Cellular behavior within tissues is driven by environmental cues that vary temporally and spatially with granularity on the order of individual cells. Local cell-cell interactions via secreted and contact-mediated signals play a critical role in these pathways. In order to study these dynamic small-scale processes, we have developed a micromechanical platform to control microscale cell organization so that cell patterns can be reconfigured dynamically. This tool has been employed to deconstruct the mechanisms by which liver-specific function is maintained in hepatocytes upon co-cultivation with stromal support cells. Specifically, we examine the relative roles of cell contact and short-range soluble signals, duration of contact, and the possibility of bi-directional signaling.

The device consists of two silicon parts that can be locked together either to allow cell-cell contact across the two parts or to separate the cells by a uniform gap of approximately 80 µm (Figs. 1 and 2). Switching between these two states is actuated simply by pushing the parts manually using tweezers; no micromanipulation machinery is necessary. Micron-scale precision is possible due to a 10:1 mechanical transmission ratio and microfabricated snap locks, both of which are monolithically incorporated into the silicon structure. The entire device is fabricated in a simple single-mask process using through-wafer deep reactive ion etching. To provide a surface compatible with cell culture, the surface is coated with a layer of polystyrene and plasma-treated, providing a standard tissue-culture surface.

▲ Figure 1: Hepatocytes separated from stromal cells by 80-micron gaps, which prevent contact between the two cell types.

▲ Figure 2: Hepatocytes and stromal cells cultured with no separation. The system can be switched back and forth between the states shown in Figures 1 and 2.