

Robert Jinkerson, Biological Engineering

Year in School: Junior

Hometown: Florissant, MO

Faculty Mentor: Dr. Gabor Forgacs, Physics

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Bioprinting : From self-assembling multicellular spheroids to three-dimensional tissue structures

Embryonic development represents a sequence of spectacular morphogenetic transformations involving intense cellular rearrangements. The living organism acquires its final form through physical shape transformations, a particular one being based on the apparent liquid-like properties of tissues composed of adhesive and motile cells. The Differential Adhesion Hypothesis (DAH) provides the molecular basis for these properties, which in turn provide the biophysical basis for a number of morphogenetic processes. In the present study we exploit these self-organizing properties to build functional 3D tissue constructs of prescribed shape. Spherical cell aggregates were embedded contiguously into biocompatible gels creating templates for geometric configurations encountered in living organisms. Depending on the properties of the gels and the initial arrangements, upon incubation the aggregates fused into histologically relevant configurations. Model simulations based on DAH reproduced the observed shapes, the only control parameter being the cell-gel interfacial tension. The results of these proof of concept experiments were employed in the development of a rapid prototyping technique, "bioprinting". Due to their liquid like properties aggregates can be regarded as "bioink" droplets. We developed a protocol and a special cutting device to produce standard aggregate size and customized the hardware and software of the bioprinter to improve the accuracy of embedding. In our efforts to develop freezing protocols for the aggregates we tested various cryoprotective agents which allow for long term storage of the bioink particles. Our experiments and modeling efforts represent a novel approach to tissue engineering, an important step toward building complex organ modules via biological self-assembly.