confirm this observation. Due to topology of interlocking feedback loops, the oscillations are remarkably robust and persistent, and the authors observed oscillations even as they varied the gene circuits' topologies, the promoter strengths and the initial population ratios. Such robustness is

particularly important for many of the projected industrial applications of synthetic biology, including bioprocessing and bioremediation{Shong2012}.

Second, specialization of consortia subpopulations allows for the engineering of consortium-wide behavior that would be difficult to perform with a monogenic strain. In another example, Tamsir et al{Tamsir2011} described complex boolean computation based on the spatial arrangement of bacterial colonies encoding simpler logic gates: the colonies communicated via chemical “wires” composed of freely-diffusing quorum-sensing molecules. As with Chen et al., the implementation of the desired behavior is divided among multiple cell types, allowing for better scalability and control over consortium behavior.

Finally, the construction of synthetic multicellular consortia has implications for understanding and manipulating natural communities of cells. Of key importance are the molecular mechanisms that stabilize the social interactions{Xavier2011}: how are intercellular signals sensed, processed and integrated? How are cheaters punished and cooperators rewarded? Many of these answers have direct relevance to health and human disease, particularly in ongoing work to understand the human microbiome{Microbiome2012}. This “virtual organ” {Evans2013} of symbiotic microbes has an increasingly clear role in metabolism, inflammation, immunity, and even neurochemistry, but the structure and dynamics of the microbial community remains unclear. Such knowledge will be crucial as we begin to manipulate the microbiome in pursuit of better health outcomes.

More broadly, understanding cells’ social context presents an array of therapeutic opportunities. Many harmful microbes modulate their pathogenesis via intercellular communication{Griffin2004}; the development of antibiotic resistance in pathogens may be due to bacterial “charity work”{Lee2010}; dysregulation in social interaction in immune cells results in autoimmune disorders{Xavier2011}. Particularly intriguing is the growing conception of human cancers as cooperating communities of clonal populations{Tabassum2015}. The emerging story is familiar: diversity and heterogeneity give rise to specificity, cooperation and robustness against therapeutic assault. A deeper understanding of the community dynamics may point the way to new therapeutic approaches that consider that target the intratumor ecology instead of specific subpopulations, and synthetic models of such communities may play a key role in advancing our understanding of them.

Synthetic communities of cooperating cells have broad potential impact, but a several key challenges remain. First, despite recent advances{Bacchus2013}, the number of orthogonal cell-cell communication channels remains limited. Intercellular communication modules imported from other kingdoms will continue to be useful, such as a recently-reported communication channel in yeast based on auxin biosynthesis{Khakhar2015}. Second, even though a small number of parameters have been shown to produce a broad range of behaviors{Youk2014}, many synthetic systems are still based on traditional density-dependent quorum sensing. Cells cooperate to implement a broad range of behaviors, including diversification, patterning, information processing and population control{Chuang2012}; a larger palette of reliable, robust design motifs would broaden the impact of our limited communication

channels substantially. Finally, interspecies (and interkingdom) communication has only been explored to a limited extent{Weber2007}, despite abundant evidence that it occurs in many natural systems{Wintermute2010}.

The study by Chen et al. demonstrates the fundamental power of specialization and cooperation, recapitulating a strategy employed by many natural systems. The authors demonstrate the forward design of an emergent behavior programmed into two non-isogenic strains of bacteria; the behavior is robust and only arises when the two strains are in close contact. Their work serves as a powerful inspiration to biologists looking to engineer synthetic communities of cooperating cells or interact with natural ones, reminding us that such communities are frequently more than the sum of their parts.

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