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High-throughput Analysis of Spatio-temporal multicellular dynamics

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I will present molecular genetics of a complex spatio-temporal patterning during the development of social amoeba *Dictyostelium*. Nutrient-deprived amoebae aggregate to form a multicellular structure by chemotaxis, moving towards propagating waves of cyclic AMP that are relayed from cell to cell. Organizing centers are dynamic entities consisting of cores of outwardly rotating spiral waves that self-organize in a homogeneous undifferentiated cell population. The number of cores determines the size of aggregation territory and hence the size of mature fruiting-bodies. Here we see a hallmark of self-organization - an emergence of a spatio-temporal pattern through amplification of initial fluctuations.

Using wavelet analysis and a rigorous detection of spatial phase singularities by the time-delay embedding technique, we discovered that mutants of the cyclic AMP/protein kinase A pathway fail to organize coherent long-range wave territories, due to the appearance of numerous spiral cores. A theoretical model that incorporates the current understanding of this pathway suggests that auto-regulation of cell excitability mediated by protein kinase A acts to optimize the number of signaling centers. I will discuss how the feedback mechanism is able to effectively make use of random firing events to achieve the desired tissue-size.

We have also examined over 2,500 mutagenized clones for defects in various steps in this process, using semi-automated highly parallel time-lapse imaging and gene sequencing to visualize at millimeter scales all stages of the life cycle with the goal of a complete record of the temporal and spatial dynamics of each mutant. Included in this analysis is the onset and evolution of traveling cAMP waves, characteristic of early development in this organism; the transition from stationary signaling cells to cells streaming toward an organizing center; and the motion of the multicellular slug as it forms a mature fruiting body. I have introduced a coarse-grained phenotypic space for clustering mutants in the form of a 'phenotypic array'. Approximately 4% of the clonal lines created in an unbiased forward screen were mutant at one of the life-cycle stages. Many of these, along with known mutants, could be ordered by hierarchical clustering into functional groups. Among the mutations identified were independent occurrences of known genes and new mutants in common phenotype clusters, and mutant phenotypes originating from intergenic insertions. The resulting dataset allows one to search and retrieve life cycle movies and analysis on a gene-by-gene and phenotype-by-phenotype basis.