

SYSTEMS AND METHODS FOR CELL ANALYSIS USING CHEMFET SENSOR ARRAYS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims benefit of U.S. Provisional Application No. 63/519,515, and of U.S. Provisional Application No. 63/519,526, both of which were filed August 14, 2023. All applications identified in this section are incorporated herein by reference, each in its entirety.

OVERVIEW

[0002] Cell-level and subcellular measurements of glycolytic activity would permit scientists previously unavailable access to the origins of known, wide scale alterations in energy utilization by healthy and diseased cells in models of cancer. Dating back 100 years to 1923, Otto Warburg first described global changes in cellular metabolism that accompany the progression of cancer in human tissues, as tumor cells lacking vascular support were starved for oxygen, shifting away from oxidative phosphorylation of carbon substrates toward glycolytic means of generating ATP. These changes in cellular fuel come with concomitant increases in lactate efflux and lowered pH of the cellular microenvironment. The Warburg Effect, as it has come to be known, has greater than 3,400 mentions in the primary scientific literature in the last decade alone, and yet the only means available to interrogate this complex biochemical reprogramming still requires tissue level measurements of oxygen and pH with cell populations numbering in the tens of thousands at the least.

[0003] The tumor environment is richly complex, with variations in cellular composition, respiratory rate, fuel consumption and waste output originating at the single or small number cellular level. For instance, if investigators could use a unique glycolytic signature to visualize the appearance of a metastatic tumor cell among an unperturbed and otherwise healthy population, the metabolic demands of those few early tumor cells could inform scientists a great deal about the relationships between cancerous and untransformed cells as they rapidly divide and overtake the resources available to the population.

[0004] In contrast to the current cell analysis systems that interrogate cell populations in the tens of thousands of cells, a cell analysis system of the present disclosure can provide an end user with real-time visualization of metabolism for a single cell functioning in and among a much greater population of cells. Cell analysis systems of the present disclosure can measure metabolic as well as bioelectric activity from single, living cells with subcellular addressability and simultaneous data acquisition from cells numbering in single digits to about 100,000 in a single analysis. Cell analysis systems of the present disclosure provide electroscopic imaging, which is an image taken at a defined

sampling interval of cellular response from sensors covering a cell footprint or an image of cellular response for sensors detecting cellular effluent.

[0005] As such, cell analysis systems of the present disclosure can provide an end user with time-course graphic and imaging data of individual cellular responses as elicited by perturbations in the cellular microenvironment and monitored by ChemFET sensors. Further, electroscopic imaging can be compared to optical imaging to provide an additional dimension of information regarding cell analysis and cell number. For example, comparing optical imaging of immunocytochemical studies using known marker panels provides a functional and phenotypic signature of data obtained for each cell analyzed using a ChemFET-based cell analysis system of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] The novel features of the present teachings are set forth with particularity in the appended claims. A better understanding of the features and advantages of what is disclosed herein will be obtained by reference to the following detailed description that sets forth illustrative examples, in which the principles of the present teachings are utilized, and the accompanying drawings of which:

[0007] FIG. 1 is a block diagram that illustrates generally various components of a cell analysis system of the present disclosure.

[0008] FIG. 2 is a schematic representation that illustrates generally a fluid delivery system of the present disclosure.

[0009] FIG. 3 is a front view that illustrates generally a manifold device of the present disclosure.

[0010] FIG. 4 is a front isometric section view that illustrates generally a manifold device of the present disclosure.

[0011] FIG. 5A through FIG. 5D are section views of a fluidic manifold of the present disclosure that illustrate generally features of the fluidic manifold.

[0012] FIG. 6 is a top isometric view of a manifold block of the present disclosure that illustrates generally features of a manifold block.

[0013] FIG. 7 is a top isometric view of a manifold block valve port of the present disclosure that illustrates generally features of a manifold block valve port.

[0014] FIG. 8 is a top isometric view of the manifold block of FIG. 6 that illustrates generally various features of a manifold block in phantom view.

[0015] FIG. 9A and FIG. 9B are schematic diagrams that illustrate generally a flow path flow path of a fluid delivery system of the present disclosure.

[0016] FIG. 9C is a graph that illustrates generally flow rates as a function of applied pressure in a fluid delivery system of the present disclosure.

[0017] FIG. 10 is a schematic exploded view that illustrates generally a chip clamp assembly of a cell analysis system of the present disclosure.

[0018] FIG. 11 is a schematic representation that illustrates generally a flow cell assembly formed between a fluidic interface device and a chip device of the present disclosure.

[0019] FIG. 12 is an exploded top perspective view illustrating generally a fluidic interface device of the present disclosure.

[0020] FIG. 13 is an exploded bottom perspective view illustrating generally a fluidic interface device of the present disclosure.

[0021] FIG. 14 is a front perspective view that illustrates generally a chip clamp assembly of the present disclosure.

[0022] FIG. 15A is a bottom perspective view that illustrates generally a chip clamp assembly of the present disclosure.

[0023] FIG. 15B is a perspective view that illustrates generally a chip clamp assembly shuttle of the present disclosure.

[0024] FIG. 16 is an exploded section view that illustrates generally a fluidic interface device of the present disclosure in relationship to a chip device and a chip thermal control assembly.

[0025] FIG. 17 is a front perspective view that generally illustrates a cell analysis instrument of the present disclosure.

[0026] FIG. 18 is a front perspective section view that illustrates generally an analysis compartment of the cell analysis instrument of FIG. 17.

[0027] FIG. 19 is an additional front perspective section view that illustrates generally an analysis compartment of the cell analysis instrument of FIG. 17.

[0028] FIG. 20 is a front perspective section view that illustrates generally environmental control and computer compartment of the cell analysis instrument of FIG. 17.

DETAILED DESCRIPTION

[0029] In order to provide a cell-compatible analysis environment, cell analysis systems and instruments of the present disclosure can include an automated fluidic system that provides an end-user control over selection and flow parameters for reagent delivery to cells in an analysis chamber, as well as selection of gases in equilibrium with various reagents and solutions that can control oxygen, pH, buffer, nutrient and pharmacological interventions desired by the user. As such, user-selected precision temperature control of ChemFET devices, reagents and solutions, as well as the analysis compartment provide consistency in the cell analysis system environment. Additionally, cell analysis systems and instruments of the present disclosure provide an end user with time-course graphic and imaging data of individual cellular responses as elicited by perturbations in the cellular microenvironment and monitored by ChemFET sensors. Graphic data can be presented illustrating a time course of response for individual cells or for any selected group of cells as an average time course of response. Imaging data of cellular responses can be presented as an electroscopic image, which is an image taken at a defined sampling interval of cellular response from sensors covering a cell footprint or an image of cellular response for sensors detecting cellular effluent.

[0030] FIG. 1 is a block diagram that illustrates generally various components of a cell analysis system of the present disclosure. Cell analysis system 3000 can include chip clamp assembly 1000. Various cell analyses performed using cell analysis system 3000 are performed using a sensor array chip, which is part of a sensor array device. Fluidic interface device 600 is depicted in FIG. 1 as mounted to chip clamp assembly shuttle 700, and is depicted positioned at an end of chip clamp assembly base 800, which is a position that chip clamp assembly shuttle 700 can be moved to while an experiment is not in progress. For performing an analysis using cell analysis system 3000, sensor array device 500 once mounted upon the underside of fluidic interface device 600 to form a flow cell assembly can be positioned by chip clamp assembly shuttle 700 over pogo pin block 550 and then seated upon it. As recited herein, the terms “sensor” and “pixel” can be used interchangeably, as can as well as “sensor array” and “ChemFET sensor array”. Additionally, the terms “sensor array chip,” “sensor array device,” “sensor device,” “sensor chip,” “chip,” and derivatives of these terms can be used interchangeably. For example, sensor array device 500 is also referred to as chip device 500, and sensor device 500. During an analysis, activity of cells plated on a sensor device surface can be detected by chemFET sensors of sensor array device 500.

[0031] Fluidic interface device 600 provides a top flow cell cover for chip device 500 that reversibly seals over a top surface of chip device 500 to functionally provide a flow cell chamber; operatively also an analysis chamber. As recited herein, “flow cell chamber” and “analysis chamber” can be used interchangeably. Fluidic system 1200 and pneumatic system 1400 form fluid delivery

system 1500, which provides fluid distribution through a flow cell via fluidic interface device 600. For example, as depicted in FIG. 1, fluidic interface device 600 is in fluid communication with fluidic manifold 1100 through fluidic manifold outlet line 1220. As will be described in more detail herein, fluidic interface device 600 can be placed into selective and controllable fluid communication via system valve V12 with any of the solution containers 1230 A-F, 1240 and 1250. Solution containers 1230 A-F, 1240 and 1250 can be in fluid communication through manifold input lines 1210A-1210H as depicted in FIG. 1. Pneumatic system 1400 is in fluid communication with fluidic system 1200 via gas lines 1310A-1310E. As depicted in FIG. 1, pneumatic system 1400 is configured to selectively and controllably apply a head pressure over solution containers 1230 A-F, 1240 and 1250, thereby providing motive force for fluid distribution through cell analysis system 3000. With respect to return to waste, fluidic interface device is in fluid communication with flow cell outlet line 1262, which is in controllable fluid communication via 2-way system valve V14 with waste container 1270. As will be described in more detail herein in reference to FIG. 2, depending on the valve state of V14, flow cell outlet line 1262 is in fluid communication with waste container 1270 via restriction line 1266 or via flow cell waste line 1264. Fluidic interface device 600 additionally provides fluid communication with waste container 1270 through fluidic manifold waste line 1260.

[0032] With respect to movement and positioning of a sensor array device, chip clamp assembly shuttle 700 of chip clamp assembly 1000 is mounted to chip clamp assembly base 800. As depicted in FIG. 1, fluidic interface device 600 can be positioned over chip device 500. With the application of a clamping force, fluidic interface device 600 can be engaged with chip device 500, thereby forming a flow cell assembly. Once flow cell assembly is formed, chip clamp assembly shuttle 700 can position the flow cell assembly over pogo pin block 550 and chip thermal control assembly 900. Chip thermal control assembly 900 of the present disclosure can include a thermoelectric cooling (TEC) device in contact with an aluminum base on one side, and in contact with a cooling assembly on the opposite side of the TEC. With the application of a clamping force, the flow cell assembly positioned over pogo pin block 550 and chip thermal control assembly 900 can be engaged with electronic connections of pogo pin block 550. Additionally, the engagement ensures contact of the TEC with the temperature control assembly. With respect to providing chip thermal control that can enable a wide variety of cell analysis protocols, chip thermal control assembly 900 can provide precision thermostating of chip device 500 over a temperature range of 4°C to 60°C within +/- 0.1 C.

[0033] Chip clamp assembly 1000 and fluid delivery system 1500 can be housed in an insulated and thermally controlled compartment of cell analysis system 3000. As such, in addition to having fluid delivery system 1500 providing a flow cell at close to atmospheric pressure and chip thermal control assembly 900 that can maintain a chip at a targeted temperature, a cell analysis system of the present

disclosure can maintain the temperature of solutions and reagents at a target temperature. For example, an insulated and thermally controlled compartment that houses chip clamp assembly 1000 and fluid delivery system 1500 can be maintained over a temperature of between about 10°C to about 50°C; moreover a selected temperature in a range of between about 20°C to about 37°C, thereby enabling an end user the flexibility to select a temperature suited to a targeted experiment. Accordingly, a cell analysis system of the present disclosure can maintain a cell-compatible environment within a flow cell.

[0034] With respect to control and processing for cell analysis system 3000 of FIG. 1, processing electronics assembly 100 of FIG. 1 can include components such as a reader board, a valve board and computer processing assembly, which can be responsive to interactive end user input through user display 150. Processing electronics assembly 100 can include an array controller that is a component on a reader board, which can provide various power supplies and bias voltages, control and timing signals to sensor array device 500, as well as provide a data and processor interface for high-speed acquisition of data from sensor array device 500. Processing electronics assembly 100 that includes a reader board and computer processing assembly that can control the valve board and fluidic processing of cell analysis system 3000, as well as manage setup of experiments, storage of sensor output from experiments, generate log files for experiment results and instrument operation, and process experiment output data for presentation to the user.

[0035] Valve board 200 of FIG. 1 is controlled by processing electronics assembly 100. As such, control of the valving for both fluidic manifold 1100 and pneumatic manifold 1300, as well as for chip thermal control assembly 900 can be actuated. Accordingly, cell analysis system 3000 is configured so that an end user can specify the selection of a reagent or solution, the gas composition in equilibrium with a reagent or solution, as well as the sequence, the flow rate, flow duration, and the measurement protocol during the flow of a selected reagent or solution. Processing electronics assembly 100 and valve board 200 can be housed in a hardware compartment of a cell analysis system of the present disclosure.

[0036] Fig. 2 is a schematic diagram that illustrates generally fluid delivery system 1500. As will be described in more detail subsequently, fluid delivery system 1500 can provide clean transitions between of various solutions and reagents from various source containers delivered through a flow path. In that regard, fluid delivery system 1500 is configured to avoid carryover, and additionally to avoid cross-contamination of solutions used during analysis. Moreover, fluid delivery system 1500 can provide a selectable range of flow rates that avoid untoward shear forces on cells plated on the surface of a sensor device, while maintaining a pressure in the flow cell of close to atmospheric pressure.

[0037] As previously described herein, fluid delivery system 1500 of FIG. 2 is in fluid communication with sensor array device 500 of the present disclosure via fluidic interface device 600. When fluidic interface device 600 is engaged with sensor array device 500, flow cell assembly 650 is formed with a top flow cell surface provided by fluidic interface device 600 and a bottom flow cell surface provided by the upper surface of chip device 500. In that regard, fluid delivery system 1500 is configured to selectively and controllably provide fluid distribution through a flow cell. As depicted in FIG. 2, fluidic system 1200 of fluid delivery system 1500 can include a variety of containers for holding various types of solutions used in conjunction with a cell analysis system of the present disclosure. For example, containers 1230A through 1230F, numbered 1 through 6, respectively, can be reagent containers that hold various reagents used during an analysis of cells. Container 1240, can contain various buffered solutions used in cell culture and cell analysis, for example, phosphate buffered saline (PBS), Ringer's solution, and the like, and can be used to maintain cells plated on a chip device under cell-compatible conditions when not being subjected to a test condition. Container 1250 can contain a solution used for system cleaning, for example, after analysis as part of a shut-down procedure. Alternatively, container 1250 can be selected by an end user for any desired solution. As used herein, "container" and "solution container" are used interchangeably. As depicted in FIG. 2, solution containers 1230A through 1230F, 1240 and 1250 can be appropriately sized according to the volumes required for the defined use.

[0038] As depicted in FIG. 2, pneumatic system 1400 is in fluid communication with fluidic system 1200 to provide pressure-driven fluid movement. Pneumatic system 1400 can include gas inlet 1410, which is connected to a gas source. For example, a gas source could be a source of clean dry air (CDA), which could be from line leading from a house supply source of CDA. Alternatively, a supply of CDA can be generated from ambient air using a compressor with filter for creating CDA. Such locally-generated CDA can be stored in a compressed form, such as a cylinder. Additionally, gas sources of a user specified composition for various cell analyses can be placed in fluid communication, for example, with selected reagent containers. For example, cells growing in bicarbonate buffered cell culture medium require an air composition that includes 5% carbon dioxide. Alternatively, for studies of cell hypoxia, ambient oxygen levels in the gas source can be varied from normal levels of 20% oxygen down to 1%. Regardless of the nature of the gas supply, gas inlet 1410 is in fluid communication with regulator 1420, which in turn can be placed in controllable fluid communication with pneumatic manifold 1300.

[0039] With respect to fluid movement through fluid delivery system 1500 of FIG. 2, pneumatic manifold lines 1310A-1310C from pneumatic manifold 1300 are in fluid communication with containers 1230A through 1230F. As depicted in FIG. 2, containers 1230A and 1230B are in fluid

communication with pneumatic manifold line 1310A, containers 1230C and 1230D are in fluid communication with pneumatic manifold line 1310B, and containers 1230E and 1230F are in fluid communication with pneumatic manifold line 1310C. Pneumatic manifold lines 1310D-1310E are in fluid communication with container 1240, and container 1250, respectively.

[0040] With respect to fluid flow control, valves of fluidic manifold 1100 in conjunction with system valve V12 and 2-way system valve V14 can be controlled so that liquid from any liquid container can be directed to flow through flow cell assembly 650 to waste container 1270. For example, fluid from a solution container can be in fluid communication with flow cell assembly 650 via fluidic manifold outlet line 1220, which is in controllable fluid communication with flow cell assembly 650 through flow cell inlet line 1222 via system valve V12. Depending on the valve state of 2-way system valve V14, effluent from flow cell assembly 650 can then controllably directed to waste container 1270 via restriction line 1266 or flow cell waste line 1264.

[0041] Accordingly, a fluidic system of the present disclosure can be configured by an end user to execute a sequence of fluidic operations for the sequential delivery of various solutions to sensor array device 500 over the course of a cell analysis experiment. During operation of fluid delivery system 1500, pneumatic manifold 1300 can be configured so that V6 is open, allowing source gas into pneumatic manifold 1300. Additionally, valves V1 through V5, which are in fluid communication with lines 1310A-1310E, can be in an open position, providing uniform head pressure over each liquid container. Valves of fluidic manifold 1100 and pneumatic manifold 1300 can be controlled, for example, using valve board 200, controlled by processing electronics assembly 100 as previously described for FIG. 1 to provide a defined and controllable pressure to source containers, such as solution containers, 1230A-1230E, 1240 and 1250.

[0042] As such, fluid movement through fluidic system 1200 is thereby controlled through selective actuation and control of valves in fluidic manifold 1100 in conjunction with selective actuation and control of both system valve V12 and 2-way system valve V14. Therefore, in order to better understand various fluidic operations of fluid delivery system 1500, an understanding of fluidic manifold 1100 as illustrated generally in FIG. 3 through FIG. 8 is given in the following section.

FLUIDIC MANIFOLD

[0043] A manifold device of the present disclosure utilizes diaphragm valves mounted on a first surface and an opposing second surface of a manifold block. A manifold block of the present disclosure can have a common zig-zag manifold block channel that includes an outlet line at one end of the common zig-zag manifold block channel and a waste line at an opposing end of the common zig-zag manifold block channel. The manifold block is fabricated with a manifold valve port that can place a

fluid source in fluid communication with the common zig-zag manifold block channel when a valve is activated to an open position. When a valve is in a closed state, fluid communication between a fluid source and the common zig-zag manifold block channel is blocked, so that fluid can flow by the manifold valve port and through the common zig-zag manifold block channel.

[0044] As will be described in more detail herein, in an initialization process, valve states of the manifold device can be actuated so that the common zig-zag manifold block channel can be filled with, for example, a solution or reagent from a selected source container. Once the common zig-zag manifold block channel is filled with the solution or reagent from the selected source container, valve states of the manifold can be actuated so that the solution or reagent is directed through the outlet line to a target device. After delivery of the selected reagent to a target device is completed, additional solutions or reagents can be sequentially selected and the initialization and delivery process repeated for each selected solution or reagent.

[0045] As the diaphragm valves and the common zig-zag manifold block channel are zero dead volume fluidic structures, there is no carryover from either the diaphragm valves or the common zig-zag manifold block channel. Once the common zig-zag manifold block channel is initialized with fluid from a selected source, there is no carryover from the common zig-zag manifold block channel flowing from an the outlet line to a target device. Accordingly, the manifold device of the present disclosure is a zero dead volume device that provides the timely multiplexing of various solutions and reagents to a target device without undesirable carryover.

[0046] FIG. 3 is a front view that illustrates generally fluidic manifold 1100 of the present disclosure. Fluidic manifold 1100 of FIG. 3 can have a first set of diaphragm valves, such as fluid source valves 1120-1, 1120-3, 1120-5, 1120-7, and 1120-9, as well as waste line valve 1120-11 mounted on a first surface of fluidic manifold 1110, and a second set diaphragm valves, such as source valves 1120-2, 1120-4, 1120-6, 1120-8, and 1120-10 mounted on a second surface of manifold block 1110. Diaphragm valves suitable for use for a manifold device of the present disclosure include, for example, Burkert type 0127 rocker solenoid valves, SMC Corporation LVM series rocker valves, and Lee Company LFR series valves. Manifold block 1110 can include outlet line port 1130-OL and waste line port 1130-WL. Additionally, manifold block 1110 can include a series of fluid source inlet ports associated with each source valve, such as source inlet ports 1130-1 through 1130-10, each of which are associated with a corresponding manifold block source valve port, as will be subsequently described herein in more detail. It should be noted “fluid source” and “source” are used interchangeably herein to describe various fluidic elements such as valves and ports.

[0047] FIG. 4 is a front isometric section view that illustrates generally manifold block 1110 of the present disclosure. In the section view of FIG. 4, two sets of diaphragm valves are disposed on each side of manifold block 1110, as illustrated in FIG. 3. Accordingly, in FIG. 4, fluid source valves 1120-1 through fluid source valve 1120-9, as well as waste line valve 1120-11 as previously described for FIG. 3 are shown mounted on a first surface of manifold block 1110, while fluid source valve 1120-2 through fluid source valve 1120-10 as previously described for FIG. 3 are shown mounted on a second surface of manifold block 1110. In the section view of FIG. 4, the zig-zag nature of manifold block common channel 1112 in manifold block 1110 is clearly illustrated. Manifold block common channel 1112 of FIG. 4 includes manifold block outlet channel 1114 and manifold block waste channel 1116. Additionally, a diaphragm rod, such as diaphragm rod 1140 shown for each valve of FIG. 4, is operably connected to each diaphragm of each diaphragm valve, as illustrated in FIG. 5B and FIG. 5C.

[0048] FIG. 5A is a section view of fluidic manifold 1100 of FIG. 1 and FIG. 2. As depicted in FIG. 5A, fluidic manifold 1100 includes 11 diaphragm valves, each diaphragm covering a valve port, such as valve port 1124 of FIG. 5B and FIG. 5C. Various aspects of one non-limiting exemplary configuration of fluidic manifold 1100 is depicted in FIG. 1 through FIG. 8. In FIG. 5A, each of the numbered diaphragm valves 1120-1 through 1120-6 corresponds to solution containers 1230 A-F, respectively, as shown in FIG. 1 and FIG. 2. In a similar fashion, diaphragm valves 1120-7 and 1120-10 correspond to solution containers 1240 and 1250, respectively, as shown in FIG. 1 and FIG. 2.

[0049] Fluidic manifold 1100 includes fluidic manifold block 1110 with a common fluid pathway, fluidic manifold block common channel 1112. As depicted in FIG. 5A and FIG. 5D, fluidic manifold block common channel 1112 is a zig-zag channel that includes fluidic manifold block outlet channel 1114 and fluidic manifold block waste channel 1116. For FIG. 5A, the movement of fluid flows through fluidic manifold block common channel 1112 as indicated by the arrows, given the valve states of as shown in FIG. 5A. In an initialization step used for initial use of a solution from a selected container, source valve 1120-3 and waste line valve-1120-11 are actuated in an open position (I), so that valve diaphragm 1122 shown in FIG. 5B is lifted away from valve port 1124 by diaphragm rod 1140 for diaphragm valves 1120-3 and 1120-11, thereby placing their respective valve ports in fluid communication with fluidic manifold block common channel 1112.

[0050] As depicted in FIG. 5C, all other valves are positioned in a closed state (O) with valve port 1124 sealed by valve diaphragm 1122 using diaphragm rod 1140, thereby allowing fluid to pass through fluidic manifold block common channel 1112. As depicted in FIG. 2, diaphragm valve 1120-3 is also in fluid communication with liquid container 1230C, thereby allowing a solution from liquid container 1230C to flow bidirectionally into fluidic manifold block common channel 1112 towards fluidic manifold block outlet channel 1114, as well as towards fluidic manifold block waste channel

1116, while waste line valve 1120-11 is in an open state during the initialization step. As depicted in FIG. 5D, once fluidic manifold block common channel 1112 has been flushed with a solution, diaphragm valve 1120-11 can be closed, so that solution from liquid container 1230C can flow toward fluidic manifold block outlet channel 1114, and into fluidic manifold outlet line 1220, shown in FIG. 1 and FIG. 2. As such, fluidic manifold 1100 utilizing zero dead volume diaphragm valves and an initialization process for priming fluidic manifold block common channel 1112 with each solution selected during use provides fluid delivery system 1500 of FIG. 1 and FIG. 2 with ready ability to multiplex between various solutions, while avoiding the problem of carryover.

[0051] FIG. 6 is a top isometric view of a of manifold block 1110 of the present disclosure, that illustrates a set of manifold block valve ports. Manifold block valve port 1124-1 through manifold block valve port 1124-5 of FIG. 6 correspond to fluid source inlet port 1130-1 through fluid source inlet port 1130-5, respectively. Manifold block waste line valve port 1124-WL corresponds to waste line port 1130-WL. Additionally shown in FIG. 6 is outlet line port 1130-OL as previously described for FIG. 3. Manifold block valve port 1124-1 through manifold block valve port 1124-5 of manifold block 1110 of FIG. 6 correspond to fluid source valves 1120-1, 1120-3, 1120-5, 1120-7, and 1120-9, respectively, as previously described for FIG. 3 and FIG. 5. Similarly, waste line valve port 1124-WL of manifold block 1110 of FIG. 6 corresponds to waste line valve 1120-11 as previously described for FIG. 3 and FIG. 5. Fluid source valves 1120-2, 1120-4, 1120-6, 1120-8 and 1120-10 of FIG. 3 and FIG. 5A can be similarly mounted upon manifold block valve ports on the opposite face not shown in FIG. 6. Regarding materials used in the fabrication of manifold block 1110 of the present disclosure, candidate materials include polymeric materials that are chemically resistant, stable to pH across a range of 3-9, resistant to swelling in organic solvents, and thermally stable. Exemplary materials for manifold block 1110 include a variety of machinable polymers, for example, but not limited by, polytetrafluoroethylene (PTFE) polyetherimide (PEI), polyether ether ketone (PEEK), acrylonitrile butadiene styrene (ABS), and polyoxymethylene (POM).

[0052] FIG. 7 is a top isometric view of a of manifold block source valve port 1124 of the present disclosure in relationship to other features of manifold block 1110. Manifold block fluid source valve port 1124 of FIG. 7 is representative of all manifold block fluid source valve ports of a manifold device of the present disclosure. Manifold block fluid source valve port 1124 of FIG. 7 is raised above manifold valve port annular groove 1123, in which fluid source valve channel port 1132 is formed. Fluid source valve channel port 1132 is in fluid communication with fluid source inlet port 1130-1 via fluid source valve channel 1134. In general, a valve channel port can be placed in fluid communication with a corresponding inlet port via a valve channel. Each diaphragm of a diaphragm valve, such as diaphragm 1122 of FIG. 5B and FIG. 5C, is seated upon valve port sealing surface 1125 when a manifold valve is

in a closed position, as depicted in FIG. 5C. When manifold valves are in a valve state as depicted in FIG. 5A, fluid from a fluid source that is in fluid communication with source inlet port 1130-1 can flow through source valve channel 1134 into manifold valve port annular groove 1123 and through manifold block source valve port 1124. For manifold valves are in a valve state as depicted in FIG. 5A, fluid then flows through manifold block common channel 1112 bidirectionally. Alternatively, when manifold valves are in a valve state as depicted in FIG. 5D, fluid from a fluid source that is in fluid communication with source inlet port 1130-1 can flow through manifold block common channel 1112 unidirectionally towards outlet line port 1130-OL.

[0053] It should be noted that manifold block waste line valve port 1124-WL of FIG. 6 has the same features as described for a manifold block source valve port, but is not directly in fluid communication with an external fluid source through a source inlet port. As previously described herein, manifold block waste line valve port 1124-WL is in fluid communication with a fluid source during an initialization process, in which there is a bidirectional flow of fluid from a fluid source through manifold block common channel 1112.

[0054] FIG. 8 is a top isometric view of a of the manifold block of FIG. 7 that illustrates generally various features of a manifold block in phantom view. As previously stated for FIG. 7, Manifold block fluid source valve port 1124 of FIG. 8 is representative of all manifold block fluid source valve ports of a manifold device of the present disclosure. In the rendering of manifold block source valve port 1124 of FIG. 8, the connection between source inlet port 1130-1 and source valve channel port 1132 through source valve channel 1134 is clearly illustrated. Fluid from a fluid source that is in fluid communication with fluid source inlet port 1130-1 can flow through source valve channel port 1132 via source valve channel 1134 into manifold valve port annular groove 1123 and then through manifold block source valve port 1124. Depending on the valve states of the manifold valves, fluid can then either flow bidirectionally through manifold block common channel 1112 of FIG. 8 as depicted in FIG. 5A or unidirectionally through outlet line channel 1121 towards outlet line port 1130-OL as illustrated in FIG. 8 and as depicted in FIG. 5D.

CELL ANALYSIS SYSTEM FLUIDIC OPERATIONS

[0055] As previously described herein, a fluidic system of the present disclosure can be configured by an end user to execute a sequence of fluidic operations over the course of an experiment for the sequential delivery of various solutions through flow cell assembly 650 of FIG. 2, and over a chip surface of sensor array device 500. Exemplary fluidic operations include priming, perfusing, reagent delivery, cell find, and system cleaning.

[0056] Initial priming can be done to flush each manifold input line 1210A through 1210H of FIG. 2 with solutions contained in each respective solution containers 1230 A-F, 1240 and 1250. Initially, a dummy chip can be inserted into flow cell assembly 650 (see FIG. 2). A dummy chip is preferably any chip that would not be used for testing. For example, a dummy chip can be a previously used test chip that is no longer useful as a test chip. With a dummy chip inserted into a cell analysis system, initial priming can be actuated. For example, to prime manifold input line 1210A with solution from 1230A, diaphragm valve V11 is actuated in an open position, while diaphragm valve V1 is actuated to an open position transiently for 3-5 seconds to allow solution from container 1230A to fill manifold input line 1210A. During this initial priming operation, system valve V12 would be actuated in a closed position to prevent flow through the dummy chip, while liquid from the fluidic manifold block flows to waste container 1270 through manifold waste line 1260. After the 3-5 second interval, diaphragm valve V1 is actuated to a closed position. To complete an initial priming step, the same procedure is sequentially repeated for each respective container/manifold input line/fluidic manifold valve combination. In the final phase of a priming operation, valves V11 and V12 are actuated to an open position, with 2-way system valve V14 actuated to connect line 1262 and restriction line 1266, while valve V7 is transiently activated to an open position for between about 60s to about 240s, or moreover for between about 100s to about 140s to ensure that the common zig-zag channel of the manifold device and fluid lines between the manifold device and chip have been flushed. These valve states allow fluid to flow from container 1240 through both the fluidic manifold 1100 to waste through line 1260 and through chip flow cell 600 of the dummy chip and then to waste through lines 1220, 1222, 1262, and 1266. This ensures that a cell-compatible solution in container 1240 will initially flow into the working chip will be primed into all lines, while preventing bubbles.

[0057] Perfusing is performed during the use of a cell analysis system throughout an experiment to provide a flow of a nutrient solution through the flow cell chamber and over cells plated on a sensor array device surface. Accordingly, the dummy chip can be removed, and a test chip prepared for analysis with cells plated on the surface can be inserted. In order to remove the dummy chip and insert a test chip into a cell analysis system of the present disclosure, system valve V12 is actuated to an off position, all fluidic manifold valves are actuated to an off position, and 2-way system valve V14 is actuated to connect to 1264 to allow the pressure at the chip to go to atmosphere. These valve states allow a dummy chip to be removed. Once a test chip has been inserted into a cell analysis system, V14 can be actuated to connect to restriction line 1266.

[0058] Accordingly, perfusing can be performed with a test chip in fluid communication with fluid delivery system 1500, as depicted in FIG. 2. As previously described herein, container 1240, can contain various buffered solutions used in cell culture and cell analysis, for example, phosphate

buffered saline (PBS), Ringer's solution, and the like, and can be used to maintain cells plated on a chip device under cell-compatible conditions when not being subjected to a test condition. In order to perform a perfusing step, diaphragm valve V7 and system valve V12 are actuated in an open position, while diaphragm valve V11 is open transiently for 3-5 seconds during an initialization step to allow solution from manifold input line 1210G to fill a common internal channel of fluidic manifold 1100 as shown in FIG. 5A. As will be described in more detail herein, the fluid resistance of manifold waste line 1260 and the fluid resistance of resistance line 1266 of FIG. 1 and FIG. 2 can be matched. In that regard, during the transient excursion to fill the common zig-zag channel with a designated fluid, the flow through manifold waste line 1260 and resistance line 1266 are the same.

[0059] After internal channel of fluidic manifold 1100 has been filled with perfusion solution, diaphragm valve V11 can be actuated to a closed position, so that perfusion solution flows through fluidic manifold outlet line 1220 (see FIG. 1, FIG. 2FIG. 5C, and FIG. 5D and related description). During a perfusion operation, system valve V12 would be open so that a solution from fluid container 1240 would flow through fluidic manifold outlet line 1220 and to flow cell assembly 650 via flow cell inlet line 1222. After flow through flow cell assembly 650, with 2-way system valve V14 actuated to connect flow cell outlet line 1262 with restriction line 1266, a perfusion solution would flow through flow cell outlet line 1262 and then through restriction line 1266 to waste container 1270.

[0060] As perfusing cells is done throughout an analysis, the volume of solution container 1240 can be substantially greater than specialized solutions used for delivery of reagents used to interrogate cell function during an experiment, or for a container used for a cleaning solution. For example, solution container 1240 holding a cell compatible solution that is used throughout an analysis can have a capacity of 1.5 to 2 liters. In comparison, reagent containers 1230B-1230F, can have for example a capacity of about 0.5 liter, while container 1250, which can be used as a cleaning solution container, can have a capacity for example of about 1 liter.

[0061] With respect to reagent delivery, reagent delivery would be similarly performed as described for perfusion of cells during an analysis. As will be explained in detail subsequently, one container, for example, container 1230A of FIG. 2, holds a cell find solution used at the completion of each experimental run. Accordingly, in the given example, any selected diaphragm valve V2-V6 for each corresponding reagent container 1230B-1230F can be actuated in an open position, while diaphragm valve V11 is open transiently for 3-5 seconds during an initialization step to allow solution from a corresponding selected reagent container 1210B-1210F to fill a common internal channel of fluidic manifold 1100 as shown in FIG. 5A. After internal channel of fluidic manifold 1100 has been filled with a selected reagent, diaphragm valve V11 is closed, so that the selected reagent flows only through fluidic manifold outlet line 1220 of FIG. 2, and then through flow cell assembly 650 to waste

as described for the perfusing operation. An end user can select a sequence and timing of fluidic operations to perform an automated analysis sequence using a cell analysis system of the present disclosure. For example, when the selected time period of the experiment using the selected reagent has lapsed, a second reagent can be initiated to flow through flow cell assembly 650 of FIG. 2, followed, for example, by perfusion of the cells using selected cell-compatible solution in container 1240.

[0062] At the completion of each experiment, a solution from a dedicated container, for example, container 1230A of FIG. 2, is a solution having a pH step of 0.1 pH unit lower in pH than the pH of the perfusion solution in container 1240. For example, if a buffered solution in container 1240 has a pH of 7.4, then the cell find solution would have a pH of 7.3. For ChemFET sensors, changes in the surface potential of the sensing surface of a ChemFET sensor result in an output signal from the sensor. For this example, the sensor device is an ISFET sensor selective for sensing hydrogen ions, so that each sensor is effectively a pH sensor. When the cell find solution of lower pH is passed over the surface, the sensors covered by the footprint of a cell are not in direct contact with the solution and therefore have a different response profile than sensors in direct contact with the solution of lower pH. Accordingly, the intensity of the response, can be used to locate the position of cells in contact with a sensor surface. The cell find operation would be executed as described for perfusing, but for selected reagent container 1230A.

[0063] Regarding cleaning fluidic lines as a last operation before system shutdown, all lines can be cleaned using a cleaning solution such as deionized water or by using a dilute bleach solution followed by flushing the lines with deionized water. For example, sensor chip 500 can be removed, allowing cells that were part of an experiment to be recovered, and a dummy chip can be inserted. Manifold input lines 1210A-1210G can be cleaned by replacing containers 1230A-F and containers 1240 and 1250 with containers holding a cleaning solution or solutions, and the operation as described for initial priming can be run. The only lines remaining that would require flushing would be those associated with the flow cell. In order to flush the fluidic lines associated with the flow cell, diaphragm valve V10 and V11, as well as system valve V12 can be actuated in an open position, while 2-way system valve would be actuated to flow through restriction line 1266. With these valve states, cleaning solution can flow through flow cell inlet line 1222 and flow cell outlet line 1262 through restriction line 1266 to waste container 1270. Finally, with all containers emptied, and system valve V12 and 2-way system valve V14 alternatingly open to each branch, air from pneumatic manifold 1400 can be flushed through the system to dry fluid delivery system 1500.

[0064] With respect to flow control for fluid delivery system 1500, in reference to the Poiseuille equation for volumetric flow rate, $\Delta V/\Delta t$, is given by equation 1:

$$\Delta V/\Delta t = \frac{\pi R^4 \Delta P}{8\eta L} \text{ Eq. 1}$$

where:

R is the tubing radius;

ΔP is pressure difference over the system flow path;

η is the viscosity of the solution; and

L is the length of the tubing

then flow control for fluid delivery system 1500 is provided by controlling the pressure provided by pneumatic system 1400, as well as the length and diameter lines used in fluid delivery system; particularly manifold outlet line 1220, which is a restriction line having selected length and internal diameter to provide a range of desired flow rates through flow cell assembly 650.

[0065] With rearranging, the equation can be expressed as shown below:

$$\Delta P/F = \frac{8\eta L}{\pi R^4} \text{ Eq. 2}$$

where:

F is the volumetric flow rate; $\Delta V/\Delta t$

[0066] This term is an expression for resistance to flow, and is useful in considering the dimensioning of outlet resistance line 1266, acting as a resistance line for providing a range of targeted flow rates through fluid delivery system 1500 of FIG. 1 and FIG. 2. For example, FIG. 9A is a schematic representation of flow lines from source container 12X0, which can be any of solution containers 1230 A-F, 1240 and 1250 of FIG. 1 and FIG. 2, for which manifold input lines 1210A-1210H are the same length and inner diameter. In addition to a manifold input line, manifold outlet line 1220, flow cell outlet line 1262, and flow cell waste line 1264, together constitute the flow path contributing to the resistance term given by equation 2. Essentially, the resistance provides an understanding of the relationship between pressure and flow rate. As can be seen by inspection of equation 2, resistance is directly proportional to pressure and inversely proportional to flow rate, so that as resistance increases, flow rate decreases. Further, resistance is directly proportional to the length of a line, and inversely proportional to the forth power of the inner diameter of a line. As such, both length and inner diameter can be tailored for a desired resistance to provide a desired range of flow rates over a target pressure range.

[0067] For example, the function of a fluidic system was evaluated using a flow path as depicted in FIG. 9A and FIG. 9B for fluidic system 1500 of FIG. 1 and FIG. 2 using a working system pressure range of 1-8 psig. In evaluating the function of the fluidic system, a target number of minimum and

maximum flow cell volume exchanges per unit time was evaluated to be 0.3 to 1, respectively, for a flow cell having a volume of 70 μL . This would thereby provide a target flow rate range of between about 1.3 to 4.2 mL/min in order to provide sufficient volume exchange for the flow cell. Additionally, resistance per unit length for lines of desired inner diameters was determined by measuring resistance using such lines of known length and then normalizing. In that regard, given target system specifications for pressure and flow rate ranges, a total system resistance can then be determined by summing the resistances for each segment of the flow path as shown in FIG. 9A.

[0068] For the non-limiting example of FIG. 9A, a manifold input line with a selected inner diameter of 0.03", such as any of manifold input line 1210A-1210H of FIG. 1 and FIG. 2, was determined to have a resistance per unit length of 6.07×10^{-4} psig/mL/min./mm. For providing effluent flow to a waste container, flow cell outlet line 1262 and flow cell waste line 1264 with a selected inner diameter of 0.062" were determined to have a resistance per unit length of 3.32×10^{-5} psig/mL/min./mm. For providing a targeted flow rate, manifold outlet line 1220 with a selected inner diameter of 0.02" was determined to have a resistance per unit length of 1.10×10^{-3} psig/mL/min./mm. In the example of FIG. 9A, the length of a manifold input line, such as manifold input lines 1210A-1210H of FIG. 1 and FIG. 2, is 600 mm, while the length of flow cell outlet line 1262 and flow cell waste line 1264 is 460 mm for each segment. It should be noted that flow cell inlet line 1222 is such a short segment that its contribution to resistance can be ignored in this example. For manifold outlet line 1220, by empirical determination to provide the target flow rate, a length of 2000 mm provided a total system fluidic resistance for flow path of FIG. 9A of 1.439 psig/mL/min. As such, for the working pressure range of 1 psig to 8 psig, a flow rate range of between about 0.7 mL/min to about 5.6 mL/min can be realized. As this flow rate range brackets the flow rate range for providing sufficient volume exchange for the flow cell, it is an example of a flow path providing a range of flow rates for the intended use of fluid delivery system 1500. It is understood that inner diameters and lengths of various segments can be adjusted to provide a target system fluidic resistance that is a structural and functional equivalent of the present example.

[0069] With respect to FIG. 9B, in order to evaluate whether or not the flow cell contributed significantly to resistance in the flow line, a connection between manifold outlet line 1220 and flow cell outlet line 1262 was made, so that flow cell assembly 650 was not in the flow path. As can be discerned by inspection of the graph of FIG. 9C, the flow rate as a function of pressure is essentially indistinguishable for the fluidic system with and without the flow cell as part of the flow path, thereby validating that the flow cell does not contribute to system fluidic resistance. Moreover, both graphs are fairly close to the calculated response, thereby validating the empirical selection of the inner diameter and length of manifold outlet line 1220 as shown in FIG. 9A and FIG. 9B. Further, testing

verified that during the 3-5 second period in which manifold valve V11 of FIG. 1, FIG 2, FIG. 5A and FIG. 5D is open to avoid carryover in fluidic manifold block common channel 1112, there was no appreciable impact on the flow rate through flow cell during that excursion.

[0070] With respect to implementation of a resistance line into a fluidic system of a cell analysis system, for such as described with respect to FIG. 1 and FIG. 2, the present inventors observed that bubble formation in a flow cell resulted from a restriction line implemented as described for FIG. 9A and FIG. 9B. Given that the flow cell is substantially close to the outlet end sitting at 0 psig, and given that fluid in a resistance line is under pressure, bubble formation may be due to volume expansion of liquid flowing under pressure to a low pressure in a flow cell. Accordingly, In order to avoid the formation of bubbles in a flow cell assembly, it was determined that an optimum position for a resistance line is at the effluent end of a flow cell assembly. Therefore, as depicted in FIG. 1 and FIG. 2, restriction line 1266 is located after flow cell assembly 650 and proximal to waste container 1270. With respect to dimension, restriction line 1266 has an inner diameter of diameter of 0.02" and a length of 1100mm, thereby providing a total system fluidic resistance for fluidic system 1200 shown in FIG. 1 and FIG. 2 of 1.439 psig/mL/min. As previously described herein, in order to ensure equivalent flow rates to waste container 1270 through manifold waste line 1260 and resistance line 1266, the fluid resistance of manifold waste line 1260 and the fluid resistance of resistance line 1266 of FIG. 1 and FIG.2 can be matched. As such, manifold waste line 1260 is also dimensioned equally having an inner diameter of diameter of 0.02" and a length of 1100mm. In that regard, during the transient excursion to fill the common zig-zag channel with a designated fluid, the flow through manifold waste line 1260 and resistance line 1266 are the same. Finally, given that manifold outlet line 1220 is no longer a resistance line, manifold outlet line 1220 can be about 520mm in length with an inner diameter of 0.030".

[0071] In addition to providing an end user the flexibility of reagent selection, and flow rates, as will be described in more detail herein, a cell analysis system of the present disclosure is configured to provide thermal regulation of the chip device surface, as well as environmental regulation of solutions and reagents used in analysis. In that regard, a cell analysis system of the present disclosure can maintain a cell-compatible environment within a flow cell.

[0072] FIG. 10 is a schematic exploded view that illustrates generally a chip clamp assembly of a cell analysis system of the present disclosure. It should be noted that the schematic representation of chip clamp assembly 1000 does not represent the relative scale of the components, moreover their relationship and function. As depicted in FIG. 10, chip clamp assembly 1000 is an apparatus that includes fluidic interface device 600. Fluidic interface device 600 is a structure providing an interface

between fluid delivery system 1500 of FIG. 1 and FIG. 2 and a flow cell formed by the reversible coupling of fluidic interface device 600 and sensor array device 500.

[0073] Fluidic interface device 600 as depicted in FIG. 10 is a unitary structure that includes fluidic interface device body 610 and fluidic interface device flange 620. Fluidic interface device upper surface 605 of fluidic interface device body 610 includes flow cell inlet line port 604 providing connection to flow cell inlet line 1222 and flow cell outlet line port 606 providing connection to flow cell outlet line 1262. Fluidic interface device body 610 additionally includes reference electrode insert hole 608, in which reference electrode 50 can be sealably inserted. Fluidic interface device flange 620 includes flow cell inlet port 624 and flow cell outlet port 626 located on fluidic interface device lower surface 625. Flow cell inlet channel 614 provides fluid communication between flow cell inlet line 1222 and flow cell inlet port 624, while flow cell outlet channel 616 provides fluid communication between flow cell outlet line 1262 and flow cell outlet port 626. As will be described in more detail subsequently herein, flow cell inlet port 624 and flow cell outlet port 626 are in fluid communication with a flow cell formed when sensor array device 500 and fluidic interface device 600 are engaged during use of a cell analysis system of the present disclosure, such as cell analysis system 3000 of FIG. 1. Fluidic interface device spacer 630 and fluidic interface device gasket 640 are part of the fluidic interface device that provide dimensioning and sealing of the flow cell formed from the reversible coupling of sensor array device 500 and fluidic interface device 600. Fluidic interface device spacer 630 is shown in FIG. 10 is abutted against fluidic interface device flange rim 622, while fluidic interface device gasket 640 is shown in FIG. 10 mounted to fluidic interface device flange ridge 623.

[0074] As depicted in FIG. 10, sensor array device 500 includes sensor device 520 mounted on sensor device substrate 510. Sensor device frame 560 of FIG. 10 is shown mounted on chip device substrate and sensor chip top surface 525. As will be described subsequently herein, sensor device frame inner surface 564 becomes an inner wall of a flow cell chamber when fluidic interface device 600 is engaged with sensor array device 500. Sensor device circuitry 515 can include a bond wire, such as bond wire 512, connected to sensor chip 520. Bond wire 512, set in encapsulant 511, is connected to electrical pad 514 through chip circuit 513, which includes lines and vias. Electrical pad 514 connects bond wire 512 to a pogo pin block. As depicted in FIG. 10, sensor array device 500 can be connected to pogo pin block 550. As previously described herein, chip clamp assembly 1000 of FIG. 1, is an apparatus that can provide a clamping force to fluidic interface device 600 to engage fluidic interface device 600 with chip device 500, and further to engage chip device 500 with pogo pin block 550. In turn pogo pin block 550 is engaged with a PC board mounted to chip clamp assembly base 800. The integrated circuit connections provide power, timing and control to, as well as data acquisition from a sensor chip by a cell analysis system.

[0075] Accordingly, several layers of electronic interconnections are involved in the function of sensor device 500, all in proximity to a flow cell fluidically connected to a fluidic system, such as fluidic system 1500 of FIG. 1 and 2. Moreover, sensor array device 500 is an open structure for the purpose of providing access to an end user for plating and manipulations of cells, as well as being a component that must be repeatedly easily removable and replaceable from an analysis platform of a cell analysis system. As such, various fluidic interface devices of the present disclosure are configured to provide consistent leak-free engagement with a sensor device, such as sensor array device 500 of FIG. 10, as well as providing leak-free repetitive engagement of various fluidic interface devices of the present disclosure with a sensor device.

[0076] Chip thermal control assembly 900 of FIG. 10 is shown with thermoelectric cooling (TEC) device 910 mounted on cooling assembly 920, with first TEC surface 912 in contact with TEC cooling assembly 920. Second surface 914 of TEC device 910 is in contact with sensor device cooling block 930, which during use of a chip device is in contact with device substrate lower surface 505. Thermal vias 507 in sensor device substrate 510 provide effective thermal contact between chip device cooling block 930, sensor device substrate 510 and sensor chip 520. TEC cooling assembly 920 is mounted to the bottom of chip clamp assembly base 800 with springs 916 to exert sufficient force on chip thermal control assembly 900 to make effective thermal contact with sensor device 500. The force exerted by springs 916 on chip thermal control assembly 900 is about 4 lbs. +/- 10%. Chip thermal control assembly 900 can provide precision thermostating of a chip device over a temperature range of 4 °C to 60 °C within +/- 0.1 °C.

[0077] FIG. 11 is a schematic representation that illustrates generally flow cell assembly 650 formed by the reversible coupling of fluidic interface device 600 and sensor device 500. It should be noted that the schematic representation of flow cell assembly 650 does not represent the relative scale of the components, moreover their relationship and function. As previously described herein, fluidic interface device 600 includes flow cell inlet channel 614 and flow cell outlet channel 616. Flow cell inlet line port 604 and flow cell outlet line port 606 of fluidic interface device upper surface 605 provide connection to flow cell inlet line 1222 and flow cell outlet line 1262, respectively. Further, inlet port 624 and flow cell outlet port 626 on fluidic interface device lower surface 625 are in fluid communication with flow cell inlet line 1222 and flow cell outlet line 1262, respectively. As depicted in FIG. 11, when fluidic interface device 600 is coupled to sensor device 500, flow cell inlet port 624 and flow cell outlet port 626 are in fluid communication with flow cell chamber 655. Accordingly, flow cell chamber 655 of flow cell assembly 650 is therefore in fluid communication with flow cell inlet line 1222 and flow cell outlet line 1262. As such, flow cell assembly 650 can be placed in fluid

communication with any of solution containers solution containers 1230 A-F, 1240 and 1250 once flow cell assembly 650 is formed between fluidic interface device 600 and sensor device 500.

[0078] It should be noted that during use, reference electrode 50 is in fluid communication with flow cell outlet channel 616, and hence in contact with the electrolyte flow stream. Reference electrode 50 is an essential component for providing a stable reference voltage to the bulk electrolyte solution flow through flow cell assembly 650, and therefore a stable reference voltage to sensor array device 500. With respect to providing stable output signals, each sensor of a sensor array device generates an output signal that depends on the value of a stable reference voltage. As depicted in FIG. 11, reference electrode 50 is in a flow path of, for example, perfusion solution from solution container 1240. To provide the stability required over the range of analysis times indicated for various cell analyses, reference electrode 50 is a Ag/AgCl electrode.

[0079] As illustrated in FIG. 10 and FIG. 11, fluidic interface device flange 620 can engage with and reversibly couple to sensor device 500 to form flow cell assembly 650. As depicted in FIG. 11, when flow cell assembly 650 is formed, fluidic interface device spacer 630 is sealably seated against sensor device frame upper surface 562. Fluidic interface device gasket 640 is depicted in FIG. 11 seated on sensor chip top surface 525, as well as being seated against sensor device frame inner surface 564 to provide a reversible seal between fluidic interface device 600 and a chip device 500. Once reversibly sealed, flow cell chamber 655 is formed between sensor chip top surface 525 and fluidic interface device bottom surface 625. Flow cell chamber 655 is operably an analysis chamber with a defined height. For a flow cell assembly of the present disclosure, the defined height can be, for example, 250 μm and can be adjusted by adjusting the thickness of fluidic interface device spacer 630; a thickness selected with respect to a compression force that needs to be applied to interface device gasket 640 to ensure effective sealing. By way of a non-limiting example, by adjusting fluidic interface device spacer 630 by $\pm 100 \mu\text{m}$, the exemplary flow cell height of 250 μm can be adjusted to between about 150 μm to about 350 μm . In the present example, for a thickness of 1mm for fluidic interface device spacer 630, flow cell assembly 650 has a flow cell height of 250 μm and a volume of 70 μL . As such, varying the thickness of fluidic interface device spacer 630 to between about 0.6 mm to about 1.4 mm, thereby adjusting the flow height between about 150 μm to about 350 μm , provides the potential to adjust the flow cell volume of between about 40 μL to about 100 μL .

[0080] FIG. 12 is an exploded top perspective view illustrating generally fluidic interface device 600 positioned relative to interface device spacer 630 and fluidic interface device gasket 640. In the top perspective exploded view of FIG. 12, flow cell inlet line port 604 and flow cell outlet line port 606 are shown on fluidic interface device upper surface 605 of interface device body 610. Also shown mounted on upper surface 605 of fluidic interface device 600 are bushing 725a and bushing 725b,

which are part of a pair of liner bearings for a clamping assembly. As will be described in more detail herein, a pair of liner bearings are important with respect to application of a clamping force for engaging a chip device with a fluidic interface device to form a flow cell assembly as described for FIG. 10 and FIG. 11. Additionally fluidic interface device 600 includes first mounting face 601 and second mounting face 603. FIG. 12 illustrates a first end of fluidic interface mounting bolt through hole 627 on second mounting face 603. Fluidic interface mounting bolt through hole 627 runs through interface device body 610 from first mounting face 601 to second mounting face 603. Fluidic interface mounting bolt through hole 627 accommodates a bolt used to mount fluidic interface device 600 to a chip clamp assembly shuttle such as chip clamp assembly shuttle 700 of FIG. 1. Reference electrode 50 of FIG. 12 and FIG. 13 is depicted proximal to reference electrode insert hole 608 of fluidic interface device body 610, into which reference electrode 50 can be sealably inserted. As previously described herein, reference electrode 50 is a Ag/AgCl electrode, which requires occasional maintenance. Accordingly, as will be described in more detail herein, fluidic interface device 600 is mounted on a cell analysis system of the present teachings so that second mounting face 603 with reference electrode 50 inserted into fluidic interface device body 610 is readily accessible to an end user for refreshing or replacing reference electrode 50. Regarding fittings suitable for sealing reference electrode 50 in reference electrode insert hole 608, either reference electrode insert hole 608 can be tapped for so that reference electrode 50 can be screwed into reference electrode insert hole 608.

[0081] In FIG. 13 the bottom perspective of fluidic interface device 600, which depicts many features depicted in FIG. 12, such as mounting bolt through hole 627 second mounting face 603, as well as reference electrode insert hole 608, and reference electrode 50 on fluidic interface device body 610. The bottom perspective view of fluidic interface device 600 particularly highlights fluidic interface device flange 620, which includes flow cell inlet port 624 and flow cell outlet port 626 located on fluidic interface device lower surface 625, as also depicted for the schematic sections views of FIG. 10 and of FIG. 11. The bottom perspective view of FIG. 13 additionally depicts fluidic interface device flange rim 622 and fluidic interface device flange ridge 623 as part of fluidic interface device flange 620. As previously described herein for FIG. 10 and FIG. 11, in a final assembly, fluidic interface device spacer 630 is sealably seated against sensor device frame upper surface 562, while fluidic interface device gasket 640 is seated on sensor chip top surface 525, as well as being seated against sensor device frame inner surface 564 to provide a reversable seal between fluidic interface device 600 and a chip device 500.

[0082] Regarding materials used in the fabrication of fluidic interface device 600, fluidic interface device spacer 630 and fluidic interface device gasket 640 of FIG. 10 through FIG. 13, such components can be fabricated from polymeric materials that are chemically resistant, stable to pH across a range

of 3-9, resistant to swelling in organic solvents, and thermally stable. Exemplary materials for fluidic interface device 600 include a variety of machinable polymers, for example, but not limited by, polytetrafluoroethylene (PTFE) polyetherimide (PEI), polyether ether ketone (PEEK), acrylonitrile butadiene styrene (ABS), and polyoxymethylene (POM). Exemplary materials for fluidic interface device spacer 630 are non-compressible materials than can provide a compression force to fluidic interface device gasket, such as fluidic interface device gasket 640 of FIG. 10 through FIG. 13. Candidate polymeric materials for fluidic interface device spacer 630 include polycarbonate and polyetherimide (PEI). Candidate polymeric materials for fluidic interface device gasket 640 can have a durometer rating of 0-90 on the Shore A scale, or 20-90 on the Shore OO scale. Some exemplary materials for fluidic interface device gasket 640 include, for example, but not limited by, fluoroelastomers, such as Viton™, silicone polymers, such as polydimethylsiloxane (PDMS), thermoplastic polyurethanes, thermoplastic Styrene-Butadiene-Styrene (SBS) polymers, such as Sofprene T®, and thermoplastic vulcanizates, such as Santoprene™.

[0083] FIG. 14 is a perspective view that illustrates generally chip clamp assembly 1000. As depicted in FIG. 14, chip clamp assembly shuttle 700 includes chip clamp assembly mounting frame 710, upon which clamping arm assembly 720 is mounted. Chip clamp assembly mounting frame 710 includes aperture 712. Fluidic valve mount 714 is depicted in FIG. 9 mounted on chip clamp assembly mounting frame 710. Fluidic valve mount 714 provides a mounting surface for mounting system valve V12 and 2-way system V14. Recalling, as illustrated in FIG. 2, system valve V12 and 2-way system valve V14 can be controlled so that liquid from any liquid container can be directed to flow through flow cell assembly 650 to waste container 1270. As depicted in FIG. 14, clamping arm assembly 720 can include clamping arm 722, which is engaged with clamping arm fulcrum 724. Fluidic interface device 600 can be mounted to chip clamp assembly shuttle 700 by being mounted to clamping arm 722 as depicted in FIG. 14. Chip clamp assembly shuttle 700 is mounted to chip clamp assembly shuttle linear positioning system 812, shown in linear positioning system run 814 of chip clamp assembly base 800.

[0084] As depicted in FIG. 14, chip clamp assembly base 800 includes chip tray dock 816 for docking chip tray 850 and chip tray stop 818. Chip tray 850 has upper surface 851 and lower surface 853 and includes chip tray insert tab 852. Chip tray tab 852 provides for either manual or automated insertion of chip tray 850 into chip dock 816. Features of chip tray 850 on upper surface 851 include chip tray chip mount 854, chip tray blotting pad 856 and chip tray trough 858. As depicted in FIG. 14, chip tray chip mount 854 provides for the insertion of a user-selected chip device onto chip tray 850. The positioning of chip device 500 on chip tray 850 allows for pre-alignment of chip device 500 with fluidic interface device 600 when chip clamp assembly shuttle 700 is positioned over chip tray 850

docked to chip clamp assembly base 800. Chip tray blotting pad 856 can include bibulous sheet material, such as any laboratory grade bibulous paper that can provide blotting the bottom surface of chip device 500, so that it is dry before it is inserted into chip device mount 820. Finally, chip tray trough 858, provides for potential containment of fluids from a chip device prepared for cell analysis and in an open configuration prior to engagement with fluidic interface device 600 to form a flow cell assembly, such as flow cell assembly 650 of FIG. 11. In that regard, as will be described in more detail subsequently, liquid from chip device 500 can be contained in chip tray trough 858 either prior to or during engagement with fluidic interface device 600.

[0085] With respect to the formation of a flow cell assembly, reference is made to FIG. 15A. In FIG. 15A, a bottom perspective view is depicted that illustrates generally chip clamp assembly 1000. Fluidic interface device 600 is mounted to clamping arm 722 via fluidic interface mounting bolt 628, thereby mounting fluidic interface device 600 to chip clamp assembly shuttle 700. As such, fluidic interface device 600 can be positioned on chip clamp assembly base 800 using a linear positioning system as previously described, as well as positioned vertically with movement applied to clamping arm 722. In Fig. 15A, chip tray 850 is retracted to show chip device 500 attached to fluidic interface device 600 to form flow cell assembly 650 of FIG. 15A (see also FIG. 11). By forming flow cell assembly 650 over chip tray 850 when positioned in chip tray dock 816 as illustrated in FIG. 15A, liquid that spills from chip device 500 during the engagement process will not spill over electronic components, for example, such as pogo pin block 550 shown in FIG. 14.

[0086] Regarding the pre-alignment of chip device 500 by chip tray 850, chip clamp assembly shuttle 700 can be positioned over a chip device secured to chip tray chip mount 854 when chip tray 850 is positioned in chip tray dock 816 of chip clamp assembly base 800. By applying a downward movement of clamping arm 722 to apply a downward force on fluidic interface device 600 while it is positioned over chip device 500 results in chip device 500 being engaged with and reversibly coupled to fluidic interface device 600. The downward movement applies a vertical force supported by two linear bearings 726a and 726b in order to fully engage fluidic interface device 600 with chip device 500. To engage chip device 500 with fluidic interface device 600, a clamping force of between about 7 lbs. to about 14 lbs. can be applied to clamping arm 722 of clamping arm assembly 720. A clamping force of between about 7 lbs. to about 14 lbs. applied to clamping arm 722 translates into a load force of between about 30 lbs. to about 60 lbs. +/- 1 lbs. applied to fluidic interface device 600. The bottom perspective view of chip device 500 provides a view of device substrate 510 of chip device 500, as well as electronic connections 515 for engaging with a pogo pin block, for example, such as pogo pin block 550 of FIG. 14.

[0087] In Fig. 15A, an end of fluidic interface mounting bolt 628 on first mounting face 601 is visible. Recalling, as described for FIG. 12, fluidic interface mounting bolt through hole 627 runs through interface device body 610, and accommodates fluidic interface mounting bolt 628 used to attach fluidic interface device 600 to clamping arm 722. As illustrated in FIG. 15B, fluidic interface mounting bolt 628 is shown in phantom view running through interface device body 610. As such, first mounting face 601 illustrated in FIG. 15A is affixed to clamping arm 722 proximal to first clamping arm bar 721 of FIG. 15B, while second mounting face 603 is affixed to clamping arm 722 proximal to second clamping arm bar 723 in a fashion that allows access to a reference electrode, such as reference electrode 50 of FIG. 10 through FIG. 12. As illustrated in FIG. 15B, a cell analysis system of the present disclosure is configured to provide an end user ready access to a reference electrode for routine maintenance or replacement.

[0088] Returning to FIG. 14, once flow cell assembly 650 has been formed, chip clamp assembly shuttle 700 can be positioned over chip device mount 820, in which pogo pin block 550 is mounted. By applying a downward movement of clamping arm 722, a flow cell assembly, such as flow cell assembly 650 of FIG. 15A formed using chip clamp assembly 1000, can be moved through aperture 712. As previously described for engagement of chip device 500 to fluidic interface device 600 of FIG. 15A, to engage flow cell assembly 650 with chip device mount 820, a clamping force of between about 7 lbs. to about 14 lbs. can be applied to clamping arm 722 of clamping arm assembly 720. A clamping force of between about 7 lbs. to about 14 lbs. applied to clamping arm 722 translates into a load force of between about 30 lbs. to about 60 lbs. +/- 1 lbs. applied to flow cell assembly 650.

[0089] Additionally, chip thermal control assembly 900 is depicted as mounted beneath chip clamp assembly 1000 of FIG. 14 and FIG. 15A. and chip claim assembly 1000C of FIG. 15A. As will be described in more detail herein, thermal control assembly 900 provides thermal control to ensure that the surface temperature of a chip device is maintained within an appropriate temperature range for performing various cell analyses.

[0090] FIG. 16 is an exploded section view that illustrates generally a fluidic interface device of the present disclosure in relationship to a chip device and a chip thermal control assembly. As illustrated in FIG. 16, the section view of fluidic interface device 600. As previously described herein for FIG. 10 and FIG. 11, and as partially depicted in FIG. 16, fluidic interface device 600 includes upper surface 605 and lower surface 625, where upper surface 605 is part of fluidic interface body 610 and lower surface 625 is part of fluidic interface device flange 620. Fluidic interface device flange 620 includes fluidic interface device flange rim 622 and fluidic interface device flange ridge 623. When fluidic interface device 600 is fully assembled, fluidic interface device spacer 630, as depicted in FIG. 10 and FIG. 11, is abutted against fluidic interface device flange rim 622. Similarly, in a fully-assembled

fluidic interface device, fluidic interface device gasket 640, as depicted in FIG. 10 and FIG. 11, is mounted to fluidic interface device flange ridge 623.

[0091] Recalling, with respect to formation of a flow cell assembly as previously described herein for FIG. 14 and FIG. 15A, a clamping force is applied to sealably engage a sensor array device with an interface device to first form a flow cell assembly while a chip clamp assembly is in a first position over a chip tray docked to a chip clamp base. A flow cell assembly so formed is then shuttled over a chip device mount, and with an applied clamping force, is a chip device portion of the flow cell assembly becomes engaged with a pogo pin block and thermal control assembly. From the depiction of FIG. 16, and in reference to FIG. 10 and FIG. 11, in a flow cell assembly, fluidic interface device gasket 640 can be seated upon sensor chip top surface 525 of chip device 500 and fluidic interface device spacer 630, as well as positioned against the sealing surface of fluid dam inner wall surface 564, thereby providing a compressive gasket seal.

[0092] In FIG. 16, exemplary chip thermal control assembly 900 is depicted with thermoelectric cooling (TEC) device 910 mounted on cooling assembly 920, with first TEC surface 912 in contact with TEC cooling assembly 920. Second surface 914 of TEC device 910 is in contact with chip device cooling block 930, which during use of a chip device is in contact with device substrate lower surface 505. Thermal vias (see FIG. 10) in chip device substrate 510 provide effective thermal contact between chip device cooling block 930, chip device substrate 510 and sensor chip 520. As previously described herein for FIG. 10, a TEC cooling assembly of the present disclosure can be mounted to the bottom of a chip clamp base, such as chip clamp assembly base 800 of FIG. 10 to exert sufficient force on chip thermal control assembly 900 to make effective thermal contact with chip device 500.

[0093] As such, with the effective thermal contact, chip thermal control assembly 900 can effectively thermally control chip device 500. As depicted in FIG. 16, cooling assembly 920 can include top plate 922, which is contact with first TEC surface 912. Thermal control assembly top plate 922 together with thermal control assembly base 924 form thermal control assembly coolant channels 925 for the circulation of coolant through cooling assembly 920. Given that effectively dissipating heat from first TEC surface 912 is important for maintaining a temperature of second TEC surface 914 at a defined setpoint, and thereby maintaining a chip device at a target temperature, the temperature and flow rate of the coolant is a consideration for effective heat dissipation from first TEC surface 912. The cooling capacity of chip thermal control assembly 900 is 400W using flow rates of coolant, for example, of 4.5 L/min at 20°C. Such conditions of flow rate and temperature for the coolant are clearly effective for dissipation of heat from a sensor device, which generates 4-5 watts under use.

[0094] FIG. 17 is a front perspective view that generally illustrates cell analysis instrument 3500 of the present disclosure. As will be described subsequently herein, cell analysis instrument 3500 of FIG. 17 shares many of the components and function of cell analysis system 3000 of FIG. 1. Cell analysis instrument 3500 is depicted including analysis compartment 1900 and hardware compartment 2000, as indicated from an exterior view. Analysis compartment doors 1910 allow access to analysis compartment 1900 of cell analysis instrument 3500, while vents 2010 of hardware compartment 2000 allow exhausting of excess heat from hardware compartment 2000.

[0095] FIG. 18 is a front perspective section view that illustrates generally components of analysis compartment 1900 of the cell analysis instrument 3500 of FIG. 17. In order to maintain analysis compartment 1900 at a desired temperature, heat transfer to and from the analysis compartment can be mitigated using insulation sheet material 1920, shown in analysis compartment sidewall panels 1902 and analysis compartment top panels 1904. Though not shown in the front perspective section view of FIG. 18, analysis compartment doors 1910 and analysis compartment floor panel 1906 are insulated as shown in FIG. 18. In addition to mitigating heat transfer from analysis compartment 1900, insulation sheet material 1920 can be selected from a foil-faced insulation material to create a Faraday cage to provide shielding of the analysis compartment from various external sources of interfering electromagnetic signals. For example, insulation sheet material 1920 can be selected from a foil-faced polyurethane insulation sheet material, for example, such as a foil-faced polyisocyanurate insulation sheet material. For the purpose of effectively mitigating heat transfer to and from analysis compartment 1900, at least 2 inches of such sheet material can be used. With respect to creating a Faraday cage, in order to form a continuous conductive surface enclosing analysis compartment 1900, seams can be formed using aluminum tape where panels abut, and floor panel 1906 is grounded through a chassis ground.

[0096] Additional components included in the temperature-controlled environment of analysis compartment 1900 are fluid delivery system components, such as described for fluid delivery system 1500 of FIG. 1 and FIG. 2. For example, solution containers 1930 provide the same function in cell analysis instrument 3500 as previously described for solution containers 1230 A-F of FIG. 1 and FIG. 2. Similarly, solution containers 1940 and 1950 can provide the same function in cell analysis instrument 3500 as previously described for solution containers 1240 and 1250, respectively, of FIG. 1 and FIG. 2. Given the need to isolate analysis compartment 1900 in a Faraday cage to prevent interfering electromagnetic signals from coupling into fluid lines and creating system signal noise thereby, effluent lines carrying waste liquid are positioned in an open configuration over a collection funnel (not shown) inside waste line housing 1970. The collection funnel has an effluent line leading to an external waste container that is readily accessible to an end user. The air gap between system fluidic

lines and the collection funnel housed in waste line housing 1970 prevent spurious current flow to or from the reference electrode. Such spurious events of current fluctuation would compromise the required stability of the reference electrode. Therefore, given the open nature of collecting liquid waste effluent in cell analysis instrument 3500, waste line housing 1970 is enclosed to prevent volatilization of liquid waste effluent from contaminating cell analysis instrument 3500.

[0097] Chip clamp assembly 1000, as previously described for FIG. 14 through FIG. 15B, is depicted in FIG. 18 as positioned proximal to the solution containers in temperature controlled analysis compartment 1900. Accordingly, as previously described for cell analysis system 3000 of FIG. 1, all fluidic and instrument components in analysis compartment 1900 are maintained at selected temperature during an analysis. For example, a cell analysis system of the present disclosure can maintain solutions and reagents at an end user selected temperature of between about 10°C to about 50°C; moreover a selected temperature in a range of between about 20°C to about 37°C, which is a range in which many cell-based assays are conducted. Additionally, partially visible in the front perspective section view of analysis compartment 1900 of FIG. 18 is fluidic manifold 1100. Accordingly, though the fluid lines as described for fluid delivery system of FIG. 1 and FIG. 2 are not shown in FIG. 18, solution containers 1930, 1940 and 1950 of FIG. 18 are in fluid communication with flow cell assembly 650 of chip clamp assembly 1000 of FIG. 18 as described for fluid delivery system 1500 of FIG. 1 and FIG. 2.

[0098] FIG. 19 is an additional front perspective section view that illustrates generally an analysis compartment of the cell analysis system of FIG. 17. In the additional front perspective section view of FIG. 19, compartment back panels 1908 are more clearly evident with a bank of containers removed in the present view. Insulated compartment back panels 1908 separate analysis compartment 1900 from hardware compartment 2000, as well as mitigating heat transfer between compartment 1900 from hardware compartment 2000. In FIG. 19, fluidic manifold 1100 is clearly visible proximal to the banks of solution containers. Additionally shown in FIG. 19 is thermally-regulated air supply duct 2412 and thermally-regulated air return duct 2414, as well as coolant supply line duct 2422 and coolant return line duct 2424.

[0099] FIG. 20 is a front perspective section view that illustrates generally hardware compartment 2000 of the cell analysis instrument 3500 of FIG. 17. Hardware compartment 2000 can include processing electronics section 2300 and environmental control section 2400.

[00100] As illustrated in FIG. 20, processing electronics section 2300 can include instrument power supply 2020, which is a power source for everything but a thermal regulation unit in environmental control section 2400. Additionally, processing electronics section 2300 can include reader board 2100

and valve board 2200, presented in the section view of FIG. 20 in phantom view, which perform the functions as described for process electronics assembly 100 and valve board 200 of FIG. 1. Computers 2310 can include a solid state drive (SSD) and a hard disk drive (HDD). Associated with computers 2310 are USB ports 2312 and network plugs 2314. Given the heat dissipated by, for example, computers 2310, vent fans 2320 can be used to exhaust excess heat through vents 2010. Also depicted in FIG. 20 are thermally-regulated air return duct 2414 as well as pneumatic manifold 1400, which was previously described herein for fluid delivery system 1500 of FIG. 1 and FIG. 2.

[00101] Environmental control section 2400 of FIG. 20 can include air thermal regulation unit 2410, which is powered through power connector 2416 and DC power relay 2418. As previously described herein for cell analysis system 3000 of FIG. 1 and cell analysis system 3500 of FIG. 18, air thermal regulation unit 2410 can maintain the environment of analysis compartment 1900 at an end user selected temperature of between about 10°C to about 50°C; moreover a selected temperature in a range of between about 20°C to about 37°C. As such, chip clamp assembly 1000, as well as a fluid delivery system as described for FIG. 1 and FIG. 2, and housed in analysis compartment 1900 of FIG. 18 and 14, are maintained at in the target selected range, thereby providing a consistent temperature of all components housed within analysis compartment 1900 during an experiment.

[00102] Environmental control section 2400 of FIG. 20 can additionally include chiller 2420 for circulating coolant through a chip thermal control assembly. to maintain a thermoelectric cooling (TEC) at a desired temperature. Recalling, TEC device 910 is a component of thermal control assembly 900, as previously described herein for FIG. 1, FIG. 10 and FIG. 16. Accordingly, as shown in FIG. 19, coolant is provided from chiller 2420 to chip clamp assembly 1000 via a coolant supply line (not shown) running through coolant supply line duct 2422. As previously described herein for FIG. 16, coolant flows through coolant channels 925 of cooling assembly 920. The flow rate of coolant can be controlled by a valve board, such as valve board 200 of FIG. 1 or valve board 2200 of FIG. 20, where the flow rate of coolant is a factor in dissipating heat from first TEC surface 912, thereby maintaining a temperature of second TEC surface 914 at a defined setpoint (see FIG. 16). The cooling capacity of chip thermal control assembly 900 is 400W using flow rates of coolant, for example, of 4.5 L/min at 20°C, provides effective dissipation of heat from sensor device 500, which generates 4-5 watts under use. Coolant flowing through coolant channels 925 of cooling assembly 920 of FIG. 16, is then returned to chiller 2420 via a coolant return line (not shown) through coolant return line duct 2424, as depicted in FIG. 19.

[00103] As such, according to the present disclosure, in a first example, a fluidic system of the present disclosure comprises a fluid delivery system including a fluidic manifold having an outlet line at one end of a common manifold channel and a waste line at an opposing end of the common

channel; the fluidic system also including a plurality of solution containers in controllable fluid communication with the outlet line and the waste line of the fluidic manifold; said fluidic system additionally including a fluidic interface device configured for reversibly coupling to a sensor device; said coupling forming a flow cell assembly thereby, and wherein the flow cell assembly comprises an inlet channel providing fluid communication between the flow cell assembly and the outlet line of the fluidic manifold; an outlet channel providing fluid communication between the flow cell assembly and a waste container; and a reference electrode sealably and removably mounted in the fluidic interface device, said reference electrode in fluid communication with the sensor device.

[00104] In a second example, the fluidic system of the first example further includes a pneumatic manifold in fluid communication with each of the plurality of solution containers, thereby providing a head pressure over each solution container.

[00105] A third example is directed to a cell analysis instrument comprising an analysis compartment housing a chip clamp assembly and a fluid delivery system, wherein the analysis compartment is a thermally insulated Faraday cage; said cell analysis instrument also including a clamping arm assembly of the chip claim assembly for reversibly coupling a fluidic interface device to a sensor device; said coupling forming a flow cell assembly; wherein the cell analysis system additionally includes a hardware compartment adjoining the analysis compartment, said hardware compartment housing thermal control equipment and processing electronics equipment.

[00106] A fourth example includes the cell analysis instrument of the third example, and further specifies that the flow cell assembly is in fluid communication with the fluid delivery system.

[00107] A fifth example includes the cell analysis instrument of the third or fourth example, wherein the fluid delivery system further comprises a fluidic manifold having an outlet line at one end of a common manifold channel and a waste line at an opposing end of the common channel; said fluid delivery system also including a plurality of solution containers in controllable fluid communication with the outlet line and the waste line of the fluidic manifold; wherein the fluid delivery system additionally includes a pneumatic manifold in fluid communication with each of the plurality of solution containers, thereby providing a head pressure over each solution container.

[00108] A sixth example comprises the cell analysis instrument of the fifth example, and further specifies that a plurality of valves providing control of the fluidic manifold are zero dead volume diaphragm valves.

[00109] A seventh example comprises the cell analysis instrument the fifth example, and further specifies that the common channel is a zero dead volume zig-zag channel.

[00110] An eighth example includes the cell analysis instrument of any one of the fifth through seventh examples, and further specifies that a thermal regulation unit in the hardware compartment can maintain the analysis compartment at a selected temperature of between 10°C to 50°C.

[00111] A ninth example includes the cell analysis instrument of anyone of the fifth through eighth examples, and further specifies that the analysis compartment further comprises a chip thermal control assembly for maintaining the sensor device at a selected temperature.

[00112] A tenth example includes the cell analysis instrument of anyone of the fifth through ninth examples, and further specifies that the selected temperature for maintaining the sensor device is a range of 4 °C to 60 °C +/- Example 0.1 °C.

[00113] In an eleventh example, a manifold device comprises a manifold block having a first side and an opposing second side, the manifold block including a first set of valve ports disposed on the first side of the manifold block and a second set of valve ports disposed on the second side of the manifold block; wherein each valve of a first set of diaphragm valves is mounted on a corresponding valve port on the first side of the manifold block, and each of valve of a second set of diaphragm valves is mounted on a corresponding valve port on the second side of the manifold block; the manifold device also including an outlet line at one end of a common manifold block channel and a waste line at an opposing end of the common manifold block channel, wherein the waste line is in controllable fluid communication with the common manifold block channel; said manifold device additionally including a plurality of source inlet ports In fluid communication with a fluid source, each source inlet port in controllable fluid communication with a corresponding source valve port.

[00114] A twelfth example includes the manifold device of the eleventh example, and further specifies that the outlet line is in fluid communication with a target device.

[00115] A thirteenth example includes the manifold device of the eleventh or twelfth examples, and further specifies that the target device is a sample carrying device.

[00116] A fourteen example includes the manifold device of the thirteenth example, and further specifies that the target device is an analysis device or apparatus.

[00117] A fifteen example includes the manifold device of the thirteenth or fourteen examples, and further specifies that the fluid source is a solution or reagent from a source container.

[00118] A sixteenth example includes the manifold device of any one of the thirteen through fifteen examples and further specifies that the manifold block is fabricated from a machinable chemically-resistant polymeric material.

[00119] In a seventeenth example, the manifold device of the sixteenth example further specifies that the machinable chemically-resistant polymeric material is selected from a polymeric material including a polytetrafluoroethylene material, a polyetherimide material, a poly ether ketone material an acrylonitrile material, and a polyoxymethylene material.

[00120] In an eighteenth example, a method for operating a manifold device comprises placing an outlet line at one end of a common manifold block channel of the manifold device in fluid communication with a selected fluid source; and simultaneously placing a waste line at an opposing end of the common manifold block channel of the manifold device in fluid communication with a waste container; initializing the manifold device by priming the common channel with a fluid from the selected fluid source; wherein the fluid flows bidirectionally to the outline line and the waste line; and closing the fluid communication between waste line and the waste container, thereby directing the fluid flow unidirectionally through the outlet line.

[00121] A nineteenth example includes the method of the eighteenth example, and further specifies that the selected fluid source is a solution or reagent from a source container.

[00122] A twentieth includes the method of the eighteenth or nineteenth example, and further specifies that the solution or reagent flows unidirectionally through the outlet line without carryover.

[00123] While various examples of the present teachings have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of illustration only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the present teachings. It should be understood that various alternatives to the various examples described herein may be employed in practicing the present disclosure. It is intended that the following claims define the scope of the present disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A fluidic system comprising:
 - a fluid delivery system comprising a fluidic manifold having an outlet line at one end of a common manifold channel and a waste line at an opposing end of the common channel;
 - a plurality of solution containers in controllable fluid communication with the outlet line and the waste line of the fluidic manifold; and
 - a fluidic interface device configured for reversibly coupling to a sensor device; said coupling forming a flow cell assembly thereby, the flow cell assembly comprising:
 - an inlet channel providing fluid communication between the flow cell assembly and the outlet line of the fluidic manifold;
 - an outlet channel providing fluid communication between the flow cell assembly and a waste container; and
 - a reference electrode sealably and removably mounted in the fluidic interface device, said reference electrode in fluid communication with the sensor device.
2. The fluidic system of claim 1, further comprising:
 - a pneumatic manifold in fluid communication with each of the plurality of solution containers, thereby providing a head pressure over each solution container.
3. A cell analysis instrument comprising:
 - an analysis compartment housing a chip clamp assembly and a fluid delivery system, wherein the analysis compartment is a thermally insulated Faraday cage;
 - a clamping arm assembly of the chip clamp assembly for reversibly coupling a fluidic interface device to a sensor device; said coupling forming a flow cell assembly; and
 - a hardware compartment adjoining the analysis compartment, wherein the hardware compartment houses thermal control equipment and processing electronics equipment.
4. The cell analysis instrument of claim 3, wherein the flow cell assembly is in fluid communication with the fluid delivery system.

5. The cell analysis instrument of claim 3 or 4, where the fluid delivery system further comprises:
 - a fluidic manifold having an outlet line at one end of a common manifold channel and a waste line at an opposing end of the common channel;
 - a plurality of solution containers in controllable fluid communication with the outlet line and the waste line of the fluidic manifold; and
 - a pneumatic manifold in fluid communication with each of the plurality of solution containers, thereby providing a head pressure over each solution container.
6. The cell analysis instrument of claim 5, wherein a plurality of valves providing control of the fluidic manifold are zero dead volume diaphragm valves.
7. The cell analysis instrument of claim 5, wherein the common channel is a zero dead volume zig-zag channel.
8. The cell analysis instrument of any one of claims 5-7, wherein a thermal regulation unit in the hardware compartment can maintain the analysis compartment at a selected temperature of between 10°C to 50°C.
9. The cell analysis instrument of anyone of claims 5-8, wherein the analysis compartment further comprises a chip thermal control assembly for maintaining the sensor device at a selected temperature.
10. The cell analysis instrument of anyone of claims 5-9, wherein the selected temperature for maintaining the sensor device is a range of 4 °C to 60 °C +/- 0.1 °C.
11. A manifold device comprising:
 - a manifold block having a first side and an opposing second side, the manifold block including a first set of valve ports disposed on the first side of the manifold block and a second set of valve ports disposed on the second side of the manifold block;
 - a first set and second set of diaphragm valves, wherein each diaphragm valve of the first set and second set of diaphragm valves is mounted on a corresponding valve port on the first side and the second side of the manifold block, respectively;
 - an outlet line at one end of a common manifold block channel and a waste line at an opposing end of the common manifold block channel, wherein the waste line is in controllable fluid communication with the common manifold block channel; and
 - a plurality of source inlet ports in fluid communication with a fluid source, each source inlet port in controllable fluid communication with a corresponding source valve port.

12. The manifold device of claim 11, wherein the outlet line is in fluid communication with a target device.
13. The manifold device of claim 11 or 12, wherein the target device is a sample carrying device.
14. The manifold device of claim 13, wherein the target device is an analysis device or apparatus.
15. The manifold device of claim 13 or 14, wherein the fluid source is a solution or reagent from a source container.
16. The manifold device of any one of claims 13-15, wherein the manifold block is fabricated from a machinable chemically-resistant polymeric material.
17. The manifold device of claim 16, wherein the machinable chemically-resistant polymeric material is selected from a polymeric material including a polytetrafluoroethylene material, a polyetherimide material, a poly ether ketone material an acrylonitrile material, and a polyoxymethylene material.
18. A method for operating a manifold device, comprising:
 - placing an outlet line at one end of a common manifold block channel of the manifold device in fluid communication with a selected fluid source;
 - simultaneously placing a waste line at an opposing end of the common manifold block channel of the manifold device in fluid communication with a waste container;
 - initializing the manifold device by priming the common channel with a fluid from the selected fluid source; the fluid flowing bidirectionally to the outlet line and the waste line; and
 - closing the fluid communication between waste line and the waste container, thereby directing the fluid flow unidirectionally through the outlet line.
19. The method of claim 18, wherein the selected fluid source is a solution or reagent from a source container.
20. The method of claim 18 or 19, wherein the solution or reagent flows unidirectionally through the outlet line without carryover.