cell in a large population of cells. The cell analysis and sorting apparatus contains individually addressable cell locations. Each location is capable of capturing and holding a single cell, and selectively releasing that cell from that particular location. In one aspect of the invention, the cells are captured and held in wells, and released using vapor bubbles as a means of cell election. In another aspect of the invention, the cells are captured, held and released using electric field traps.

According to one aspect of the present invention, the cell analysis and sorting apparatus has an array of geometric sites for capturing cells traveling along a fluid flow. The geometric sites are arranged in a defined pattern across a substrate such that individual sites are known and identifiable. Each geometric site is configured and dimensioned to hold a single cell. Additionally, each site contains a release mechanism to selectively release the single cell from that site. Because each site is able to hold only one cell, and each site has a unique address, the apparatus allows the user to know the location of any particular cell that has been captured. Further, each site is independently controllable so that the user is able to arbitrarily capture cells at select locations, and to release cells at various locations across the array.

In one embodiment of the present invention, the geometric sites are configured as wells. As a fluid of cells is flown across the array of specifically sized wells, cells will fall into the wells and become trapped. Each well is sized and shaped to capture only a single cell, and is configured such that the cell will not escape into the laminar flow of the fluid above the well. The single cell can be held inside the well by gravitational forces. Each well can further be attached via a narrow channel to a chamber located below the well. Within the chamber is a heating element that is able to induce bubble nucleation, the mechanism for releasing the cell from the site. The bubble creates volume expansion inside the chamber which, when filled with fluid, will displace a jet of fluid out of the narrow channel and eject the cell out of the well. Fluid flow above the well will sweep the ejected cell away to be either collected or discarded.

In another embodiment of the present invention, the geometric sites are formed from a three-dimensional electric field trap. Each trap comprises four electrodes arranged in a trapezoidal configuration, where each electrode represents a comer of the trapezoid. The electric fields of the electrodes create a potential energy well for capturing a single cell within the center of the trap. By removing the potential energy well of the trap, the cell is ejected out of the site and into the fluid flow around the trap. Ejected cells can then be washed out and collected or discarded.

In yet another embodiment of the present invention, an integrated system is proposed. The system can be a microfabrication-based dynamic array cytometer ($\mu$DAC) having as one of its components the cell analysis and sorting apparatus previously described. To analyze a population of cells, the cells can be placed on a cell array chip containing a plurality of cell sites. The cells are held in place within the plurality of cell sites in a manner similar to that described above and analyzed, for example, by photometric assay. Using an optical system to detect fluorescence, the response of the cells can be measured, with the intensity of the fluorescence reflecting the intensity of the cellular response. Once the experiment is complete, the cells exhibiting the desired response, or intensity, may be selectively released into a cell sorter to be further studied or otherwise selectively processed. Such an integrated system would allow researchers to also look at the cell's time response.

Further features and advantages of the present invention as well as the structure and operation of various embodiments of the present invention are described in detail below with reference to the accompanying drawings.

## BRIEF DESCRIPTION OF THE DRAWINGS

This invention is pointed out with particularity in the appended claims. The above and further advantages of this invention may be better understood by referring to the following description when taken in conjunction with the accompanying drawings, in which:

FIGS. **1**A, **1**B, **1**C, and **1**D show the mechanism by which one embodiment of the present invention uses to capture, hold and release a single cell.

FIGS. **2**A, **2**B, and **2**C show a process by which another embodiment of the present invention uses to capture, hold and release a single cell.

FIGS. **3**A and **3**B show a top-down view of the cell sorting apparatus of FIG. **2**.

FIG. **4** shows an exploded view of the cell sorting apparatus of FIG. **2**.

FIG. **5** shows an exploded view of yet another embodiment of the present invention in which a cell sorting apparatus is integrated into a fluorescence-detecting system.

FIG. **6** is the thermodynamic pressure-volume diagram for water.

FIG. **7**A shows a top view of a resistor of the present invention.

FIG. **7**B shows a cross-section of the resistor of FIG. **7**A.

FIG. **8** shows thermal resistances as seen by a heater of the present invention.

FIGS. **9**A and **9**B show flow lines for flow over rectangular cavities of different aspect ratios.

FIG. **10** shows a schematic of forces on a particle in a well.

FIG. **11**A shows a top view of a heater of the present invention.

FIG. **11**B shows a cross-section of the heater of FIG. **11**A.

FIG. **12**A shows a side view of a cell well of the present invention.

FIG. **12**B shows a top-down view of the cell well of FIG. **12**A.

FIGS. **13**A, **13**B, and **13**C shows a top-down view of a silicon processing mask set for use in the present invention.

FIG. **14** shows a top-down view of a glass processing mask.

FIG. **15** shows a diagram of a flow system for testing devices of the present invention.

FIG. **16**A shows a top-down view of a flow chamber of the present invention.

FIG. **16**B shows a side view of the flow chamber of FIG. **16**A.

FIG. **17** is a graph of pressure drop vs. flow rate for the flow chamber of FIGS. **16**A and **16**B.

FIG. **18**A shows a top-down view of the chamber base of flow chamber of FIG. **16**A and **16**B.

FIG. **18**B shows a side view of the chamber base of FIG. **18**A.

FIG. **18**C shows a top-down view of the chamber lid of flow chamber of FIG. **16**A and **16**B.

FIG. **18**D shows a side view of the chamber lid of FIG. **18**C.