US 20090242173A1

(19) **United States**

(12) **Patent Application Publication**

**MITCHELL et al.**

(10) **Pub. No.: US 2009/0242173 A1**

(43) **Pub. Date: Oct. 1, 2009**

(54) **TEMPERATURE CONTROL SYSTEM**

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(21) Appl. No.: **12/410,724**

(22) Filed: **Mar. 25, 2009**

**Related U.S. Application Data**

(60) Provisional application No. 61/039,382, filed on Mar. 25, 2008.

**Publication Classification**

(51) **Int. Cl.**

| | |
|---|---|
| ***F28D 15/00*** | (2006.01) |
| ***B65D 35/22*** | (2006.01) |
| ***F28F 7/00*** | (2006.01) |

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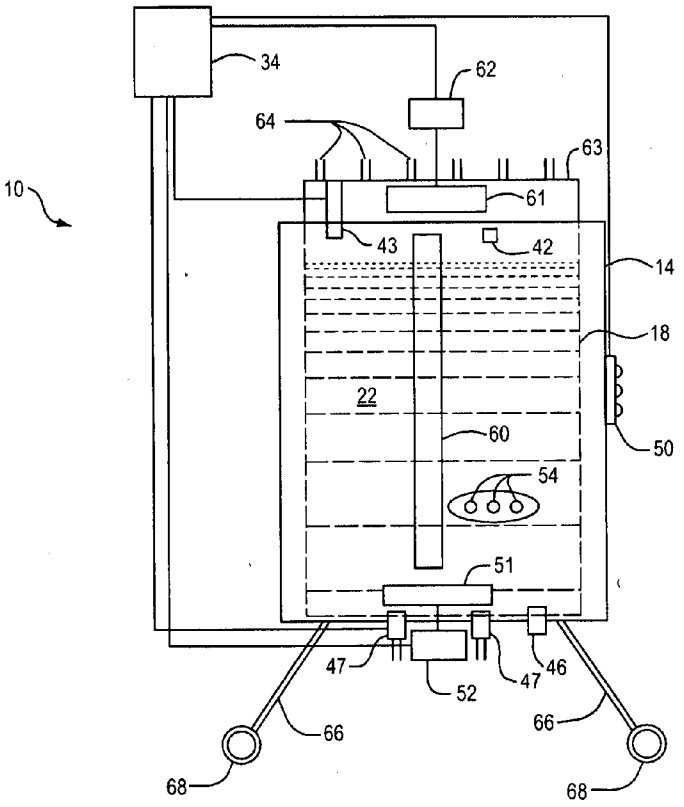
(52) **U.S. Cl.** ..... **165/104.19**; 222/94; 165/46

(57) **ABSTRACT**

An improved system and method for controlling the temperature of fluids during a mixing procedure or a chemical, pharmaceutical, or biological process is disclosed. One embodiment of the system comprises: a first collapsible bag including

a perimeter and a maximum dimension thereacross measured at full expansion of the first collapsible bag; a first interior surface portion; a second interior surface portion;

one or more welds connecting the first and second interior surface portions of the first collapsible bag so as to form a channel between the first and second interior surface portions, an inlet connected to a first portion of the channel; an outlet connected to a second portion of the channel, the channel defining a bulk fluid flow pathway through the first collapsible bag from the inlet to the outlet; and a first temperature-controlling surface in contact with a first exterior surface portion of the first collapsible bag. A heat exchanger in fluid communication with another vessel that can hold or store the heated or cooled fluid is also disclosed.



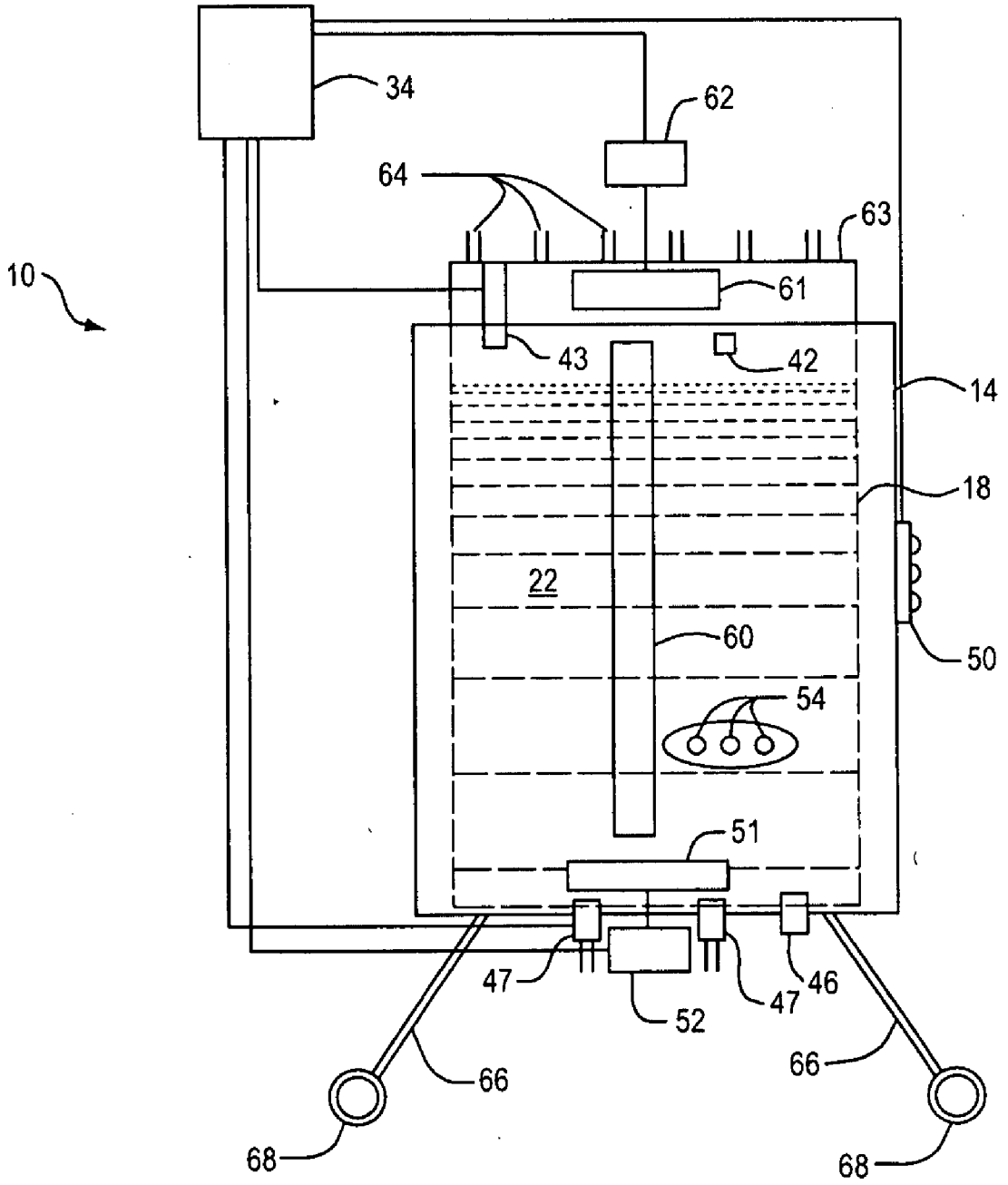



FIG. 1

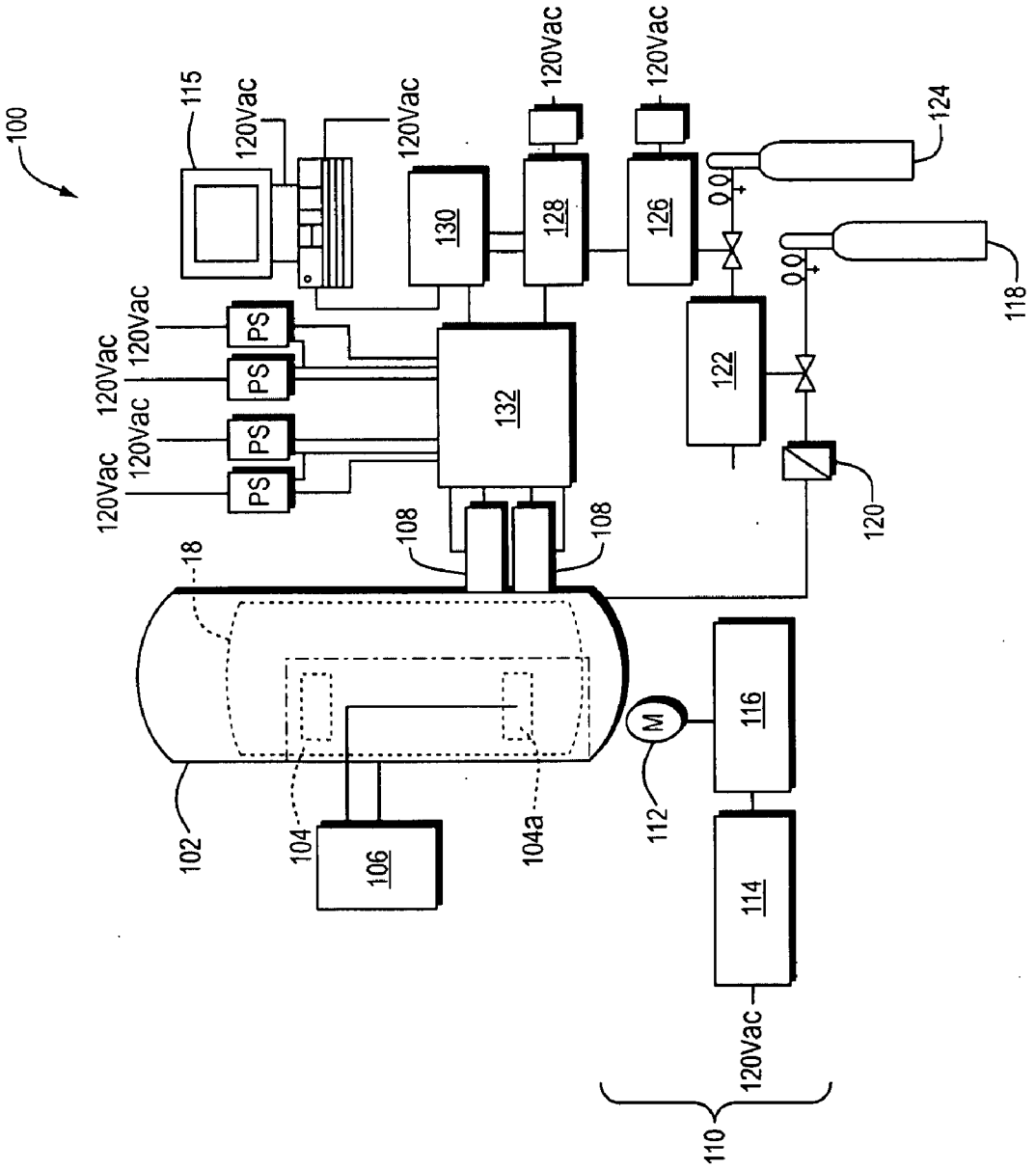

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FIG. 2

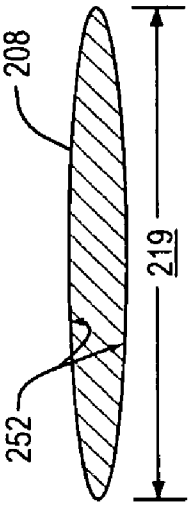



FIG. 3B

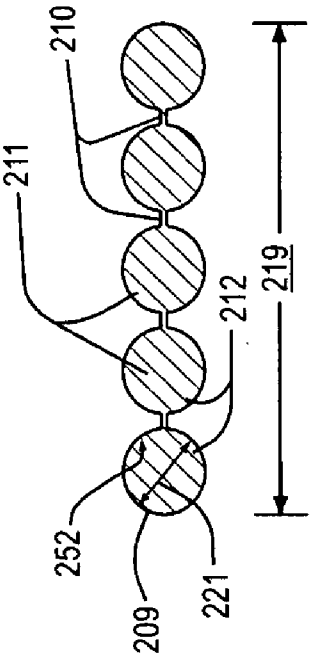



FIG. 3C

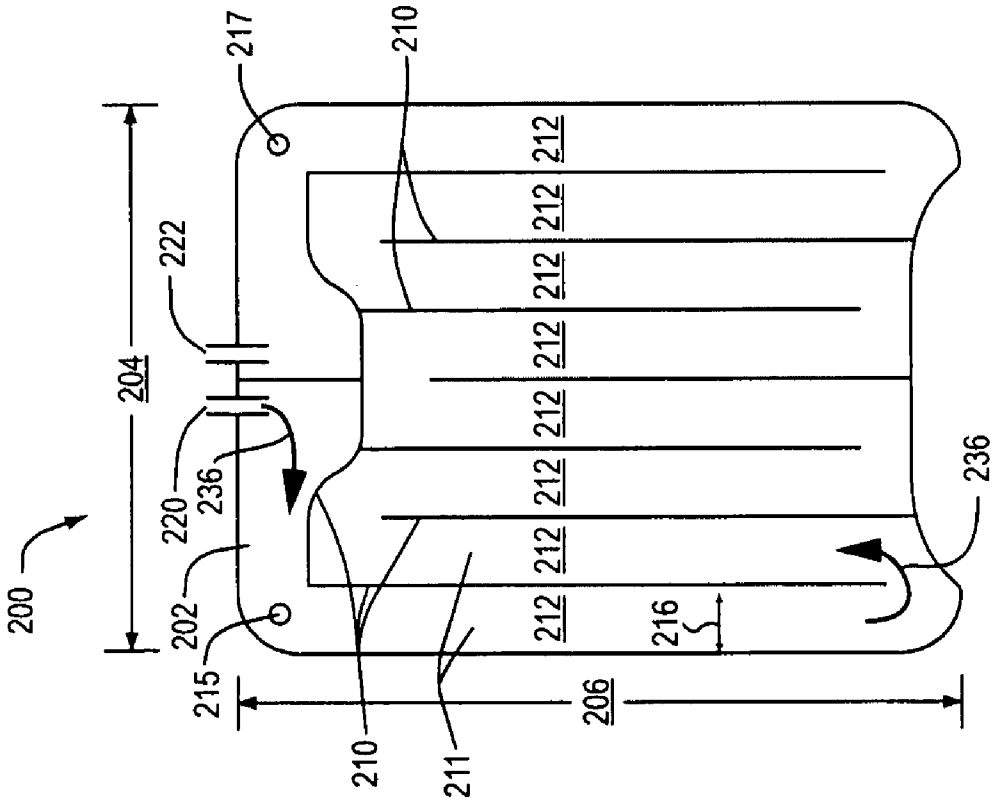



FIG. 3A

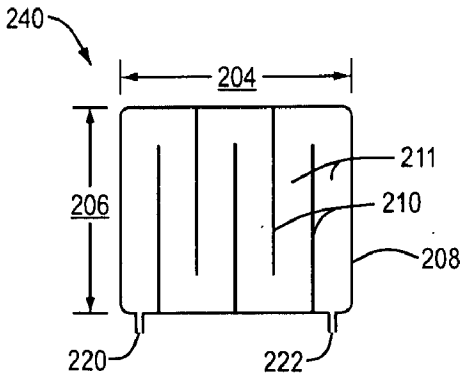



FIG. 4A

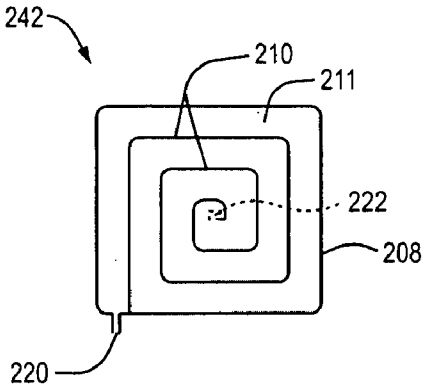



FIG. 4B

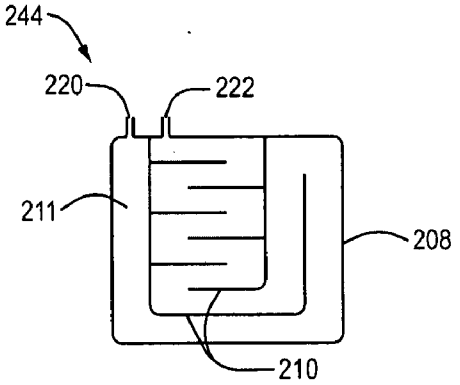



FIG. 4C

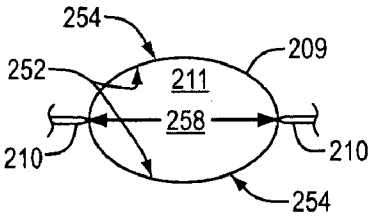



FIG. 4D

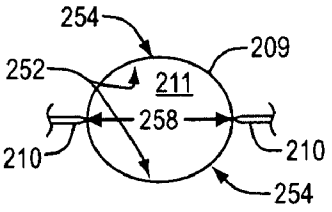



FIG. 4E

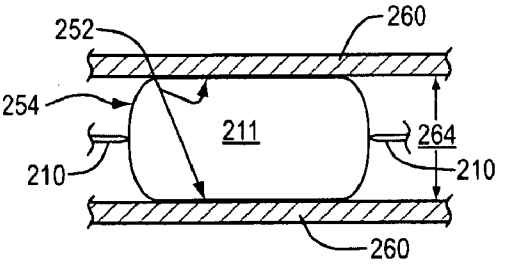



FIG. 4F

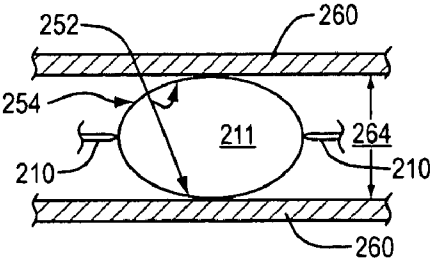



FIG. 4G

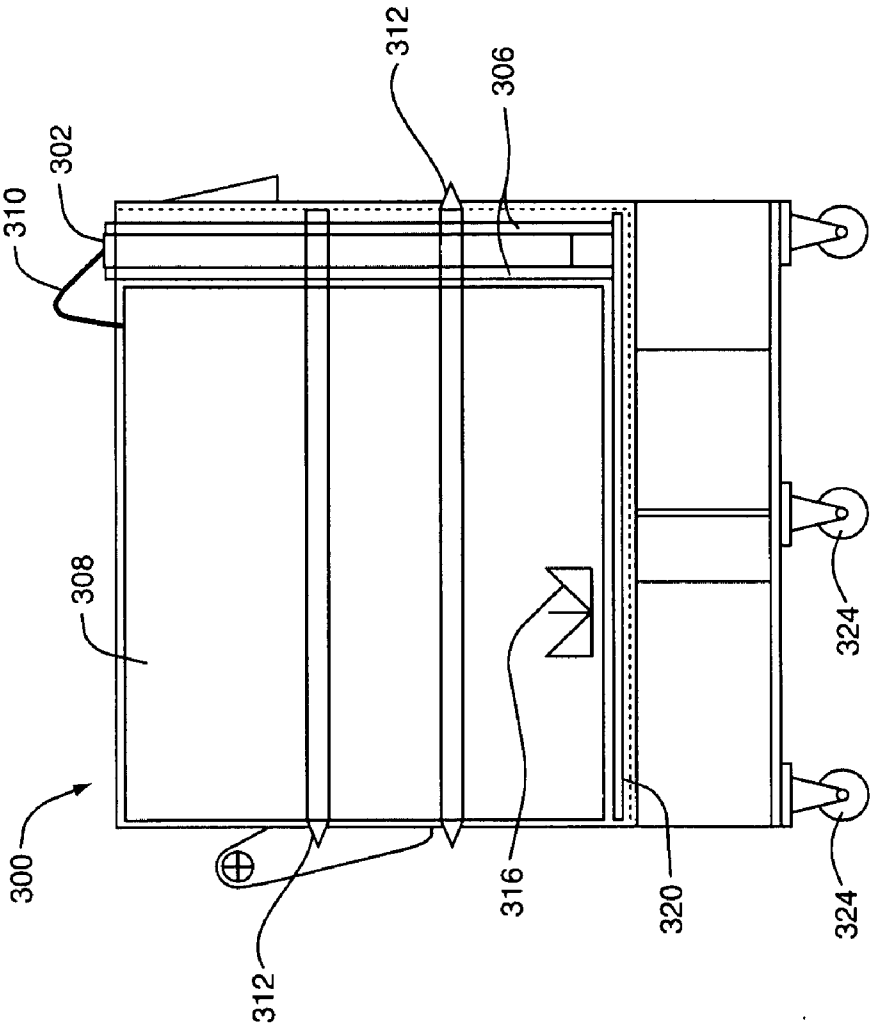



FIG. 5

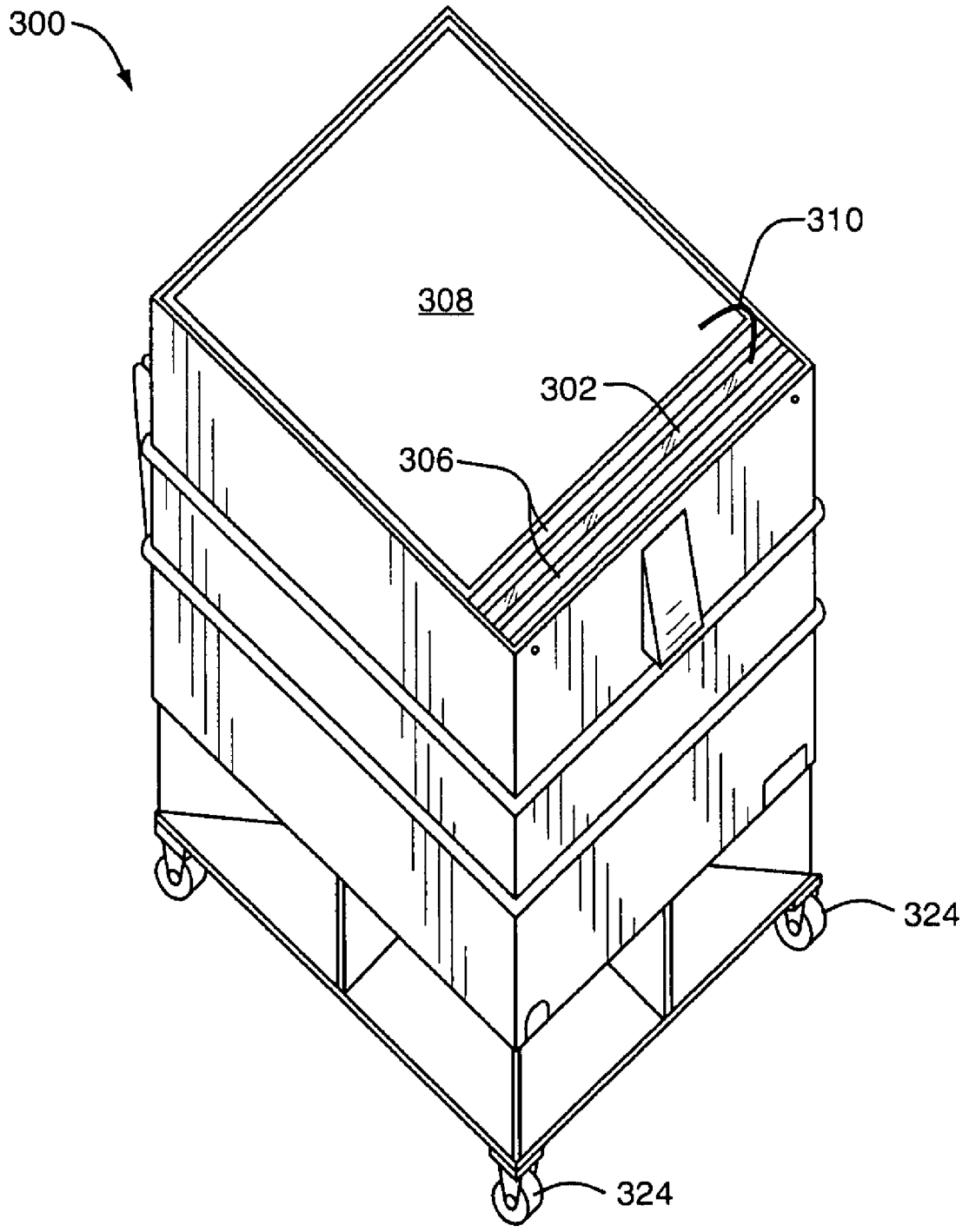



FIG. 6

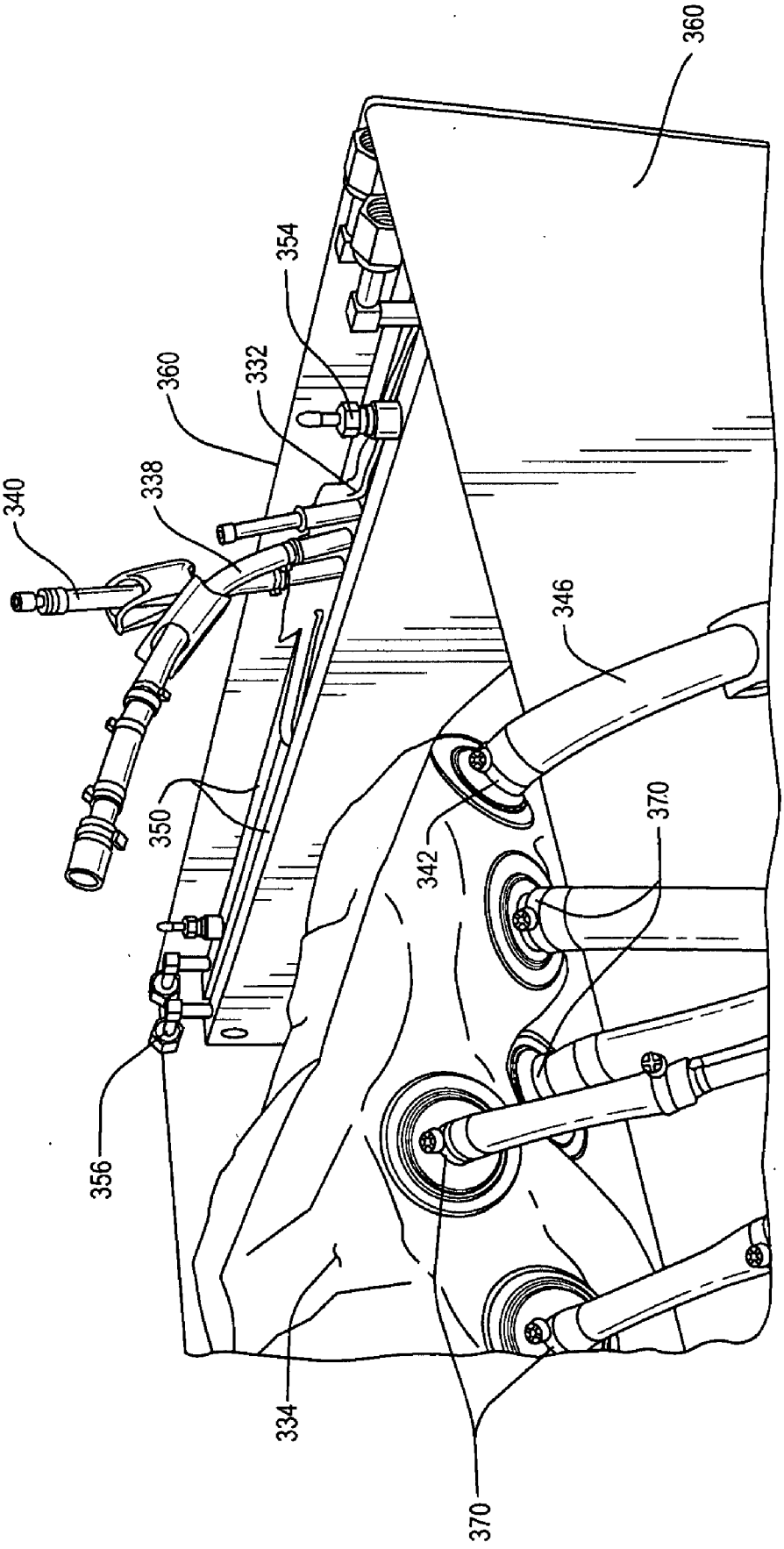



FIG. 7

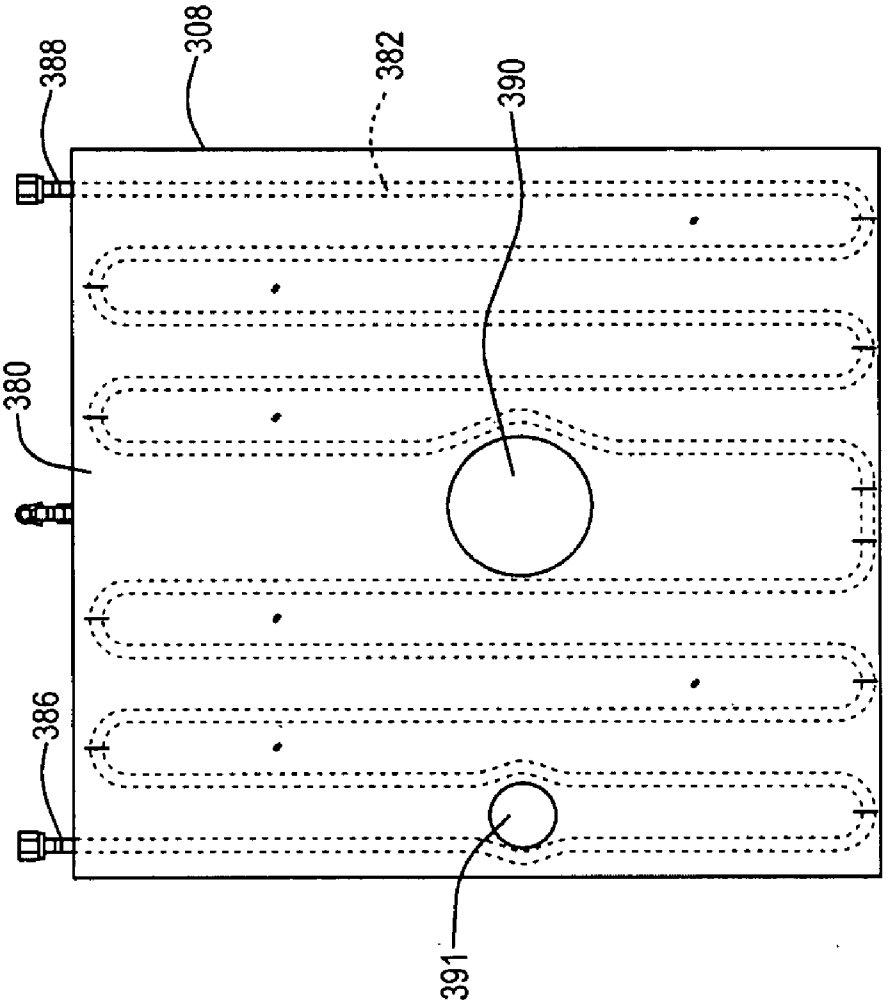



FIG. 8

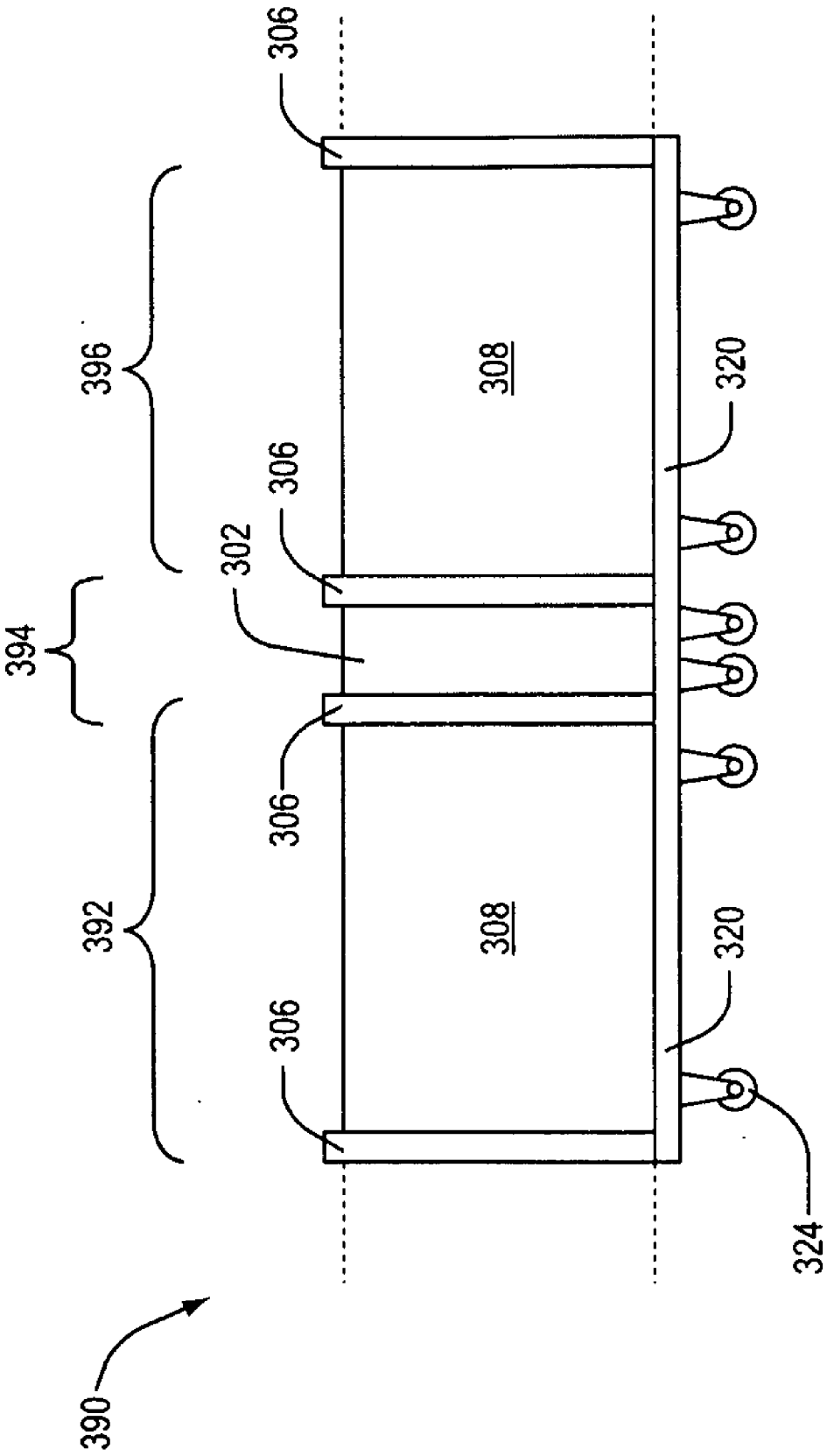



FIG. 9

# TEMPERATURE CONTROL SYSTEM

## RELATED APPLICATION

**[0001]** This application claims the benefit of U.S. Provisional Application No. 61/039,382 filed on Mar. 25, 2008, the teachings of which are incorporated herein by reference in their entirety.

## BACKGROUND

**[0002]** A variety of vessels for manipulating fluids and/or for carrying out chemical or biological reactions are available. For example, biological materials such as mammalian, plant or insect cells and microbial cultures can be processed using traditional or disposable bioreactors. Although such bioreactors and other fluid manipulating systems incorporating temperature control systems are known, there is a need for improvements to such systems.

## SUMMARY OF THE INVENTION

**[0003]** The present invention relates to the discovery of an improved system for controlling the temperature of fluids during a mixing procedure or a chemical or biological process. One embodiment of the invention provides a system configured for use in a chemical, biological, or pharmaceutical process, the system comprising: a first collapsible bag comprising: perimeter and a maximum dimension thereacross measured at full expansion of the first collapsible bag; a first interior surface portion; a second interior surface portion; one or more welds connecting the first and second interior surface portions of the first collapsible bag so as to form a channel between the first and second interior surface portions; an inlet connected to a first portion of the channel; an outlet connected to a second portion of the channel, the channel defining a bulk fluid flow pathway through the first collapsible bag from the inlet to the outlet; and a first temperature-controlling surface in contact with a first exterior surface portion of the first collapsible bag.

**[0004]** In accordance with a second aspect of the invention, a method of changing the temperature of fluids during mixing or during a chemical or biological process is disclosed. The method comprises: flowing a reaction fluid having a first temperature from a chemical, biological or pharmaceutical reactor into the collapsible bag of the system described above, the collapsible bag in fluid communication with the reactor; changing a temperature of the reaction fluid in the collapsible bag by at least 5 degrees Celsius while the reaction fluid is flowing in the collapsible bag; and flowing the reaction fluid from the collapsible bag into a container in fluid communication with the collapsible bag.

**[0005]** The present invention has many advantages, including an improved heat exchanger system having improved temperature control for a bioreactor or mixer. In the process of growing cells, it is often necessary to dissipate some of the heat generated by the cells, or in some cases, to warm the fluid in the bioreactor or mixer. For example, in one embodiment, the presence of the welds in a bioreactor bag provides a longer flow path for reaction, or for efficient heating or cooling for a longer period of time. Another advantage is that channels provided in various embodiments of the invention can reduce the amount of random or non-directed fluid flow, for example, turbulence and eddies, in a fluid in a bioreactor or mixer. Yet another advantage is that the disclosed channel configurations can also prevent or reduce "dead zones" that may lead to non-uniform heating or cooling of fluid.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0006]** The foregoing and other non-limiting objects, features and advantages of the invention will be apparent from the following more particular description of illustrative embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are schematic and not intended to be drawn to scale, emphasis instead being placed upon illustrating the principles of the invention. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. In the figures:

**[0007]** FIG. **1** is a schematic representation of a system comprising a container contained within a support structure according to one embodiment of the invention.

**[0008]** FIG. **2** is a schematic representation of a system for carrying out fluid manipulations including biological, chemical, and biochemical processes, according to another embodiment of the invention.

**[0009]** FIG. **3**A is a schematic representation of an elevational view of a heat exchanger comprising a collapsible bag having a channel within, according to one embodiment of the invention.

**[0010]** FIG. **3**B shows a cross-sectional view of a collapsible bag without welds according to one embodiment of the invention.

**[0011]** FIG. **3**C depicts a cross-sectional view of a collapsible bag having welds and channel segments according to one embodiment of the invention.

**[0012]** FIGS. **4**A-**4**C depict various configurations of heat exchangers in the form of collapsible bags according to some embodiments of the invention.

**[0013]** FIGS. **4**D-**4**G illustrate cross-sectional views of a channel segment of a collapsible bag according to some embodiments of the invention.

**[0014]** FIG. **5** depicts an elevational, cutaway view of a heat exchange system in fluid communication with a container for holding or storing a fluid according to one embodiment of the invention.

**[0015]** FIG. **6** depicts a perspective view of the heat exchange system shown in FIG. **5** according to one embodiment of the invention.

**[0016]** FIG. **7** depicts a perspective view of a heat exchange system according to one embodiment of the invention.

**[0017]** FIG. **8** depicts a temperature-controlling surface that includes a channel for flowing a heating or cooling fluid therethrough according to one embodiment of the invention.

**[0018]** FIG. **9** depicts a heat exchanger and containers in the form of modules according to one embodiment of the invention.

## DETAILED DESCRIPTION

**[0019]** A description of preferred embodiments of the invention follows. It will be understood that the particular embodiments of the invention are shown by way of illustration and not as limitations of the invention. At the outset, the invention is described in its broadest overall aspects, with a more detailed description following. The features and other

details of the compositions and methods of the invention will be further pointed out in the claims.

**[0020]** Disclosed herein are systems and methods for containing and manipulating fluids, and for regulating the temperature of fluids associated with a chemical, biological, or pharmaceutical reaction or process. Certain embodiments of the invention involve a series of improvements and features for fluid containment systems, for example, by providing a vessel including a heat exchanger which may be in the form of a flexible, collapsible bag.

**[0021]** Although much of the description herein involves an exemplary application of the present invention related to bioreactors and chemical, reaction systems, the invention and its uses are not so limited, and it should be understood that aspects of the invention can also be used in other settings, including those involving containment systems in general, as well as systems for containment or for mixing or other processing.

The Collapsible Bag or Other Container

**[0022]** Many disclosed examples include the use of collapsible bags, liners, or flexible containers. In addition, an embodiment of the invention can include systems utilizing non-collapsible bags, rigid containers, semi-flexible containers and other configurations involving liquid containment.

**[0023]** "Flexible container", "flexible bag", or "collapsible bag" as used herein, indicates that the container or bag is unable to maintain its shape and/or structural integrity when subjected to the internal pressures, for example, pressures resulting from the weight or hydrostatic pressure of liquids or gases contained therein without the benefit of a separate support structure. A reusable support structure may be utilized to surround and support the collapsible bag.

**[0024]** The collapsible bag may be made out of inherently flexible materials, such as many plastics, or may be made out of what are normally considered rigid materials such as glass or certain metals, but having a thickness or other physical properties rendering the container as a whole unable to maintain its shape or structural integrity when subjected to the internal pressures expected during operation without the benefit of a separate support structure. In some embodiments, collapsible bags include a combination of flexible materials and substantially rigid materials such as a rigid polymer, metal, or glass. For example, the collapsible bag, liner or other container may include rigid components such as connections, ports, supports for a mixing and/or antifoaming system.

**[0025]** In some embodiments, a rigid container or a collapsible bag comprises a polymeric material, for example, as a bulk material. Polymeric materials, such as the ones described herein, can be selected or formulated to have suitable physical and mechanical characteristics, for example, by tailoring the amounts of components of polymer blends to adjust the degree of any expected cross-linking. For instance, those of ordinary skill in the art can choose suitable polymers for use in containers based on factors such as the polymer's thermal conductivity, compatibility with certain processing techniques, compatibility with thermally-conductive materials, compatibility with any materials, such as cells, nutrients, solvents, contained in the container, and compatibility with sterilizations or other treatments or pre-treatments associated with performing a reaction inside the container.

**[0026]** In some embodiments, a collapsible bag is formed of a suitable flexible material, such as a homopolymer or a copolymer. The flexible material may be one that is USP Class VI certified, for example., silicone, polycarbonate, polyethylene, and polypropylene. Non-limiting examples of flexible materials include polymers such as polyethylene (for example, linear low density polyethylene and ultra low density polyethylene), polypropylene, polyvinylchloride, polyvinyldichloride, polyvinylidene chloride, ethylene vinyl acetate, polycarbonate, polymethacrylate, polyvinyl alcohol, nylon, silicone rubber, other synthetic rubbers and/or plastics. Portions of the flexible container may comprise a substantially rigid material such as a rigid polymer, for example, high density polyethylene, metal, or glass. Substantially rigid materials may be utilized in areas for supporting fittings, for example.

**[0027]** In other embodiments, the container is a substantially rigid material. Optionally, all or portions of the container may be optically transparent to allow viewing of contents inside the container. The materials or combination of materials used to form the container may be chosen based on one or more properties such as flexibility, puncture strength, tensile strength, liquid and gas permeability, opacity, and adaptability to certain processes such as blow molding for forming seamless collapsible bags. The container may be disposable in some cases.

**[0028]** The container may have any suitable thickness for holding a liquid and may be designed to have a certain resistance to puncturing during operation or while being handled. The thickness of a material such as a container wall is often specified in "mils." A mil is a unit of length equal to one thousandth ($10^{-3}$) of an inch, which is equivalent to 0.0254 millimeter. The unit "millimeter" is abbreviated herein as "mm." For example, a thickness of the flexible wall portions of a collapsible bag suitable for use in an embodiment of the invention may be less than 10 mils (less than 0.254 mm), or from about 10 mils to about 100 mils (from about 0.254 mm to about 2.54 mm) or from about 15 mils to about 70 mils (from about 0.38 mm to about 1.78 mm), or from about 25 mils to about 50 mils (from about 0.64 mm to about 1.27 mm). In yet another example, the walls of a container may have a total thickness of about 250 mils.

**[0029]** In some embodiments, the container includes more than one layer of material that may be laminated together or otherwise attached to one another in order to impart certain properties to the container. For instance, one layer may be formed of a material that is substantially oxygen impermeable. Another layer may be formed of a material to impart strength to the container. Yet another layer may be included to impart chemical resistance to a fluid that may be contained in the container. One or more layers of the container may include a thermally-conductive material to facilitate heat transfer to and from the interior of the container to an environment outside of the container, as described in more detail below.

**[0030]** A container, liner, or other article disclosed herein may be formed of any suitable combinations of layers. Non-limiting examples include an article comprising from 1 layer to about 5 layers of the same or different materials. Each layer may have a thickness of, for example, from about 3 mils to about 200 mils (from about 0.076 mm to about 5.08 mm), or combinations thereof.

**[0031]** The containers, for example, collapsible bags, may be adapted to include components of various sizes. In certain embodiments, the thickness of a collapsible bag or other container and the thickness of a portion of a component to be

joined, for example, fused, with the collapsible bag are, relative to the thickest portion, within about 5 percent to about 30 percent, or from about 10 percent to about 20 percent of one another.

**[0032]** A component to be incorporated with the container may have at least one cross-sectional dimension, thickness, or height of, for example, from about 0.05 centimeter (cm) to about 10 cm, or from about 1 cm to about 5 cm, or from about 1.5 cm to about 2 cm. A suitable thickness or height of a component may also be from about 15 cm to about 30 cm, or from about 20 cm to about 25 cm. A suitable thickness or height of a component can also be greater than 30 cm.

**[0033]** Components that are integrated with collapsible bags or other containers may be formed in any suitable material, that may be the same or different from the material of the bag or container. In one embodiment, a container is formed in a first polymer and a component is formed in a second polymer that is different, for example, in composition, molecular weight, or chemical structure, from the first polymer. Those of ordinary skill in the art will be familiar with material processing techniques and will be able to use such techniques in the methods described herein to choose suitable materials and combinations of materials.

**[0034]** A rigid container or a collapsible bag suitable for use in an embodiment of the invention may have any size for containing a liquid. For example, the container may have a volume from about 0.1 liter to about 10,000 liters (from about 100 cubic centimeters to about $1\times10^7$ cubic centimeters.) The term "cubic centimeter" will be abbreviated herein as "$cm^3$." In other non-limiting examples, the container may have a volume from about 5 liters to about 5,000 liters (from about 5,000 $cm^3$ to about $5\times10^6$ $cm^3$), or from about 40 liters to about 1,000 liters (from about $4\times10^4$ $cm^3$ to about $1\times10^6$ $cm^3$). Volumes greater than 10,000 liters ($1\times10^7$ $cm^3$) are also possible. The suitable volumes may depend on the particular use of the container. For example, a collapsible bag used as a heat exchanger may have a smaller volume than a collapsible bag used to hold and store a large amount of fluid.

**[0035]** A suitable container as part of a heat exchange system may be in fluid communication with a second container that is used to store or hold fluids. Either container or both containers may be in the form of a collapsible bag. The two containers may have about the same volume, or may have significantly different volumes. For example, the volume of the larger container may be from about 5 times to about 100 times greater than the volume of the smaller container. Other combinations of containers having different volumes are also possible.

**[0036]** In certain embodiments, especially in certain embodiments involving fluid manipulations or for carrying out a chemical or biological reaction in a container, the container is substantially closed, for example, substantially sealed from the environment outside of the container. As used herein, the term "sealed" is used to describe containers that are completely sealed from the environment such that no substances can move out of the container or into the container; containers that are essentially sealed such that only trace amounts of substances can move into or out of the container; and containers including one or more inlet or outlet ports that allow addition to, or withdrawal of contents from the container.

**[0037]** If a collapsible bag is used, it may be substantially deflated prior to being filled with a liquid, and may begin to inflate as it is filled with liquid. In other embodiments, the invention may include open container systems.

**[0038]** Many existing collapsible bags are constructed from two sheets of a plastic material joined by thermal or chemical bonding to form a container having two longitudinal seams. The open ends of the sheets are then sealed using known techniques, and access apertures are formed through the container wall. During use, collapsible bags having seams can cause the formation of crevices at or near the seams where materials contained therein are not thoroughly mixed. Such unmixed reagents can cause a reduction in yield of a desired product of a chemical or biological process. The presence of the seams in a collapsible bag can also result in non-uniform heat distribution of fluids or the inability of the collapsible bag to conform to the shape of a reusable support structure surrounding the bag.

Seamless Collapsible Bags

**[0039]** The above-described problems can be avoided by using collapsible bags without any seams. In one embodiment, seamless collapsible bags can be made specifically to fit a particular reusable support structure having a unique shape and configuration. Substantially perfect-fitting collapsible bags can be used, for example, as part of a bioreactor system or a biochemical or chemical reaction system. Seamless rigid or semi-rigid containers may also be beneficial in some instances.

**[0040]** A seamless collapsible bag suitable for use in an embodiment of the invention is a collapsible bag that does not include any seams joining two or more wall portions of the collapsible bag. The collapsible bag may be produced by blow molding, injection molding, or spin cast molding. In some embodiments, the referenced seamless collapsible bag may have one or more of a rigid, a semi-rigid, and a flexible wall portion.

**[0041]** A functional pre-made component may be formed integrally with the seamless collapsible bag as the seamless bag is produced. For example, a method of forming a seamless collapsible bag having a pre-made component embedded in a wall portion of the bag may include the steps of: positioning a pre-made component in a mold having a shape configured to mold a container having a pre-selected volume; introducing a at least one polymer precursor into the mold; forming a seamless container within the mold by solidifying the polymer precursor to form the container, while embedding at least a portion of the pre-made component with one or more wall portions of the container to form an integral piece of material without seams.

**[0042]** In another embodiment, a functional component such as an impeller shaft may be formed simultaneously and integrally with the seamless collapsible bag as the seamless bag is produced. For example, the method may include introducing a first polymer precursor into a mold having a shape configured to mold a collapsible bag having a pre-selected volume, and also configured to mold a base including a shaft configured to support a magnetic impeller; forming a collapsible bag within the mold; introducing a second polymer precursor into the mold; forming the shaft by solidifying the second polymer precursor; and joining the shaft and the collapsible bag without welding. In one embodiment of the invention, the first and second polymers are introduced into the mold approximately simultaneously.

**[0043]** Additional description of seamless containers can be found in U.S. patent application Ser. No. 11/818,901, filed

Jun. 15, 2007, entitled, "Gas Delivery Configurations, Foam Control Systems, and Bag Molding Methods and Articles for Collapsible Bag Vessels and Bioreactors," by G. Hodge, et al., published as US2008/0068920 A1 on Mar. 20, 2008, the entire teachings of which are incorporated herein by reference.

Exemplification

**[0044]** The invention is described in more detail in the following examples, which are provided by way of illustration and are not intended to limit the invention in any way. In one embodiment, a vessel configured to contain a volume of liquid is a part of a bioreactor system. Turning now to the drawings, the schematic diagram of FIG. **1** depicts vessel **10**, which includes a reusable support structure **14**. An example of the support structure **14** is a stainless steel tank that surrounds and contains a container **18**. In some embodiments, the container **18** is configured as a collapsible bag or liner, for example, a polymeric bag, and may optionally include tubing, a magnetic drive pump, and/or a foam breaker. In other embodiments, the container **18** is made of a substantially rigid material. The container **18** may be disposable, and may be configured to be easily removable from the support structure, or configured to be irreversibly connected to the support structure.

**[0045]** If a collapsible bag is used as container **18**, it may be constructed and arranged for containing a liquid **22**, which may contain reactants, media, or other components necessary for carrying out a desired process such as a chemical, biochemical or biological reaction. The collapsible bag may also be configured such that liquid **22** remains substantially in contact only with the collapsible bag during use and not in contact with support structure **14**. In such embodiments, the collapsible bag may be disposable and used for a single reaction or a single series of reactions, after which the bag is discarded. Because the liquid in the collapsible bag in such embodiments does not come into contact with the support structure **14**, the support structure **14** can be reused without cleaning. After a reaction takes place in container **18**, the container **18** can be removed from the reusable support structure **14** and replaced by a second disposable container. A second reaction can be carried out in the second container without having to clean either the first container **18** or the reusable support structure **14**. If any liquid **22** does come into contact with the reusable support structure due to leakage from the bag, in certain embodiments, one or more leak detection systems that are associated with vessel **10** detect the leak and notify the user so that appropriate measures can be taken.

**[0046]** Also shown in FIG. **1** are an optional inlet port **42** and optional outlet port **46**, which can be formed in the container **18** or reusable support structure **14**, and can facilitate more convenient introduction and removal of a liquid **14** or gas from the container **18**. The container **18** may have any suitable number of inlet ports **42** and any suitable number of outlet ports **46**. For example, a plurality of inlet ports **42** may be used to provide different gas compositions via a plurality of spargers **47**, or to allow separation of gases prior to their introduction into the container **18**. These ports may be positioned in any suitable location with respect to container **18**. For instance, for certain vessels including spargers **47**, the container **18** may include one or more gas inlet ports located at a bottom portion of the container **18**. Tubing may be connected to the inlet and outlet ports **42** and **46** to form delivery and harvest lines, respectively, for introducing and removing liquid from the container **18**. Optionally, the container **18** or support structure **14** may include a utility tower **50**, which facilitates interconnection of one or more devices internal to the container **18** or support structure **14** with one or more pumps, controllers, or electronics, such as sensor electronics, electronic interfaces, and pressurized gas controllers or other devices. Such devices may be controlled using a control system **34**. The control system **34** may also be used to send signals to and receive signals from a leak detection system and a wrinkle removal system.

**[0047]** For systems including multiple spargers **47**, control system **34** may be operatively associated with each of the spargers **47** and configured to operate the spargers **47** independently of each other. This can allow control of multiple gases being introduced into the container **18**.

**[0048]** In general, as used herein, a component of an inventive system that is "operatively associated with" one or more other components indicates that such components are directly connected to each other, in direct physical contact with each other without being connected or attached to each other, or are not directly connected to each other or in contact with each other, but are interconnected mechanically, electrically, fluidically, or remotely via electromagnetic signals, so as to cause or enable the components so associated to perform their intended functionality.

**[0049]** The vessel **10** may optionally include a mixing system such as an impeller **51**, which can be rotated about an axis using a motor **52** that can be external to the container **18**. In some embodiments, as described in more detail below, the impeller **51** and motor **52** are magnetically coupled. The mixing system can be controlled by control system **34**. Mixing systems are described in further detail below.

**[0050]** Additionally or alternatively, the vessel **10** may include an antifoaming system such as a mechanical antifoaming device. As shown in the embodiment illustrated in FIG. **1**, an antifoaming device may include, for example, an impeller **61** that can be rotated magnetically using a motor **62**, which may be external to the container **18**. The impeller **61** can be used to collapse a foam contained in a head space **63** of the container **18**. In some embodiments, the antifoaming system is in electrical communication with a sensor **43**, for example, a foam sensor, via control system **34**. The sensor **43** may determine, for instance, the level or amount of foam in the head space **63** or the pressure in the container **18**. The determination by the sensor **43** can trigger regulation or control of the antifoaming system. In other embodiments, the antifoaming system is operated independently of any sensors.

**[0051]** The support structure **14** and/or the container **18** may also include, in some embodiments, one or more ports **54** that can be used for sampling, determining and/or analyzing conditions such as pH or the amount of dissolved gases in the liquid **22** or for other purposes. The support structure **14** may also include one or more site windows **60** for viewing a level of liquid **22** within the container **18**. One or more connections **64** may be positioned at a top portion of the container **18** or at any other suitable location. Connections **64** may include openings, tubes, and/or valves for adding or withdrawing liquids, gases, and the like from the container **18**, each of which may optionally include a flow sensor and/or filter (not shown). The support structure **14** may further include a plurality of legs **66**, optionally with wheels **68** for facilitating transport of the vessel **10**.

**[0052]** It should be understood that not all of the features shown in FIG. **1** need be present in all embodiments of the invention and that the illustrated elements may be otherwise positioned or configured. Also, additional elements may be present in other embodiments, such as the elements described herein. For example, in some embodiments, a vessel **10** or one or more components of the vessel **10** is associated with an "identifier". The identifier may be used to guide proper assembly of system components, verify that the system components are correctly assembled, and protect against the use of counterfeit, improper or unauthorized components, for example. Each identifier may itself be "encoded with" information. In other words, the encoded information may be carry or contain information about the component including the identifier, such as by use of an information-carrying, storing, generating, or conveying device, such as a radio frequency identification (RFID) tag or bar code. In another embodiment, each identifier may not itself be encoded with any information about the component, but rather may only be associated with information that may be contained in, for example, a database on a computer or on a computer readable medium. In the latter instance, detection of such an identifier can trigger retrieval and usage of the associated information from the database.

**[0053]** Additional examples and uses of identifiers are described in more detail in U.S. patent application Ser. No. 12/011,492, filed on Jan. 25, 2008, entitled, "Information Acquisition and Management Systems and Methods in Bioreactor Systems and Manufacturing Facilities", which is incorporated herein by reference.

**[0054]** In other embodiments, one or more components shown in FIG. **1** are configured to be a part of a bioreactor system **100**, as illustrated in FIG. **2** and as described in more detail below.

Bioreactor or Mixer with Heat Exchange System

**[0055]** In some embodiments, a heat exchange system described herein is in fluid communication with one or more components of a bioreactor system, such as bioreactor system **100** shown in FIG. **2**. For example, container **18** may be operatively associated with and/or in fluid communication with a temperature controller **106** which may comprise a heat exchanger **200** described in connection with FIGS. **3-9**. In other embodiments, however, a closed loop water jacket, an electric heating blanket, a PELTIER heater or cooler, or other temperature control system known to those of ordinary skill in the art can also be used in combination with container **18**. The temperature control system may also include a thermocouple and/or a resistance temperature detector for sensing a temperature of the contents inside the container **18**. The thermocouple may be operatively connected to the temperature controller/heat exchanger to control temperature of the contents in the container **18**. Optionally, as described herein, a thermally-conductive material may be associated with a surface of the container **18**, for example, to provide a heat transfer surface **104**, **104**A in FIG. **2**, to overcome the insulating effect of the material used to form portions of the container **18**.

**[0056]** In some cases, sensors **108** and/or probes may be connected to a sensor electronics module **132**, the output of which can be sent to a terminal board **130** and/or a relay box **128**. Various sensors and/or probes for controlling and/or monitoring one or more process parameters inside the container such as, for example, temperature, pressure, pH, dissolved oxygen (DO), dissolved carbon dioxide ($DCO_2$), mixing rate, and gas flow rate, can be used. The results of the sensing operations may be input into a computer or computer-implemented control system **115** for calculation and control of various parameters such as temperature and weight/volume measurements, and for display and user interface. Such a control system **115** may also include a combination of electronic, mechanical, and/or pneumatic systems to control heat, air, or liquid delivered to or withdrawn from the container **18** as required to stabilize or control the environmental parameters of the process operation. It should be appreciated that the control system **115** may perform other functions and is not limited to having any particular function or set of functions.

**[0057]** The one or more control systems **115** can be implemented in numerous ways, such as with dedicated hardware and/or firmware, using a processor that is programmed using microcode or software to perform the functions recited above or any suitable combination of the foregoing. A control system **115** may control one or more operations of a single reactor for a biological or chemical reaction, or of multiple reactors that are separate or interconnected. The embodiment depicted in FIG. **2** depicts a drive control system **110** comprising a drive motor **112** for the agitator/impeller system, the controller **114** for controlling drive, and the drive **116** for controlling the motor **112**.

**[0058]** Each embodiment of a system described herein, for example, with reference to FIG. **2**, and components thereof, may be implemented using any of a variety of technologies, including software, for example, C, C#, C++, Java, or a combination thereof; hardware, for example, one or more application-specific integrated circuits; firmware, for example, electrically-programmed memory; or any combination of the foregoing.

**[0059]** Various embodiments described herein may be implemented on one or more computer systems. These computer systems, may be, for example, general-purpose computers such as, for example, those based on INTEL®) processors such as PENTIUM® or XSCALE® (INTEL Corporation, Inc.). It should be appreciated that one or more of any type of computer system may be used to implement various embodiments described herein. The computer system may include specially-programmed, special-purpose hardware, for example, an application-specific integrated circuit (ASIC). Various components may be implemented in software, hardware or firmware, or any combination thereof. Further, such methods, acts, systems, system elements and components thereof may be implemented as part of the computer system described above or as an independent component.

**[0060]** In one embodiment, a control system **115** operatively associated with a vessel described herein is portable, and may require a significantly shorter time period for set-up than do conventional fluid manipulation control systems. The control system **115** may include, for example, all or many of the necessary controls and functions required in a bioreactor system to perform a fluidic manipulation such as temperature control, mixing, and carrying out a reaction. The control system **115** may include a support and wheels for facilitating transport of the vessel. Advantageously, such a portable control system can be programmed with set instructions, and if desired, transported separately or with the vessel, and hooked up to a vessel, ready to perform a fluid manipulation.

**[0061]** A vessel may also be connected to one or more sources of gases **118**, **124** such as air, oxygen, carbon dioxide, nitrogen, ammonia, or mixtures thereof, in some embodi-

ments. The gases may be compressed or may be pumped, for example. Such gases may be used, for example, to provide suitable growth or reaction conditions for producing a product inside the container **18**. The gases may also be used to provide sparging to the contents inside the container, for mixing, or for other purposes. For instance, in certain embodiments employing spargers, bubble size and distribution can be controlled by passing an inlet gas stream through a porous surface prior to being added to the container. Additionally, the sparging surface may be used as a cell separation device by alternating pressurization and depressurization, for example, by application of vacuum on the exterior surface of the porous surface, or by any other suitable method.

**[0062]** In FIG. **2**, the inlet gases from sources of gases **118** and **124** may optionally pass through filter **120** and/or a flow meter and/or valve **122**, which may be controlled by controller system **115**, prior to entering the container **18**. Valve **122** may be a pneumatic actuator, actuated by, for example, compressed air, carbon dioxide, or other gas **124**, which may be controlled by a solenoid valve **126**. These solenoid valves **126** may be controlled by a relay **128** connected to terminal board **130**, which is connected to the controller system **115**. The terminal board may comprise, for example, a PCI terminal board, or a USB/parallel, or fire port terminal board of connection. In other embodiments, flush closing valves can be used for addition ports, harvest and sampling valves. Progressive tubing pinch valves that are able to meter flow accurately can also be used. In some cases, for example, for inlet ports, outlet ports, and sampling ports, the valves may be flush closing valves. The inlet gases may be connected to any suitable inlet of the vessel. In one embodiment, the inlet gases are associated with one or more spargers which can be controlled independently, as described in more detail below.

**[0063]** As shown in the exemplary embodiment illustrated in FIG. **2**, the container **18** and support structure **14** illustrated in FIG. **1** can be operatively associated with a variety of components as part of an overall bioreactor system **100**. Accordingly, in FIG. **2**, the container **18** and/or support structure **102** may include several fittings to facilitate connection to functional component such as filters, sensors, and mixers, as well as connections to lines for providing reagents such as liquid media, gases, and the like. The container **18** and the fittings may be sterilized prior to use so as to provide a "sterile envelope" protecting the contents inside the container **18** from airborne contaminants outside. In some embodiments, the contents inside the container **18** do not contact the reusable support structure **102** and, therefore, the reusable support structure **102** can be reused after carrying out a particular chemical or biological reaction without being sterilized, while the container **18** and/or fittings connected to the container **18** can be discarded. In other embodiments, the container, fittings, and/or reusable support structure **102** may be reused (for example, after cleaning and sterilization).

Temperature Controlling Surface

**[0064]** As used herein, the term "temperature-controlling surface" has the same meaning as "heat transfer surface." A temperature-controlling surface may be in contact with one or more exterior or interior surface portions of a collapsible bag. A temperature-controlling surface may comprise a thermally-conductive material, a plurality of particles embedded in a surface of the bag, a plate comprising channels for allowing fluid to flow therethrough, channels for allowing fluid to flow therethrough wherein the channels are not associated with a plate, and combinations of the foregoing.

**[0065]** The temperature of the fluid flowing in the collapsible bag **18** can be changed, in one embodiment, by associating one or more surfaces of the collapsible bag with a heat transfer surface, for the purpose of promoting transfer of heat to and/or from the collapsible bag **18**. In some embodiments, a system of the invention includes a heat exchanger in fluid communication with another vessel that can hold or store the heated or cooled fluid. The vessel may be positioned adjacent a thermally-conductive material to help maintain the temperature of the fluid inside the vessel. Optionally, the vessel may include an impeller or agitator to uniformly distribute heat throughout the interior of the vessel. Advantageously, the embodiments described herein may be sterile and configured for a single use or a single series of uses, after which the components can be discarded.

**[0066]** Another aspect of the invention includes a heat exchanger that can be used to control the temperature of a fluid from container **18** of FIG. **1**, or a fluid from any other suitable fluid source. Accordingly, the heat exchanger may be in the form of a container, for example, a collapsible bag, that is constructed and arranged to receive a fluid. By flowing a fluid through the collapsible bag, heat can be transferred from the fluid to an environment exterior to the bag or from an exterior environment to the fluid via the bag. This process can allow the fluid to be heated or cooled to a particular temperature before it exits the collapsible bag into another vessel.

**[0067]** To enhance heat conduction, one or more surfaces of the collapsible bag may be associated with a heat transfer surface, for example, a thermally-conductive material. For instance, in one embodiment, the material used to form the collapsible bag may have thermally-conductive particles embedded therein. In another embodiment, an exterior surface portion of the collapsible bag is in contact with a temperature-controlling surface, such as a heating or cooling surface. These and other thermally-conductive materials/systems are described in more detail below.

**[0068]** In one embodiment of the invention, the collapsible bag may include one or more welds connecting a first interior surface portion to a second interior surface portion of the bag so as to form a channel between the first and second interior surface portions. Compared to a bag without welds or channels, the presence of a channel within the bag can result in a longer path for bulk fluid flow permitting fluid to be cooled or heated uniformly for a longer period of time. A channel can also prevent or reduce "dead zones" that may lead, for example, to non-uniform heating or cooling of fluid.

**[0069]** As shown in a side view of the embodiment illustrated in FIG. **3**A, heat exchanger **200** is in the form of a collapsible bag **202** and has a width **204** and a length **206**. As illustrated, fluid can be introduced into the collapsible bag **202** via inlet **220**; the fluid may flow in the direction of arrows **236** in channel **211**, and in each of the channel segments **212** until it reaches outlet **222**.

**[0070]** In this particular embodiment, the width is the maximum dimension **219** across the perimeter **208** of the collapsible bag **202**. The width can be measured while the collapsible bag **202** is fully expanded, or fully collapsed. Heat exchanger **200** also includes a plurality of welds **210** connecting a first interior surface portion to a second interior surface portion of the collapsible bag **202**. The welds **210** can be positioned at various interior portions of the collapsible bag **202** so as to form a channel **211** between the first and second interior

surface portions. As illustrated, channel **211** includes a plurality of channel segments **212** having a width **216**.

**[0071]** Channel **211** defines a bulk fluid flow pathway through the collapsible bag **202**; that is, a fluid flowing from a first portion to a second portion of the bag may flow in a predetermined orientation and/or at a predetermined flow rate by applying a pressure differential between the first and second portions. This and other configurations comprising channels can reduce the amount of random or non-directed fluid flow, for example, turbulence, eddies, and so forth, in the collapsible bag **202**.

**[0072]** Typically, the channel **211** comprises from about 4 channel segments to about 10 channel segments. The presence of the channel segments **212** allows a directed and longer fluid flow pathway than a bag of a similar shape and volume which does not include the welds **210** and channel segments **212**. For example, the selected bulk fluid flow pathway length may be from about 2 times to about 12 times the maximum dimension **219** across the collapsible bag **202** outer perimeter **208**, or from about 3 times to about 8 times the maximum dimension across the collapsible bag **202** outer perimeter **208**. Because the fluid pathway is lengthened by the presence of the channel **211**, the fluid can flow in the collapsible bag **202** for a longer period of time and can allow the fluid to be heated or cooled for a longer period of time than the flow period and heating or cooling period for a bag without channel segments **212**. Such a configuration can also prevent or reduce "dead zones" that may lead, for example, to non-uniform heating or cooling of fluid.

**[0073]** As depicted in FIG. **3**C, in some embodiments, the welds **210** results in the formation of channel **211** with a plurality of channel segments **212**, each having a maximum cross-sectional dimension **216**, which is smaller than a maximum dimension **219** across a perimeter **208** of the collapsible bag **202** at full expansion of the collapsible bag **202**. FIG. **3**B shows a cross-sectional view of a collapsible bag **202** that does not include welds **210**, and which has a perimeter **208** and a maximum dimension **219** across the perimeter. As illustrated in the cross-sectional view of FIG. **3**C, the same collapsible bag **202** as the one shown in FIG. **3**B, but with welds **210**, also has a maximum dimension **219** across perimeter **208** of the bag. The presence of the welds **210** provides a longer flow path for reaction, or for heating and cooling

**[0074]** In one embodiment, the average cross-sectional dimension of the channel **211** at full expansion of the collapsible bag **202** is from about one tenth to about one fourth of the maximum dimension **219** of the collapsible bag **202**. The maximum cross-sectional dimension **221** of a channel segment **212** may be, for example, from about ½ to about 1/20 of the maximum dimension **219** across a perimeter **208** of the collapsible bag **202**, or from about ⅓ to about ⅛ of the maximum dimension **219** across a perimeter **208** of the collapsible bag **202**, measured at full expansion or full collapse of the collapsible bag **202**.

**[0075]** The cross-sectional dimension of the channel may be designed to allow a particular flow rate, internal pressure, and/or length of time of fluid flow inside the bag. These parameters, in turn, may be chosen depending on, for example, the particular fluid to be flowed in the bag, the volume of the collapsible bag **202**, the desired temperature change, and the like. Accordingly, depending on these and other factors, a channel **211** of the collapsible bag **202**, at full expansion, or full collapse, of the collapsible bag **202**, may have, for example, a maximum cross-sectional dimension **221** taken perpendicular to the centerline of the channel **211** of from about 1 centimeter to about 20 centimeters. In some embodiments, the maximum cross-sectional dimension **221** of a channel **211** portion is from about 5 centimeters to about 10 centimeters. Furthermore, a container may include any suitable number of channel segments **212**, for example from about 2 to about 20, or from about 4 to about 10 channel segments. Typically, a greater number of channel segments **212** results in channels **211** having smaller cross-sectional dimensions compared to a container of the same volume and shape having a smaller number of channel segments **212**. A greater number of channel segments **212** may be suitable for applications involving relatively slower fluid flow, lower internal pressures, and/or for applications where it is desirable to maintain fluid flow in the collapsible bag **202** for a longer period of time.

**[0076]** The volume of the collapsible bag **202** may depend on the volume of fluid to be heated or cooled, as well as the volume of a container that may be in fluid communication with the collapsible bag **202**, as described in more detail below.

**[0077]** As stated above, a collapsible bag **202** may optionally include one or more sensors, such as temperature sensors, for determining a component or a condition within the collapsible bag **202**. For example, a temperature sensor may be used to determine the temperature of a fluid inside the collapsible bag **202**. A pressure sensor may be used to determine the amount of pressure inside the collapsible bag **202**, for example, during the flow of fluid in the collapsible bag **202**. A flow rate sensor may determine the flow rate of a fluid flowing in the collapsible bag **202**, for example, so that a particular flow rate can be maintained. Sensors for determining components, for example, reactants and products, of a fluid may also be incorporated into the collapsible bag **202**. The sensor may be positioned at any suitable location such as inside the collapsible bag **202**, within a wall of the collapsible bag **202**; or it may be embedded in a wall of the collapsible bag **202**. Furthermore, a collapsible bag may include more than one sensor. For example, FIG. **3**A shows a first sensor **215** positioned near inlet **220** and a second sensor **217** near outlet **222**. Sensors **215** and **217** can be used to measure the difference in temperature between the fluid flowing into and out of the collapsible bag **202**.

**[0078]** It should be understood that welds **210** may be formed by any suitable process and, in some cases, may depend on the particular materials used to form the container. Accordingly, a weld **210** may include any suitable joining of two or more wall portions, for example, two or more interior surface portions of a container, and may be achieved by methods such as welding, including, for example, heat welding and ultrasonic welding, use of the adhesive, clamping, fastening, or other attaching techniques.

**[0079]** In some cases, a plurality of welds **210** are present in a container to form a channel **211** having a non-linear configuration. For example, as illustrated in FIG. **3**A, channel **211** may be in the form of a serpentine configuration. A second serpentine configuration is shown in a side view of the embodiment illustrated in FIG. **4**A. Other configurations of channels **211** and welds **210** are shown in FIGS. **4**B and **4**C. As illustrated in the side view of a container **242** shown in FIG. **4**B, a single, continuous weld **210** may be used to form channel **211** in the form of a spiral configuration. FIG. **4**C shows a side view of a container **244** in yet another configuration that can allow formation of a fluid pathway that can

allow uniform heating or cooling of a fluid. These and other configurations can allow inlet **220** and outlet **222** to be positioned at different locations within the container.

**[0080]** FIG. **4**D shows a cross section of a channel segment according to one embodiment of the invention. Channel **211** includes interior surface portions **252** and exterior surface portions **254**. The channel is formed by welds **210** that connect two interior surface portions of the bag. FIG. **4**D shows channel **211** upon full expansion of the bag. As illustrated in this exemplary embodiment, channel **211** includes a perimeter **209** having a maximum cross section **258**, as described above, therethrough. The maximum cross section, in some embodiments, can be varied by changing the distance between welds **210**. For instance, as shown in the embodiment illustrated in FIG. **4**E, a closer distance between welds **210** may result in a smaller maximum cross section **258**, a smaller cross-sectional area, and a different shape of the channel.

**[0081]** As shown in the embodiments illustrated in FIGS. **4**F and **4**G, a collapsible bag may be positioned between two surfaces **260** in some embodiments. One or both of surfaces **260** may be a heat transfer surface or temperature-controlling surface; that is, the temperature of all or a portion of the surface may be varied, controlled and/or set to a particular temperature or range of temperatures. Temperature-controlling surfaces may comprise a thermally-conductive material and can be used to locally heat or cool a container positioned adjacent the surface. Examples of temperature-controlling surfaces are provided below.

**[0082]** In some embodiments, surfaces **260** may be positioned so as to inhibit full expansion of the bag and channel **211**. FIG. **4**F shows a relatively small separation distance **264** between surfaces **260** that can promote greater inhibition of full expansion of channel **211** compared to that shown in FIG. **4**G, which shows a greater separation distance **266** between surfaces **260**. The configuration shown in FIG. **4**F can allow, in some embodiments, a greater amount of exterior surface portion **254** to be in contact with surface **260**. This configuration may be advantageous for certain applications, for example, when surface **260** is a thermally-conductive surface that can promote heat transfer into and out of a fluid in channel **211**. As shown in FIG. **4**G, the positioning of surfaces **260** which allows greater expansion of channel **211** can result in less surface area of contact between surfaces **260** and exterior surface portions **254** of the bag.

**[0083]** Accordingly, any suitable separation distance may be maintained between surfaces **260**. For example, the average minimum separation distance between the two surfaces may be from about 1 centimeter to about 30 centimeters, or from about 5 centimeters to about 20 centimeters, or from about 7 centimeters to about 10 centimeters. As described herein, the separation distance may depend on the size and volume of the container positioned between the surfaces, the number of channel segments, the flow rate to be used with the system, the internal pressure in the container, etc. In some embodiments, the separation distance is chosen to inhibit full expansion of a collapsible bag during use.

**[0084]** Surfaces **260** may also be used to contain and support a collapsible bag. For instance, the surface may form at least one wall of a reusable support structure for supporting and containing the collapsible bag. The reusable support structure may simply include two plates separated by a distance to allow support of a collapsible bag, or it may be part of a larger structure that additionally includes support for a second collapsible bag, which may hold a fluid. The plates may allow variation of the separation distance. As one or more surfaces **260** may be thermally-conductive, the heat exchanger may be used to heat or cool fluids at various steps in a chemical or biological reaction process, as described in more detail below. In some embodiments, the reusable support structure is portable and can include wheels **324** or other components to facilitate transport of the system.

**[0085]** A collapsible bag or other container can be maintained between two surfaces by any suitable method such as by friction, pressure (for example, pressure exerted on the surfaces upon expansion of the collapsible bag), gravity, fastening with screws, pegs, clamps, or the like, and use of adhesives. In some embodiments, the two surfaces are a part of a single component that acts as a reservoir for containing the collapsible bag. The component may have a shape that is complementary to the shape of the collapsible bag.

Heat Exchanger in the Form of a Collapsible Bag

**[0086]** Another aspect of the invention includes a heat exchange system in fluid communication with a container for holding and/or storing a fluid. As shown in the system **300** illustrated in FIG. **5**, a heat exchanger may be in the form of a collapsible bag **302**. The heat exchanger collapsible bag **302** may optionally include one or more thermally-conductive materials, which may be, for example, embedded in a wall of the collapsible bag **302**. In the configuration depicted in FIG. **5**, the collapsible bag **302** is contained in and supported by two heat transfer surfaces **306**. A heat transfer surface such as **306** and **320** may comprise a thermally-conductive material for temperature control, including cooling or heating. Collapsible bag **302** may be in fluid communication with a container **308**, which may be in the form of a second collapsible bag or a rigid container, via tubing **310**, for example. As illustrated, an impeller **316** may be associated with container **308** and can be used to agitate or mix a fluid and/or to maintain a particular temperature of a fluid inside the container. Impellers are described in more detail below.

**[0087]** A heat transfer surface **320** for conducting heat either to or away from container **308** may be in contact with one or more surfaces of container **308**. Additionally or alternatively, a heat transfer surface **306** can also be used to control a temperature of a fluid in container **308** by positioning container **308** adjacent heat transfer surface **306**.

**[0088]** As illustrated, system **300** may include wheels **324** or any other suitable means, such as rails, rollers, and the like, for transporting system **300**. System **300** also comprises two horizontal support bands **312**, which support the sidewalls of container **308**. In one embodiment, support bands **312** are plastic-encased stainless angle-iron, and are connected throughout the circumference of the tank.

**[0089]** FIG. **6** shows a perspective view of system **300**, including support bands **312**, the container **308** adjacent one of the heat transfer surfaces **306**, and the heat exchanger collapsible bag **302** sandwiched in between the two heat transfer surfaces **306**.

**[0090]** FIG. **7** shows another example of a heat exchange system **330**. As illustrated in this exemplary embodiment, a collapsible bag may be a heat exchanger bag **332** positioned adjacent a second collapsible bag **334** which can contain and/or store a fluid. An inlet **338** is arranged for introducing a fluid into the heat exchanger bag **332**. An outlet **340** of heat exchanger bag **332** may be connected to an inlet **342** of second collapsible bag **334** via tubing **346**. In some embodi-

ments, a fluid is transferred from a first container, for example, a bioreactor, to heat exchanger bag **332**, where the fluid is heated or cooled. Without storing any fluid in collapsible bag **332**, the fluid may be immediately transferred to the second collapsible bag **334** where it is stored. After the fluid is transferred into heat exchanger bag **332**, inlet **338** may be closed off by one or more valves to maintain a sterile environment inside the heat exchanger bag **332**. The fluid pathway between heat exchanger bag **332** and the second collapsible bag **334** may also be closed off by a valve after transferring the fluid.

**[0091]** As shown in the embodiment illustrated in FIG. **7**, heat exchanger bag **332** may be positioned between two heat transfer surfaces **350**, which may be in the form of plates. The plates may be positioned relative to the bag so as to inhibit the full expansion of the bag and channels during use. One of the two heat transfer surfaces **350** may also be in contact with a side portion of the second collapsible bag **334**, so as to maintain a temperature of a fluid transferred to the second collapsible bag **334**.

**[0092]** Any suitable temperature-controlling surface may be used to control the temperature of a fluid. In one embodiment, a temperature-controlling surface, for example, heat transfer surface **350**, includes one or more fluid channels for flowing a cooling or heating fluid therethrough. For instance, a cooling or a heating fluid may be flowed into inlet **354**, through the channels of the thermally-conductive surface, and may exit the channels via outlet **356**. The fluid can then be re-circulated if desired. The temperature of heat transfer surface **350** may be controlled by the temperature of the cooling fluid flowing in one or more channels of the thermally-conductive surface. Optionally, heat transfer surfaces **350** may include one or more sensors. The sensors may include a temperature sensor for determining the temperature of the fluid circulating in the channels of heat transfer surface **350**.

**[0093]** In another embodiment, a heat transfer surface **350** includes a single sheet of thermally-conductive material that is operatively associated with a heating or cooling source. Various heating and cooling sources are known to those of ordinary skill in the art and can be combined with heat exchange systems described herein. A heat transfer surface **350** may be configured so as to vary and regulate temperature of the surface and/or a fluid in a container adjacent the surface within, for example, plus or minus 0.1° Celsius (° C.), 0.2° C., 0.5° C., 1.0° C., or 2.0° C. of the desired temperature.

**[0094]** Also illustrated in FIG. **7** is a reusable support structure **360** that may contain and support the second collapsible bag **334**. As shown in this exemplary embodiment, the reusable support structure **360** may also contain and support heat exchanger bag **332** and heat transfer surface surfaces **350**.

**[0095]** The second collapsible bag **334** may include additional ports **370** for transferring a fluid into and/or out of second collapsible bag **334**. For instance, in one embodiment, second collapsible bag **334** is used to store and/or mix one or more fluids prior to transferring the fluids into a chemical or biological reactor system. The fluid in second collapsible bag **334** can be maintained at a particular temperature which can facilitate the next process to be performed with the fluid. The fluid can then be transferred out of the second collapsible bag **334** via ports **370**. In another embodiment, second collapsible bag **334** is used to perform a chemical, biological, or pharmaceutical reaction, and ports **370** can be used to introduce and remove fluids or reagents from the second collapsible bag **334**.

**[0096]** FIG. **8** depicts a container **308** for holding a fluid comprising, for example, reactants or products of a chemical or biological process, the container **308** having at least one heat transfer surface **380** that includes channels **382** for flowing a heating or cooling fluid therethrough. The heating or cooling fluid can be introduced into the channel **382** via inlet **386** and may exit the channel **382** via outlet **388**. The heat transfer surface **380** may optionally include an opening **390** for positioning therethrough an impeller to allow agitation or mixing inside the container **308**, which may be a collapsible bag. The heat transfer surface **380** may also include another opening **391**, which may be for draining a fluid from the container.

**[0097]** As shown in the embodiment illustrated in FIG. **9**, a heat exchanger system **390** includes one or more containers **308** positioned in series to allow simultaneous temperature control of fluids. For example, a heat exchanger in the form of a collapsible bag heat exchanger **302** may be positioned between two containers **308** for storing and/or holding fluid. A plurality of heat transfer surfaces **306** may be positioned adjacent the containers **308**. The heat exchanger bag **302** and containers **308** may be in the form of independent, interchangeable modules **392**, **394** and **396**. Accordingly, as shown if FIG. **9**, in one embodiment of the invention, the system may comprise a collapsible heat exchanger bag positioned in contact with the first or the second exterior surface portion of the first collapsible bag and in contact with the first or the second exterior surface portion of the second collapsible bag. After completion of a fluid manipulation process, the modules **392**, **394**, **396** can be separated and rearranged into a different configuration to allow the performance of a second fluid manipulation process. Containers **308** and heat exchanger bag **302** can be removed after the first manipulation process, and replaced with new containers and/or collapsible bags so as to maintain the sterile environment for the second process without the need for washing any components of the system.

**[0098]** Specific examples of the use and rearrangement of modules are described in International Patent Application No. PCT/US2005/002985, filed Feb. 3, 2005, entitled "System and Method for Manufacturing," by G. Hodge, et al., published as WO 2005/076093 on Aug. 18, 2005 and U.S. application Ser. No. 11/879,033, filed Jul. 13, 2007, entitled "Environmental Containment Systems", which are incorporated herein by reference.

**[0099]** The heat exchangers described herein may be used to change the temperature of a fluid to varying degrees. For instance, the temperature of a fluid may be varied by at least 2° C., at least 5° C., at least 10° C., at least 15° C., at least 20° C., or at least 30° C. In some cases, the temperature change is measured using one or more sensors, as described in more detail below.

**[0100]** One particular method of operating a heat exchanger may include, for example, flowing a reaction fluid from a chemical, biological, or pharmaceutical reactor into a collapsible bag which is in fluid communication with the reactor, the reaction fluid having a first temperature,. The collapsible bag can include a channel that may be formed by one or more welds connecting first and second interior surface portions of the bag. While the reaction fluid is flowing in the collapsible bag, the temperature of the reaction fluid may be changed by one of the temperatures mentioned above, for example, at least 5° C. The reaction fluid can then be flowed from the collapsible bag into a container in fluid communi-

cation with the collapsible bag. In some cases, the reaction fluid can be re-circulated between the heat exchanger and another container. The reaction fluid may be maintained at a temperature different than that of the reaction fluid prior to being flowed in the heat exchanger.

**[0101]** As described herein, in some embodiments a container is associated with a thermally-conductive material in order to facilitate heat exchange between a fluid inside the container and an environment exterior to the container. In some cases, the rate of heat exchange is limited below desirable or optimal levels by the material used to form the container. For instance, systems involving the use of disposable liners in the form of collapsible bags are generally made of low thermally-conductive materials such as polyethylene, polytetrafluoroethylene (PTFE), or ethylene vinyl acetate. To address this problem, containers described herein, such as collapsible bags or rigid containers, may include in certain embodiments one or more thermally-conductive material(s) associated therewith. In one embodiment, the container comprises a thermally-conductive material embedded in at least a portion of a wall of the container. Additionally or alternatively, the thermally-conductive material may line a wall of the container. For instance, the thermally-conductive material and the wall of the container may form a laminate structure.

**[0102]** Advantageously, the container may be formed and configured such that the thermally-conductive material is adapted to conduct heat away from an interior of the container to an environment outside of the container, or to conduct heat into the container from an environment outside of the container. In embodiments in which the container is supported by a reusable support structure, for example, thermally-conductive plates or a stainless steel tank, heat conduction away from or into the container can be facilitated by the support structure. For instance, heat from the contents inside the container can be dissipated, via the thermally-conductive material of the container, to the support structure which may also be thermally-conductive. The support structure may optionally be cooled using a suitable cooling system, such as the system shown in FIG. **9**, to enhance the rate of heat exchange.

**[0103]** In some embodiments, the thermally-conductive material is in the form of a plurality of particles. The particles may be in the form of nanoparticles, microparticles, powders, and the like. The thermally-conductive material may also be in the form of nanotubes, nanowires, nanorods, fibers, meshes, or other entities. The thermally-conductive material can be embedded in the material used to form the container, for example, such that all or a portion of each entity is enveloped or enclosed by the material used to form the container.

**[0104]** In some embodiments, an embedded thermally-conductive material is substantially uniformly dispersed throughout a bulk portion of a material used to form a container. "Substantially uniformly dispersed," in this context, means that, upon viewing a cross-sectional portion of any such material, where the cross-section comprises the average makeup of a number of random cross-sectional positions of the material, investigation of the material at a size specificity, for example, on the order of grains, or atoms, reveals essentially uniform dispersion of the thermally-conductive material in the bulk material. A photomicrograph, scanning electron micrograph, or other similar microscale or nanoscale investigative process may reveal essentially uniform distribution.

**[0105]** It should be understood that in other embodiments, a thermally-conductive material is not substantially uniformly dispersed throughout a bulk portion of the material used to form a container. For example, a gradient of particles may be formed across a cross-section of the container. For example, the thermally-conductive material may be configured such that one portion of the container includes a thermally-conducive material and another, adjacent portion of the container also comprises the thermally-conductive material. Alternatively, the thermally-conductive material may be present as strips, wires, or may have other configurations such that one portion of the container includes a thermally-conducive material and another, adjacent portion of the container does not comprise a thermally-conductive material.

**[0106]** The thermally-conductive material may in certain embodiments be encapsulated between two polymeric sheets. Alternating layers of thermally-conductive material and polymeric layers are also possible. Alternatively, in some embodiments, an outer surface of the container may include a layer of thermally-conductive material, while an inner surface of the container does not include the thermally-conductive material. This configuration may allow heat to be conducted away from (or into) the contents of the container, while avoiding or limiting any reactivity between the contents of the container and the thermally-conductive material. For example, silver has a high thermal conductivity and may be used as a thermally-conductive material, but is known to have antimicrobial effects. By positioning the silver at an outer surface of the container (or embedded between two polymer layers), but not in contact with any contents inside the container, heat conduction of the container may be enhanced without adversely affecting the contents inside the container (for example, cells, proteins, etc.).

**[0107]** The thermally-conductive material may have any suitable size or dimension. The size of the thermally-conductive entities may be chosen, for example, to achieve a certain dispersion, for example, a gradient or a substantially uniformly dispersion, within the bulk material used to form the container, to prevent protrusion of the entity through a portion of the container, or to have a certain surface area or thermally conductive material to container volume ratio. For example, the thermally-conductive material may have at least one cross-sectional dimension less than 500 microns, or in another embodiment less than 1 nanometer.

**[0108]** Any suitable thermally conducting material can be used as a thermally-conductive material in an embodiment of the invention. The thermally-conductive material may be chosen based on factors such as its thermal conductivity, particle size, magnetic properties, compatibility with certain processing techniques, for example, ability to be deposited by certain deposition techniques, compatibility with the bulk material used to form the container, compatibility with any materials contained in the container, compatibility with any treatments or pre-treatments associated with performing a reaction inside the container, as well as other factors.

**[0109]** In one set of embodiments, the thermally-conductive material comprises a metal. In other cases, the thermally-conductive material comprises a semiconductor. Materials potentially suitable for use as thermally-conductive materials include, for example, an element in any of Groups 1-17 of the Periodic Table. Typical examples include a Group 2-14 element, or a Group 2, 10, 11, 12, 13, 14, 15 element. Non-limiting examples of potentially suitable elements from Group 2 of the Periodic Table include magnesium and barium; from Group 10 include nickel, palladium, or platinum; from Group 11 include copper, silver, or gold; from

Group 12 include zinc; from Group 13 include boron, aluminum, and gallium; from Group 14 include carbon, silicon, germanium, tin, or lead. In some cases, the thermally-conductive material is aluminum, copper, iron, or tin.

**[0110]** The thermally-conductive material may comprise one or more metals. Similarly, where the thermally-conductive material comprises a semiconductor, one or more semiconducting materials can be used. Additionally, alloys can be used, and a mixture of metals and semiconductors can be used. That is, the thermally-conductive material can be a single metal, a single semiconductor, or one or more metals or one or more semiconductors mixed. Non-limiting examples of suitable metals are listed above, and suitable components of semiconductors are listed above. Those of ordinary skill in the art are well aware of semiconductors that can be formed from one or more of the elements listed above, or other elements.

**[0111]** In certain cases, the thermally-conductive material is a nonmetal. For example, the thermally-conductive material may comprise carbon. The thermally-conductive material may be in the form of a conductive polymer, for instance. Non-limiting examples of conductive polymers include polypyrroles, polyanilines, polyphenylenes, polythiophenes, and polyacetylenes.

**[0112]** Those of ordinary skill in the art can easily select, without undue burden or undue experimentation, from materials described above or other materials known in the field, suitable metals, semiconductors, and/or nonmetals. The teachings described herein also enable those of skill in the relevant art to screen materials for suitable use in connection with embodiments described herein. Optionally, thermally-conductive materials may be coated or treated to enhance certain chemical or physical properties of the materials. For example, the surfaces of the thermally-conductive materials may be treated with a surfactant, an oxide or any other suitable material, to make the materials more hydrophilic, more hydrophobic, less reactive, have a certain pH, and so forth. These and other processes can allow the thermally-conductive materials to be more compatible with the material used to form the container and/or with certain processing techniques. For example, treatment of the thermally-conductive material may allow it to adhere to the material used to form the container to a desired degree, be more soluble in a particular solvent, or be more dispersible.

**[0113]** Containers comprising a thermally-conductive material may be formed by any suitable method. In one embodiment, a thermally-conductive material is physically mixed with a material used to form the container, optionally with other components such as reactants, solvents, gases, and surfactants. The thermally-conductive material may be injected into the bulk material, for example. The resulting mixture may be in the form of a solution, emulsion, or suspension.

**[0114]** The mixture may be shaped into a container, or a precursor of a container, by a method such as blow molding, injection molding, spin cast molding, and extrusion, for instance, as described above and/or by methods known to those of ordinary skill in the art. For example, in one embodiment, the thermally-conductive material and material used to form the container may be co-extruded at a sufficiently high temperature at which the materials are pliable. The materials can then be shaped into a container or a precursor to the container such as a sheet. Containers including thermally-conductive materials may be seamless or may include seams that are welded together to form the container. In some cases, more controlled welding can be achieved by heating the thermally-conductive material by an energy source such as a microwave source or a laser.

**[0115]** In some embodiments, the thermally-conductive material is applied to all or a portion of a material used to form a container by methods such as physical deposition methods, chemical vapor deposition methods, plasma enhanced chemical vapor deposition techniques, thermal evaporation, for example, resistive, inductive, radiation, and electron beam heating, sputtering, for example, diode, DC magnetron, RF, and reactive sputtering, jet vapor deposition, electrophoretic deposition, magnetophorectic deposition, spin coating, dip coating, spraying, brushing, screen printing, ink-jet printing, toner printing, sintering, laser ablation, electroplating, ion plating, cathodic arc, and combinations thereof. Such methods can be carried out in a vacuum or inert atmosphere.

**[0116]** The thermally-conductive material may optionally be aligned, especially in embodiments in which the materials are embedded in a bulk material, using magnetic interactions, electrostatic interactions, and the like. The container or any other article described herein may include any suitable amount of thermally-conductive material. The container may comprise, for example, from about 0.1 wt percent to about 50 wt percent of thermally-conductive material, based on the total weight of the container. In some cases, these percentages are based on the total weight of the flexible portions, for example, the wall portions, of the container.

**[0117]** The amount and type of thermally-conductive material(s), the material used to form the container, the arrangement of the thermally-conductive material with respect to the material used to form the container, and the thickness of the container can be chosen such that the container achieves a certain overall level of thermal conductivity. The overall thermal conductivity of the container may be, for example, from about 0.1 Watts$\cdot m^{-1}\cdot K^{-1}$ to about 15 Watts$\cdot m^{-1}K^{-1}$. In some cases, the thermal conductivity of a container including a thermally-conductive material is from about 1.5 times to about 50 times greater than a container without a thermally-conductive material. The thermal conductivity can be measured by those of ordinary skill in the art by determining the quantity of heat transmitted, during a period of time, through a thickness of the container in a direction normal to a surface area of the container, wherein the quantity of heat transmitted is due to a temperature difference under steady state conditions and when the heat transfer is dependent only on the temperature gradient.

**[0118]** In addition to the benefits of enhanced heat conduction using containers comprising thermally-conductive materials, such articles may also have enhanced sensing capabilities. For instance, the containers may be use to determine temperature, conductance, impedance, as well as dissipation and control of static charge. In some embodiments, the containers can be used to detect any leakage of materials from the interior to the outside of the container. Such measurements can be performed, for example, by determining a change in the thermal and/or electrical conductivity of one or more portions of the container.

**[0119]** One embodiment of the disclosed system for use in a chemical, biological, or pharmaceutical process comprises: a first collapsible bag having a perimeter and a maximum dimension thereacross measured at full expansion of the first collapsible bag; a first interior surface portion; a second interior surface portion; one or more welds connecting the first

and second interior surface portions of the first collapsible bag so as to form a channel between the first and second interior surface portions, an inlet connected to a first portion of the channel; an outlet connected to a second portion of the channel, the channel defining a bulk fluid flow pathway through the first collapsible bag from the inlet to the outlet; a first temperature-controlling surface in contact with a first exterior surface portion of the first collapsible bag; and a second temperature-controlling surface in contact with a second exterior surface portion of the first collapsible bag. The disclosed system may be configured and arranged to allow variation of the distance between the first and second temperature-controlling surfaces. The system may further include a component associated with the first collapsible bag that inhibits full expansion of the first collapsible bag during use.

**[0120]** The component that inhibits full expansion of the first collapsible bag during use may include the first and second temperature-controlling surfaces maintained at a separation distance from one another that does not allow full expansion of the first collapsible bag. The system may further include a second collapsible bag having a first exterior surface portion and a second exterior surface portion, the second collapsible bag comprising an impeller in fluid communication with the first collapsible bag. The system may be configured such that the first temperature-controlling surface is in contact with the first exterior surface portion of the second collapsible bag, in addition to being in contact with a first exterior surface portion of the first collapsible bag.

**[0121]** The system may further include a second temperature-controlling surface in contact with the second exterior surface portion of the first collapsible bag. The system may further include a third temperature-controlling surface in contact with the second exterior surface portion of the second collapsible bag. The system may be configured and arranged to allow recirculation of fluid between the first and second collapsible bags.

The Support Structure

**[0122]** A support structure that may be used to support a collapsible bag may have any suitable shape able to surround and/or contain the bag. In some cases, the support structure is reusable. The support structure may be formed of a substantially rigid material. Non-limiting examples of materials that can be used to form the support structure include stainless steel, aluminum, glass, resin-impregnated fiberglass or carbon fiber, polymers such as high-density polyethylene, polyacrylate, polycarbonate, polystyrene, nylon or other polyamides, polyesters, phenolic polymers, and combinations thereof. The materials may be certified for use in the environment in which it is used. For example, non-shedding materials may be used in environments where minimal particulate generation is required. In addition, the support structure may include other components, such as channels, for flowing a fluid and/or containing a material to modify the properties of the support structure.

**[0123]** A reusable support structure may have any suitable volume and, in some instances, has a volume substantially similar to that of the container contained in the support structure. The reusable support structure may have a volume between, for example, of from about 5 liters to about 5,000 liters. Volumes greater than 10,000 liters are also possible.

**[0124]** In other embodiments, however, a vessel does not include a separate container, for example, a collapsible bag and support structure, but instead comprises a self-supporting disposable container. For example, a container that may be used to hold and/or store fluids may be in the form of a plastic vessel and may optionally include an agitation system integrally or releasably attached thereto. The agitation system may be disposable along with the container. In one particular embodiment, such a system includes an impeller welded or bolted to a polymeric container. In another embodiment, a container that is used as a heat exchanger is in the form of a rigid container. It should therefore be understood that many of the aspects and features of the vessels described herein with reference to a container and a support structure are also applicable to a self-supporting disposable container.

**[0125]** As described herein a vessel such as a collapsible bag may include a mixing system for mixing contents of the vessel. In some cases, more than one agitator or impeller may be used to increase mixing power, and the impellers may be the same or different. In some cases, the agitator may be one in which the height can be adjusted, for example, such that the drive shaft allows raising of an impeller above the bottom of the tank and/or allows for multiple impellers to be used. A mixing system of a vessel may be disposable or intended for a single use, along with the container in some cases. Various methods for mixing fluids can be implemented in the container. For instance, impellers based on magnetic actuation, sparging, and/or air-lift can be used. Direct shaft-drive mixers that are sealed and not magnetically coupled can also be used. Additionally or alternatively, a mixing system may include an impeller with varying impeller blade configurations.

**[0126]** In certain embodiments, a magnetic impeller is used. A magnetic impeller may use magnets such as fixed, permanent, or electromagnets to rotate or otherwise move the impeller. In some cases, the magnets within the magnetic impeller are stationary and can be turned on or activated in sequence to accelerate or decelerate the impeller, for example, via an inner magnetic impeller hub. As there is no penetration of the container by a shaft, there may be no need to maintain the impeller in a sterile condition.

Equivalents

**[0127]** While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. Those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, or configurations will depend upon the specific application for which the teachings of the present invention are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein, and to any combination of the foregoing.

**[0128]** The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one." Throughout the description and claims of this specification, the words "comprise," "contain," "include," "having," "composed of," and variations of them mean "including but not limited to", and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

**[0129]** It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

**[0130]** Features groups described in conjunction with a particular aspect of the invention are to be understood to be applicable to any other aspect described herein unless incompatible therewith. All of the features disclosed in the specification, and claims, abstract and drawings, and/or all of the steps of any method or process disclosed, may be combined in any combination, except combinations where at least some of such features or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

What is claimed is:

**1**. A system configured for use in a chemical, biological, or pharmaceutical process, the system comprising:

a first collapsible bag comprising:

a perimeter and a maximum dimension thereacross measured at full expansion of the first collapsible bag;

a first interior surface portion;

a second interior surface portion;

one or more welds connecting the first and second interior surface portions of the first collapsible bag so as to form a channel between the first and second interior surface portions,

an inlet connected to a first portion of the channel;

an outlet connected to a second portion of the channel, the channel defining a bulk fluid flow pathway through the first collapsible bag from the inlet to the outlet; and

a first temperature-controlling surface in contact with a first exterior surface portion of the first collapsible bag.

**2**. The system of claim **1**, wherein the channel comprises a serpentine configuration.

**3**. The system of claim **1**, wherein the channel comprises a spiral configuration.

**4**. The system of claim **1**, wherein the first collapsible bag has a volume equal to from about 1 liter to about 10,000 liters.

**5**. The system of claim **1**, wherein the average cross-sectional area of the channel at full expansion of the first collapsible bag is from about one tenth to about one fourth of the maximum dimension of the bag, the system further comprising a reusable support structure for supporting and containing the first collapsible bag.

**6**. The system of claim **1**, wherein the channel comprises from about 4 channel segments to about 10 channel segments.

**7**. The system of claim **1**, wherein the first temperature-controlling surface is selected from: a thermally-conductive material, a plurality of particles embedded in a surface of the bag, and a plate comprising channels for allowing fluid to flow therethrough, and combinations of the foregoing.

**8**. The system of claim **1**, further comprising a second temperature-controlling surface in contact with a second exterior surface portion of the first collapsible bag.

**9**. The system of claim **8**, wherein the second temperature-controlling surface is selected from a thermally-conductive material, a plurality of particles embedded in a surface of the bag, and a plate comprising channels for allowing fluid to flow therethrough, and combinations of the foregoing.

**10**. The system of claim **8**, wherein the system is configured and arranged to allow variation of the distance between the first and second temperature-controlling surfaces.

**11**. The system of claim **8**, further comprising a component associated with the collapsible bag that inhibits full expansion of the collapsible bag during use.

**12**. The system of claim **11**, wherein the component that inhibits full expansion of the collapsible bag during use comprises the first and second temperature-controlling surfaces maintained at a separation distance from one another that does not allow full expansion of the collapsible bag.

**13**. The system of claim **1**, wherein the first collapsible bag comprises a second exterior surface portion, the system further comprising:

a second collapsible bag having a first exterior surface portion and a second exterior surface portion, the second collapsible bag comprising an impeller in fluid communication with the first collapsible bag.

**14**. The system of claim **13**, wherein the first temperature-controlling surface is in contact with the first exterior surface portion of the second collapsible bag.

**15**. The system of claim **13**, further comprising a second temperature-controlling surface in contact with the second exterior surface portion of the first collapsible bag.

**16**. The system of claim **15**, further comprising a third temperature-controlling surface in contact with the second exterior surface portion of the second collapsible bag.

**17**. The system of claim **13**, configured and arranged to allow recirculation of fluid between the first and second collapsible bags.

**18**. The system of claim **13**, further comprising a collapsible heat exchanger bag positioned in contact with the first or the second exterior surface portion of the first collapsible bag and in contact with the first or the second exterior surface portion of the second collapsible bag.

**19**. A method, comprising:

flowing a reaction fluid having a first temperature from a chemical, biological or pharmaceutical reactor into the collapsible bag of the system of claim **1**, the collapsible bag in fluid communication with the reactor;

changing a temperature of the reaction fluid in the collapsible bag by at least 5 degrees Celsius while the reaction fluid is flowing in the collapsible bag; and

flowing the reaction fluid from the collapsible bag into a container in fluid communication with the collapsible bag.

**20**. The method of claim **19**, further comprising flowing a heating or a cooling fluid adjacent the first temperature-controlling surface for a period of time sufficient to cause a change in temperature of the reaction fluid.

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