Synthetic multicellular assemblies differentiate in morphogen gradients

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The development of living organisms from a single cell to a multicellular differentiated system occurs through successive patterning events and presents a prominent example of self-organization. During this process, cells read morphogen gradients to infer their position along the multicellular organism and differentiate accordingly [1]. However, morphogen diffusion, positional interpretation and information propagation are challenging processes to investigate *in vivo*. In a bottom-up approach, we assemble emulsion-based synthetic cells into multicellular structures and we study the response of a cell-free gene network in a morphogen gradient. We find that the interplay of diffusion kinetics and the induction of the gene network patterns the assemblies into several regions. We study how reliably cells can determine their position within an assembly using an information-based framework developed for morphogenesis [2]. We quantify the positional information extracted by the gene network in the presence of uncertainties. We learn with computational modeling that positional information is limited by variability in the gene expression that interprets the morphogen gradient. We characterize how the total positional information of the system is affected by the temporal evolution of system components [3]. This approach demonstrates how principles of self-organization in living organisms can be investigated in artificial systems.

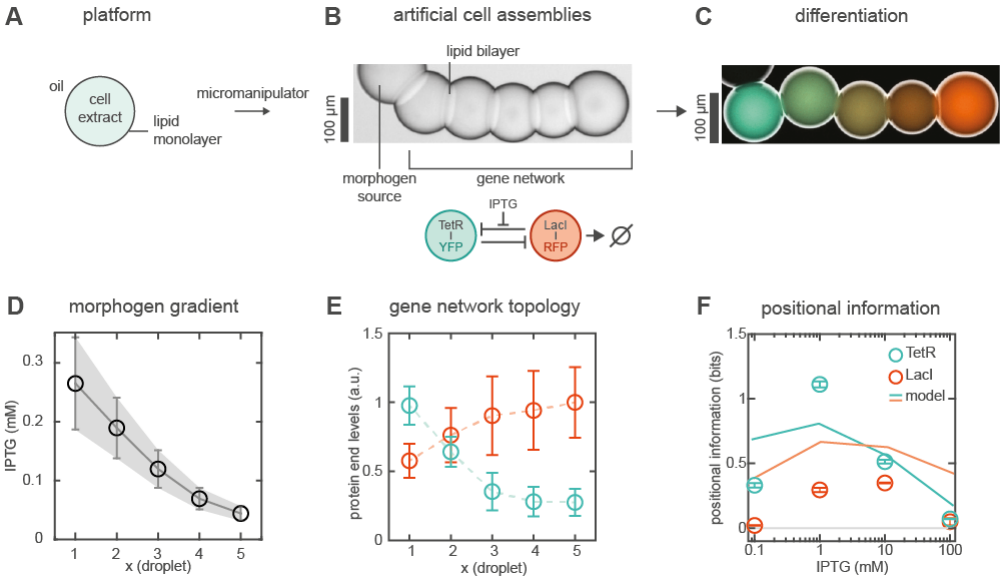

Figure – Synthetic cell assemblies interpret a morphogen gradient into positional information. Water-in-oil droplets (A) are assembled into multi-cellular structures with lipid bilayer interfaces (B). A morphogen diffuses from a source droplet into an array of identical receivers, activating a gene network and generating differentiated protein expression across the assembly (C). The morphogen gradient (D) induces two opposite gene expression gradients (E) and causes the system to gain positional information (F).

[1] Shilo, B.-Z. & Barkai, N. Buffering global variability of morphogen gradients. *Developmental Cell* (2017).

[2] Tkacik, G., Dubuis, J. O., Petkova, M. D. & Gregor, T. Positional information, positional error, and readout precision in morphogenesis: A mathematical framework. *Genetics* (2014).

[3] Dupin, A., Aufinger, L., Styazkhin, I., Rothfischer, F., Kaufmann, B., Schwarz, S., Galensowske, N., Clausen-Schaumann, H., Simmel, F.C. Synthetic cell-based materials extract positional information from morphogen gradients. *Science Advances*, in press.