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- (71) Applicant: DIALYFLUX, LLC [US/US]; 131 Green Street, Medfield, MA 02052 (US).
- (72) Inventors: KENNEY, George, B.; 131 Green Street, Medfield, MA 02052 (US). HULSEMAN, Ralph; 12 Lan-neau Drive, Greenville, SC 29605 (US). PFEFFER, Christian; 95 Lowell Street, Somerville, MA 01243 (US).

HULSEMAN, Sarah; 502 Caledon Court, Greenville, SC 29615 (US).

- (74) Agent: TAI, Kuangshin; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).
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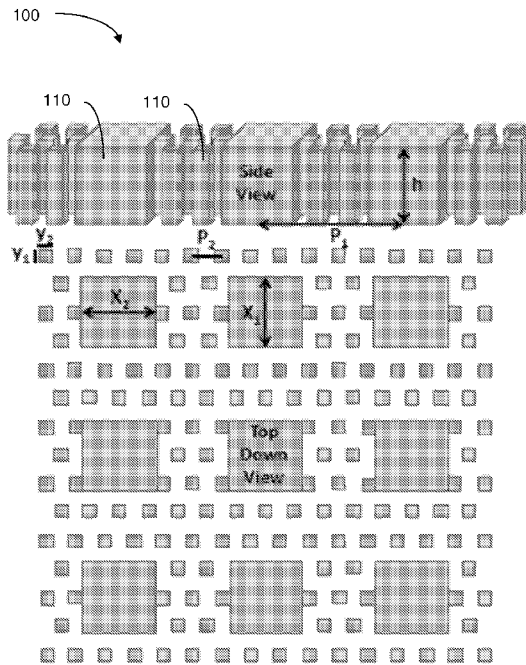


Fig. 4

(57) Abstract: The present disclosure relates to micro-textured surfaces that are constructed such that upon exposure of a multi-component fluid (e.g., blood, urine, other complex fluids) thereto, particles within the fluid are repelled or otherwise caused to move away from the surface. Apparatuses described herein may include an artificial substrate having a patterned structure, which includes a number of protrusions that extend from the surface of the substrate. By virtue of their configuration, the patterned structures may be relatively phobic toward particles contained within fluid to which the structures are exposed. Accordingly, such surfaces may be less prone to clogging, coagulation and/or fouling, and the distribution of various components within a complex fluid at the surface may be suitably controlled.

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SURFACES FOR MANIPULATING PARTICLE FLOW

BACKGROUND

1. Field

5 Aspects described herein relate generally to surfaces for manipulating flow, such as fluid and/or particle flow.

2. Discussion of Related Art

When separating or filtering one or more components from a complex fluid, 10 such as a fluid flowing within a vessel (e.g., blood vessel, dialysis tube), for some applications in filtration, it may be preferable to segregate the permeate component(s) from the retentate component(s) within the vessel. It may also be preferable for medical personnel to be able to control clot formation in blood. Segregation of components of the blood may aid in or otherwise influence such control.

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SUMMARY

In an illustrative embodiment, an apparatus for manipulating particle flow is provided. The apparatus includes an artificial substrate; and a patterned structure having a plurality of protrusions that extend from the substrate and are configured to 20 cause movement of at least one particle away from the patterned structure, upon flow of a fluid containing the at least one particle over the patterned structure.

In another illustrative embodiment, an apparatus for manipulating particle flow is provided. The apparatus includes an artificial substrate; and a patterned structure having a plurality of protrusions that extend from the substrate, wherein an 25 average height of the plurality of protrusions, or holes formed by the protrusions, is between 5 microns and 50 microns, an average width of the plurality of protrusions or holes is between 5 microns and 50 microns, and an average spacing between the protrusions or holes is between 5 microns and 50 microns.

In yet another illustrative embodiment, an apparatus for manipulating particle 30 flow is provided. The apparatus includes an artificial substrate; and a patterned structure having a plurality of protrusions that extend from the substrate and are

configured such that, upon flow of blood over the patterned structure, less than 6% of platelets of the blood, less than 5.0% of lymphocytes of the blood, less than 40% of monocytes of the blood, or less than 70% of polymorphonuclear leukocytes of the blood adhere to the patterned structure.

5 In a further illustrative embodiment, an apparatus for manipulating particle flow is provided. The apparatus includes an artificial substrate; and a patterned structure having a plurality of protrusions that extend from the substrate, wherein the plurality of protrusions comprises a first plurality of protrusions and a second plurality of protrusions, wherein the first plurality of protrusions are arranged to form a
10 plurality of elongate ridges and the second plurality of protrusions are arranged to form a grid-like pattern of posts or holes.

 In another illustrative embodiment, a method for manipulating particle flow is provided. The method includes flowing a fluid containing at least one particle over a patterned structure having a plurality of protrusions that extend from an artificial
15 substrate resulting in movement of the at least one particle away from the patterned structure.

 In yet another illustrative embodiment, a method for manipulating particle flow is provided. The method includes contacting blood with a patterned structure having a plurality of protrusions that extend from an artificial substrate resulting in
20 less than 6% of platelets of the blood, less than 5.0% of lymphocytes of the blood, less than 40% of monocytes of the blood, or less than 70% of polymorphonuclear leukocytes of the blood adhering to the patterned structure.

 In another illustrative embodiment, an apparatus for manipulating particle flow is provided. The apparatus includes an artificial substrate; a patterned structure
25 that is configured to cause movement of at least one particle of biological material away from the patterned structure, upon flow of blood containing the at least one particle of biological material over the patterned structure. The patterned structure includes a first plurality of protrusions, or holes formed by the protrusions, having an average height of between 5 microns and 50 microns, an average width of between 2
30 microns and 30 microns and an average spacing between the protrusions of between 2 microns and 10 microns, and a second plurality of protrusions, or holes formed by the

protrusions, having an average height of between 5 microns and 50 microns, an average width of between 20 microns and 100 microns and an average spacing between the protrusions of between 2 microns and 10 microns. And, the average width of the first plurality of protrusions or holes is less than the average width of the second plurality of protrusions or holes.

Various embodiments provide certain advantages. Not all embodiments of the present disclosure share the same advantages and those that do may not share them under all circumstances.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Various embodiments will now be described, by way of example, with reference to the accompanying drawings, in which:

Fig. 1 is a schematic showing blood flow through a blood vessel;

Fig. 2 is a diagram showing the relationship between tube diameter and viscosity of a fluid;

Fig. 3 shows patterned structures in accordance with some embodiments;

Fig. 4 depicts another patterned structure in accordance with an embodiment;

Fig. 5 shows results of blood applied on to various surfaces in accordance with some embodiments;

Fig. 6 illustrates a schematic of a cross-section through a patterned structure in accordance with an embodiment;

Fig. 7 shows a model of a patterned structure in accordance with an embodiment;

Fig. 8 shows a table of physical characteristics of various blood vessels;

Fig. 9 illustrates schematics of various blood vessels;

Fig. 10 shows a cross-section through various blood vessels;

Fig. 11 depicts a schematic of a cross-section through a membrane in accordance with an embodiment;

Fig. 12 depicts a schematic of a cross-section through another membrane in accordance with an embodiment;

Fig. 13 depicts a schematic of a cross-section through a further membrane in accordance with an embodiment;

5 Fig. 14 shows results of blood applied on to various surfaces in accordance with some embodiments; and

Fig. 15 depicts a model of a particle flow over a patterned structure in accordance with an embodiment.

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DETAILED DESCRIPTION

The inventors have appreciated that it would be advantageous to produce a surface having certain characteristics such that upon exposure of a fluid, such as blood, another suspension, or other fluid, to the surface (e.g., fluid flow over the surface, stationary contact with the surface, etc.), the particles within the fluid are repelled away from the surface. The present disclosure relates to physical micro-structures and textures fabricated, by any suitable manner, on a surface (e.g., polymer, metal, ceramic, composite thereof, etc.) that causes particles (e.g., solid particles, liquid droplets, biological cells/components, etc.) that are suspended in a liquid medium, to be forced in a direction away from the surface, so as to enhance separation of various components within a complex fluid. Accordingly, such surfaces may be less prone to clogging, coagulation and/or fouling, as particles contained within the fluids exposed to the patterned structures are caused to move away from the surface.

Embodiments of the present disclosure may be applicable for any suitable complex fluid, such as multi-component mixtures that may exhibit solid-like or fluid-like behavior, with transitions therebetween. Those of skill in the art will appreciate that complex fluids may include multiple phases, for example, solid and liquid phases (e.g., suspensions, solutions of macromolecules such as polymers), solid and gas phases (e.g., granular), liquid and gas phases (e.g., foams) and/or distinct liquid phases (e.g., emulsions). A number of biological fluids (e.g., blood, urine, lymphatic

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fluid, etc.) and other fluids (e.g., food/beverage mixtures, gas/petroleum, geological fluids, etc.) may be categorized as complex fluids.

For some applications in filtration, it may be preferable to segregate permeate component(s) from retentate component(s) within a vessel. It may also be preferable to simultaneously segregate the retentate component(s) away from the inner wall. Such a result would avoid concentration polarization and fouling of the wall surface of the vessel, thereby facilitating continuous and efficient filtration through the wall.

In some embodiments, the apparatus may include an artificial substrate having a patterned structure located thereon. The patterned structure may, in turn, include a plurality of protrusions that extend from the substrate. The patterned structure may be configured such that, when a fluid (e.g., blood, urine) containing one or more particles (e.g., red/white blood cells, platelets, etc.) is exposed to the patterned structure, particles of the fluid are repelled or otherwise caused to move away from the patterned structure. The fluid may be exposed to the patterned structure in a number of ways, for example, the fluid may flow over or around the protrusions of the structure, or the fluid may remain in relatively stationary contact with the protrusions.

Particles, contained within the fluid, that are repulsed from the patterned structure may have any appropriate size. In some embodiments, the particles may have an average size of between 500 nm and 100 microns, between 500 nm and 50 microns, between 1 micron and 50 microns, 1 micron and 25 microns, between 5 microns and 50 microns, between 5 microns and 30 microns, between 5 microns and 20 microns, between 10 microns and 20 microns, between 15 microns and 25 microns, between 2 microns and 10 microns, between 2 microns and 5 microns, between 8 microns and 12 microns, or between 5 microns and 10 microns. Particles outside of the above-noted ranges may also be suitably influenced by patterned structures in accordance with the present disclosure.

In artificial kidney dialysis, a micro-tubular membrane filter is often employed which is designed to give rise to a mechanism that is similar to blood flow in micro-diameter arteries and veins, called the Fahraeus-Lindquist effect. In the Fahraeus-Lindquist effect, the viscosity of the fluid (e.g., blood) is observed to decrease as the diameter of the vessel decreases, and is effective for vessel diameters between 10 and

300 microns. This is due, at least in part, to hydrodynamic effects of fluid flow around the particles traveling within the vessel.

In laminar flow systems containing particles, such as red blood cells, whose dimensions approach those of the channel through which the cells migrate, the fluid
5 flow around the rotating particles results in a net recirculating radial flow of the fluid perpendicular to the axial flow direction through the channel. In general, the particles from which this net perpendicular flow is generated remain laterally fixed as they translate downstream. At the same time, according to the Segré–Silberberg effect, the concentration of particles within the channel flow of a dilute suspension of neutrally
10 buoyant particles that exhibit laminar flow naturally equilibrate to an equilibrium distance, due to opposing viscous drag and inertial lift forces on the suspended particles. This equilibrium distance of the particles is approximately 0.6 of the radius of the tube from the center axis.

Fig. 1 shows a blood vessel where erythrocytes travel generally along the
15 centerline of the vessel, leaving a substantial amount of cell-free plasma to travel along the inner wall of the vessel. As explained by the Fahraeus-Lindquist effect, the velocity gradient is zero or negligible at the core region (i.e., axial centerline of the vessel), the velocity itself is zero or negligible at the surface of the inner wall, and the velocity and shear stress are continuous at the interface between the two regions.

20 In the case of a dialyser tube, which is typically approximately 200 microns in diameter, a cell-free layer of plasma, which carries uremic wastes and excess water, segregates to the surface of the inner wall and establishes a concentration gradient of permeate across the membrane wall, as determined by the Fahraeus-Lindquist effect, though, this is for tubes of appropriate size. This concentration gradient allows for
25 gradient driven flux of uremic waste and water from the plasma across the permeable dialyser membrane.

The viscosity of plasma is only a third that of whole blood. As shown in Fig. 2, the net effect of the cell-free zone of plasma at the inner surface of a tube through which blood flows is that the apparent viscosity of flow through the micro tube is
30 reduced. It is observed that as the diameter of the tube through which blood flows decreases to approximately 8 microns, which corresponds to the approximate

diameter of red blood cells, the viscosity of plasma is approached. As the tube diameter increases, for example, to approximately 1 mm, the variation in viscosity due to the Fahraeus-Lindquist effect of the cell-free zone declines and the viscosity asymptotically approaches the value for whole blood.

5 In accordance with the present disclosure, the inventors have found that certain micro-textured surfaces, when exposed to fluid overhead, are patterned in such a manner that gives rise to a net repulsion of particles away from the surface. Though, the inventors have also observed that, for other textured surfaces, such a repulsive effect does not occur. Accordingly, it is noted that a number of factors
10 related to the patterned structures themselves contribute to whether particle repulsive behavior is present.

For instance, the patterned structure may include protrusions that extend above the surface of an underlying substrate. These protrusions may be arranged so that when a complex fluid containing particles flows or is otherwise present overhead, the
15 fluid impinges against the surface of the protrusions resulting in a disruption of the flow patterns of the fluid. This disruption of fluid flow results in the generation of a net pressure away from the patterned structure. This net pressure arises due to a local pressure differential that is present between the surface of the protrusions and the particles of the fluid themselves, causing the fluid to push the particles away from the
20 surface and, hence, leaving a particle-free region of fluid flow closer to the patterned structure. This pressure differential is created by the drag forces of the fluid flowing across the micro-textured surface, and pushing against the particle. The amount of drag against the particle may vary depending on the fluid velocity.

In some embodiments, the protrusions of the patterned structure that extend
25 from the underlying substrate are arranged such that an average height of the protrusions is between 5 microns and 50 microns (e.g., approximately 25 microns), an average width of the protrusions is between 5 microns and 50 microns (e.g., approximately 10 microns and/or 50 microns), and an average spacing between the protrusions is between 5 microns and 50 microns (e.g., approximately 10 microns
30 and/or 50 microns). In some embodiments, the patterned structure is arranged into multiple phases of protrusions, periodically arranged. For example, in a first phase, or

plurality, of protrusions, the average width may be between 5 microns and 20 microns (e.g., approximately 10 microns); and in a second phase, or plurality, of protrusions, the average width may be between 40 microns and 70 microns (e.g., approximately 50 microns). Further, in the first phase, the protrusions may have an average spacing of
5 between 5 microns and 20 microns (e.g., approximately 10 microns); and in the second phase, the protrusions may have an average spacing of between 40 microns and 70 microns (e.g., approximately 50 microns). In various embodiments, the protrusions may be arranged as posts, or may form holes; or, the protrusions may form elongated ridges, substantially straight and/or curved in configuration. Though,
10 other configurations of protrusions in a suitable patterned structure may be possible.

While the Fahraeus-Lindquist and Segré–Silberberg effects are described above, particularly with respect to blood flow and dialysis applications, such effects are limited to tubes that are approximately 200 microns or less. However, embodiments of the present disclosure relate to surfaces that are not limited to tubes
15 having the above size restraints. That is, while micro-textured surfaces described herein may be used for applications that involve tubes or vessels, in some embodiments, such micro-textured surfaces may be used in cases that do not involve a tube or vessel at all, yet may still be effective to repel particles included within a fluid in a direction away from the surface.

Accordingly, the present disclosure provides for the ability to control the fluid
20 dynamics and the phobic, philic or combined phobic/philic nature of various components of a complex fluid on the surface of a wall, membrane or other substrate, which serves to provide selective control of the molecular species and/or solution components accumulating or not accumulating at the surface of the substrate. This
25 control of surface tension and/or fluid dynamics driven normal pressure control of fluid component philic and phobic segregation at a surface is based, at least in part, on the inclusion of an appropriate micro-texture to the surface. This micro-texture based segregation phenomenon is a synergistic combination of both physical and chemical effects that can be used in separations applications with a number of various
30 materials, such as biological, aqueous, oleo, chemical and other complex fluids and liquids.

For filtration and/or dialysis related applications, such surface texturing provides a mechanism for managing and optimizing the concentration gradient across the membrane and concentration polarization at the membrane surface which together affect membrane flux and performance. The ability to control the local segregation of molecules and other components of a fluid at the membrane surface may enable the introduction and application of additional functionalities, so as to further enhance the efficiency and performance of the membrane and filtration system.

In some embodiments, the physical microstructures of a suitable micro-textured surface may exhibit one or more repeating patterns. For example, the physical microstructures may include a generally three dimensional pattern in the form of pillars and/or indented spaces/dimples or holes, such as in a grid-like or other arrangement. Alternatively, the physical microstructures may include a generally two dimensional pattern, for example, elongated ridges and valley structures, which may be substantially straight or curved in configuration. It can be appreciated that other patterns are also possible.

In either three dimensional or two dimensional configurations, the patterned physical microstructure may exhibit suitable repulsive effects on particles within fluid that flows overhead or is otherwise exposed to the patterned structure(s) in an appropriate manner. In some cases, the patterned structures impart the surface with particle-repulsive characteristics regardless of the direction of fluid flow. Though, in other cases, the degree of particle repulsion from the patterned structures may depend, at least in part, on the direction of fluid flow there across. For example, currents, eddies and/or turbulence generated by fluid flow over and through patterned structures may arise due to the orientation of the structures themselves and the manner in which the fluid impinges or impacts there against.

Such repulsive effects may be present for fluid flows that vary in multiple directions. For instance, repulsive effects may be present despite fluid flow across a rotating seal, valve, pump or other device or structure; or in flows of a fixed orientation/direction, such as in a small tube or on the surface of a tube or lead.

As noted above, micro-textured surfaces described herein can be configured in any suitable manner, such as in a patterned arrangement. The patterned structure may

exhibit an appropriate configuration that causes particles to be repelled therefrom or, in some cases, be attracted thereto.

Embodiments of surfaces in accordance with the present disclosure may include any suitable material. In some embodiments, such surfaces may be organic, 5 inorganic, polymeric (e.g., synthetic, naturally occurring, rubber, silicone, plastic, polyethylene (high and low density), polypropylene, etc.), silicon, metallic (e.g., ferrous, nonferrous, alloys, etc.), ceramic (e.g., oxides, carbides, nitrides, etc.), or combinations thereof.

Such surfaces may or may not include one or more appropriate chemical 10 coatings which may, for example, be useful to control the flow, segregation, filtering, etc. of organic, oleo, aqueous, and other multi-phase or complex fluids. Coatings of any appropriate type may be applied to the micro-textured surfaces, for example, coatings which conformally cover the patterned structures and having a thickness smaller than various dimensions (e.g., height, width, spacing) of the micro features. 15 Alternatively, a coating or surface layer may be substantially thicker than the micro structures themselves.

It can be appreciated that surfaces described herein may be fabricated by any suitable manner. For example, such surfaces may be manufactured by molding, stamping, forging, embossing, extrusion, drawing, rolling, or any other appropriate 20 method known in the art. In some embodiments, extrusion or drawing may be well suited for fabricating two dimensional structures, such as elongated ridges or other such structures. In some embodiments, molding may be suitable for fabricating three dimensional structures, such as grid-like configurations, elongated ridges, etc.

In some embodiments, as shown in Fig. 3, embodiments of the patterned 25 structure 100 may include a grid-like pattern where each protrusion 110 (shown on the left side of Fig. 3 as posts or pillars) extending from the underlying surface of the substrate 102 has a diameter (D), height (h) and pitch (P) or separation between protrusions. Alternatively, patterned structures 100 may include an elongated ridge pattern where the protrusions 110 extending from the underlying surface of the 30 substrate 102 are shown as ridges having peaks and valleys, and that exhibit a width (W), height (h) and pitch (P).

Or, not expressly shown in this figure, the protrusions of the patterned structure may be arranged so as to effectively form a number of holes or openings in the patterned structure. That is, as discussed further below, the protrusions may cover the majority of the underlying surface of the substrate so that holes (e.g., dimples, indents, etc.) having a depth that reaches from the upper surface (plateau) to the underlying surface of the substrate are formed within a larger structure. Holes may reach from the upper surface of the patterned structure fully to the underlying surface of the substrate (e.g., plane defined by the lowermost surface of the substrate), or holes might not reach to the lowermost surface of the substrate (e.g., depth of the hole may be less than the distance between the uppermost surface of the patterned structure and the lowermost surface of the substrate).

Accordingly, the protrusions and/or holes in the patterned structure may have any suitable cross-sectional shape, for example, a polygon, rectangle, circle, ellipse, or any other appropriate shape. The cross-sectional shape of the protrusion(s) and/or hole(s) may also vary along the height of the protrusion(s). For example, as described further below, the angle that a surface of the protrusion(s) make with the plane defined by the underlying surface of the substrate may fall within an appropriate range, or may vary as desired.

It can be appreciated that embodiments of patterned structures in accordance with the present disclosure may also be provided as a suitable combination of structures and configurations described herein.

In some embodiments, embodiments of patterned structures provided herein may be effective to alter the overall surface tension and/or corresponding contact angle of the fluid in contact with the micro-textured surface. For example, the patterned structure(s) may give rise to a hydrophobic surface, in contrast with a smooth surface that does not have the patterned structure(s). When designed to be super phobic, a particular component of a liquid or complex fluid can be repelled so as to exhibit a relatively high contact angle and/or may stand-off from the surface altogether. It can be appreciated that such protrusions (e.g., posts, ridges, etc.), as discussed above, can be any shape, carry a secondary nano-texture, and/or be chemically coated so as to suitably enhance a desired philic/phobic effect.

Aspects of the present disclosure address challenges in designing a surface micro-texture that is selectively repulsive or attractive to the various components of a fluid. In some cases, it may be desirable for certain components of the fluid to be attracted to the surface. For example, in a membrane filtration system, philic
5 components (e.g., fluid/liquid permeate) attracted to the surface may accumulate at a membrane surface so as to increase the concentration gradient driven flux of the attracted component across the permeable membrane. On the other hand, phobic components (e.g., solid/retentate) may tend to be repelled from the micro-textured surface of the membrane, which thereby provides a localized separation of the phobic
10 components of the fluid from the philic components at the membrane or device surface.

The force and effect of this local segregation of components within the fluid at the surface of the membrane may accommodate the superposition of specific flow and other system functionalization(s) that can further enhance membrane permeability,
15 flux and separation function and efficiency for the philic components of the complex fluid. For example, for blood, some patterned structures described herein may be relatively philic with respect to the plasma component of blood, yet relatively phobic with respect to certain particles of blood (e.g., red/white blood cells, platelets, etc.)

As discussed above, certain embodiments of the present disclosure may
20 include multi-dimensional, inter-digitated, multiple phase post patterns, such as those illustrated in Fig. 4. Here, the patterned structure includes two phases of protrusions, each phase characterized by a particular type. For instance, a first phase may be made up of a first plurality of protrusions, and a second phase may be made up of a second plurality of protrusions. As shown in Fig. 4, the average width of the first plurality of
25 protrusions is less than the average width of the second plurality of protrusions. Such structures, in some cases, may be suitable to produce surface tension driven phobic and/or philic effects for certain components of complex fluids that come into contact with the micro-textured surface. Of course, it can be appreciated that other arrangements are possible as the present disclosure is not limited in this respect.

30 In an embodiment provided for illustrative purposes, shown in Fig. 4, P_1 , X_1 and X_2 are approximately 5 times P_2 , Y_1 and Y_2 , respectively, where $X_1 = X_2$, $Y_1 = Y_2$

- 13 -

= ~8 microns and $h = \sim 25$ microns. By way of example, in this embodiment, when blood is flowed over the patterned structure, large cellular components of whole blood, such as red and white blood cells and platelets, are observed to be phobic with respect to the patterned structure. That is, as shown in Fig. 5, it was observed that the particles of the blood (i.e., red/white blood cells, platelets, etc.) had a tendency not to adhere, wet, clot or otherwise accumulate to the micro-textured surface of Fig. 4. Accordingly, embodiments of the present disclosure may be patterned such that human blood does not coagulate or clot on the surface. Yet, for some embodiments, plasma may be philic with and wet such surfaces.

In an embodiment, shown in Fig. 5, and described further below with respect to a number of examples, fresh blood is poured onto both a smooth and micro-textured silicone rubber surface. A straight edged metal spatula and a paper towel are then used, separately, to wipe the blood from the smooth and micro-textured surface. Here, the spatula provides a relatively non-absorbent wiping/cleaning mechanism and the paper towel provides a relatively absorbent wiping/cleaning mechanism.

It is observed that both the spatula and paper towel wipe leave a significant blood smear on the smooth silicone rubber surface while the micro-textured silicone rubber surface having a patterned structure in accordance with embodiments described herein is wiped clean, using either of the spatula or paper towel, of the red and other blood cells. It was also observed that both the spatula and paper towel wipe would leave a blood smear at the bottom edge of the silicone rubber surface where the patterned structure was absent, further illustrating the effect of such patterned structures.

As discussed above, the patterned structure may include a number of protrusions that extend from the surface of an underlying substrate. The protrusions may have dimensions such that particles contained within a fluid flowing over or otherwise in contact with the patterned structure are repelled therefrom. Or, in the case of blood, the protrusions may be configured such that the blood does not easily clot, coagulate or otherwise collect on the surface. For example, while plasma may flow along the upper surface of the patterned structure and between interstices of the

protrusions, the protrusions may cause blood cells and platelets to be pushed away therefrom, reducing coagulation and/or fouling of the surface.

The pattern and arrangement of protrusions extending from the surface of the substrate may determine whether particles flowing over the substrate are repelled therefrom or attracted thereto. The dimensions and shapes of the protrusions may be particularly relevant in giving rise to such effects. In various aspects of the present disclosure, the protrusions may be shaped in such a manner so as to create vortices, turbulence or other types of flow that give rise to localized pressure variations when particle-containing fluid flows along the patterned structure(s). For instance, the height, angle, periodicity, or other structural feature(s) of a series of pillars or other protrusions may be selected so as to cause favorable fluid flow effects, which may also vary according to the particular type of fluid and particle flow.

The protrusions of the patterned structure may have a suitable average height (or depth). In some embodiments, the average height or depth of the protrusions or holes is between 500 nm and 50 microns, between 1 micron and 50 microns, between 5 microns and 50 microns, between 5 microns and 30 microns, between 5 microns and 20 microns, between 10 microns and 20 microns, between 20 microns and 40 microns, between 20 microns and 30 microns, between 2 microns and 10 microns, or between 5 microns and 10 microns. In some embodiments, the average height or depth of the protrusions or holes is greater or less than the average size of the particles that are being repulsed from the patterned surface. For example, the average height or depth of the protrusions or holes may be approximately the same as, greater than 2 times, greater than 3 times, greater than 5 times, greater than 10 times, less than 2 times, less than 3 times, less than 5 times, or less than 10 times the average size of the particles repulsed therefrom. In certain embodiments, the average height or depth of the protrusions of the patterned structure falls outside of the above noted ranges.

The protrusions, and/or holes formed by the protrusions, of the patterned structure may have an appropriate average width (or diameter). In some embodiments, the average width or diameter of the protrusions or holes is between 500 nm and 100 microns, between 500 nm and 50 microns, between 1 micron and 50 microns, between 5 microns and 50 microns, between 5 microns and 30 microns,

- 15 -

between 5 microns and 20 microns, between 10 microns and 20 microns, between 2 microns and 10 microns, or between 5 microns and 10 microns. In some embodiments, the average width or diameter of the protrusions or holes is greater or less than the average size of the particles that are being repulsed therefrom. For example, the average width or diameter of the protrusions or holes may be approximately the same as, greater than 2 times, greater than 3 times, greater than 5 times, greater than 10 times, less than 2 times, less than 3 times, less than 5 times, or less than 10 times the average size of the particles repulsed. Or, the protrusions or holes of the patterned structure for other embodiments may have an average width or diameter that falls outside of these ranges. As noted above, the cross-sectional shape of the protrusions, or holes formed by the protrusions, may vary along the height. Where the width or diameter of the protrusion(s) or hole(s) vary along the height, the average width or diameter is measured/calculated for the particular protrusion(s) or hole(s).

The protrusions, and/or holes formed by the protrusions, of the patterned structure may have a suitable spacing, or pitch, therebetween. In some embodiments, the average spacing between the protrusions or holes is between 500 nm and 100 microns, between 50 microns and 100 microns, between 30 microns and 70 microns, between 40 microns and 60 microns, between 500 nm and 50 microns, between 1 micron and 50 microns, between 5 microns and 50 microns, between 5 microns and 30 microns, between 5 microns and 20 microns, between 10 microns and 20 microns, between 20 microns and 40 microns, between 20 microns and 30 microns, between 2 microns and 10 microns, or between 5 microns and 10 microns. In some embodiments, the average spacing between protrusions or holes is greater or less than the average size of the particles that are being repulsed therefrom. For example, the average spacing between protrusions or holes may be approximately the same as, greater than 2 times, greater than 3 times, greater than 5 times, greater than 10 times, less than 2 times, less than 3 times, less than 5 times, or less than 10 times the average size of the particles repulsed. It can be appreciated that ranges of spacing between protrusions or holes other than those noted may be possible for certain embodiments.

- 16 -

The patterned structure may cover an appropriate amount of the underlying surface of the substrate. Fig. 6 shows an illustrative embodiment where the protrusions 110 cover a portion of the underlying surface of the substrate 102. Here, the area 102b of the underlying substrate located underneath the protrusions is covered by the patterned structure, and the exposed area 102a of the substrate where the protrusions are not located (i.e., outside of the schematic trapezoidal cross-sections) is not covered by the patterned structure. Accordingly, the exposed area 102a and the covered area 102b make up 100% of the underlying surface of the substrate. For example, for a smooth substrate having no protrusions thereon, there is no patterned structure, so 0% of the underlying surface of the substrate is covered. Or, for a patterned structure having holes that run through the protrusions (or plateaus) such that 5% of the underlying surface of the substrate (i.e., lowermost surface) is showing, the patterned structure covers 95% of the underlying surface of the substrate.

In some embodiments, the patterned structure covers greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, between 20% and 95%, between 20% and 80%, between 20% and 70%, between 20% and 60%, between 20% and 50%, between 50% and 80%, between 30% and 95%, between 40% and 95%, between 50% and 95%, between 60% and 95%, or between 70% and 95% of the underlying surface of the substrate. In certain embodiments, the patterned structure covers an area of the underlying surface of the substrate that falls outside of the above noted ranges.

The protrusions and/or holes of the patterned structure may form appropriate angles with the plane defined by the underlying surface of the substrate. Fig. 6 further shows an illustrative embodiment where protrusions form an angle θ with the plane (not labeled in Fig. 6) defined by the underlying surface of the substrate. In some embodiments, the average angle formed between the plurality of protrusions or holes and the underlying surface of the substrate is between 20 degrees and 90 degrees, between 30 degrees and 90 degrees, between 40 degrees and 90 degrees, between 50 degrees and 60 degrees, between 70 degrees and 90 degrees, between 20 degrees and 70 degrees, between 30 degrees and 70 degrees, between 40 degrees and 70 degrees,

or between 50 degrees and 70 degrees. It can be appreciated that, for certain embodiments, angles formed by the protrusions or holes with the underlying surface of the substrate other than those described above may be possible.

5 Patterned structures having protrusions or holes that optionally form angles with the plane defined by the substrate surface may have any suitable configuration. For example, the cross-sectional shape in a transverse cut of a protrusion or hole may be circular, square, rectangular, elliptical, elongate, etc.

10 In some embodiments, as discussed above, repulsive effects arising from the patterned structures on particles contained within fluid that flows across the surface of the patterned structures may depend, at least in part, on the direction of fluid flow. In some cases, the orientation of the angle θ with the plane defined by the underlying surface of the substrate may be designed so as to correspond with the direction of fluid flow. For example, the protrusion(s) or hole(s) may be constructed to form an angle θ with the plane defined by the substrate surface in a direction that is
15 substantially perpendicular, at a suitable angle, or substantially parallel, with the desired direction of fluid flow.

In some embodiments, the patterned structure may have protrusions or holes that exhibit a sub-structure. For example, various protrusions or holes may have branches that extend from the protrusions or holes themselves. Such branches may
20 have an average width or diameter of less than 1 micron, less than 700 nm, less than 500 nm, or less than 300 nm, less than 100 nm. For holes, the branches, similar to the holes themselves, may be characterized by an absence of material. In some cases, the branches or sub-structures may impart certain phobic or philic properties to the overall surface texture. For example, the sub-structures may give rise to a lotus leaf
25 effect where the surface becomes more hydrophobic in nature.

As discussed above, in some embodiments, the patterned structure exhibits dimensions that relate to the size(s) of the particle(s) that are being repulsed. For example, as platelets are approximately 2-4 microns in size, red blood cells are approximately 8-12 microns in size, and white blood cells are approximately 20
30 microns in size, the particular range(s) of dimensions of the patterned structures may correlate to whether the above particles are repelled away from the surface. That is,

one or more of the parameters described herein with respect to the patterned structures (e.g., width, height, spacing, shape, two/three dimensional, amount of underlying surface covered by the protrusions, etc.) may affect whether certain particles are pushed or otherwise caused to move away from the micro-textured surface, for
5 example, due to fluid flow patterns, creation of turbulence, currents/eddy formation, etc. However, for some embodiments, the size or dimensions of features of the patterned structure may have little bearing on whether certain types of particles are repulsed from the surface.

As noted herein, the patterned structure may include multiple phases of
10 protrusions and/or holes. For example, one phase of protrusions or holes may have a particular average height/depth, width/diameter or spacing therebetween, which may be different from another phase of protrusions or holes which have a different average height/depth, width/diameter or spacing therebetween. In some embodiments, the type of phase of the patterned structure may correspond to the type of particle(s)
15 whose flow behavior are affected. For example, the flow behavior of a larger particle (e.g., blood cells) may be more influenced by a patterned structure with larger protrusions as compared to the flow behavior of a smaller particle (e.g., platelets), which may be more influenced by a patterned structure with relatively smaller protrusions.

As discussed herein, embodiments of patterned structures in accordance with
20 the present disclosure may give rise to flow profiles around the protrusions of the patterned structures such that a normal pressure away from the surface is created on the particles of a multi-component fluid. This pressure and associated velocity flow field push the particles (e.g., droplets, biological cells, etc.) away from the surface. In
25 some cases, the size and dimensions of the patterned structures are selected to result in a desired normal pressure that may depend on a number of factors, such as viscosity, velocity, applied pressure of the fluid, as well as the size, shape, density, viscosity, surface tension, and desired distance away from the surface of the particles themselves.

It is noted that, at a sufficiently high velocity, liquid droplets may begin to break up. Thus, for some embodiments, the micro features may be used to further emulsify and concentrate a mixture to two or more immiscible fluids.

Accordingly, the philic and/or phobic nature of multi-dimensional,
5 interdigitated, uniform or mixed pattern, micro-textured surfaces, driven by fluid dynamics and surface tension effects, may be tailored, in large part, based on pattern design. As discussed herein, for applications with respect to biological fluids, micro-textured patterns for both manipulating and facilitating biological fluid flow at or on a surface may be applicable in dialysis (e.g., interior and/or exterior surface of dialyser
10 tubes), anti-coagulation and non-clotting surfaces cardiovascular artificial grafts (e.g., venous, arterial, etc.) and stents, heart valves and leads, pumps, artificial bladders, flow barriers, and other devices in contact with such fluids, such as blood or urine.

Embodiments described herein may also be applicable to the concentration or separation of emulsions of immiscible liquids such as oil and water, concentration and
15 separation of cells, bacterial or viruses from a liquid media, separation of pulp from juice/beverages, improved operation of filter media for a range of applications from sewage dewatering to pulp and paper processing, improved operation of battery and fuel cell separators to keep gas bubbles from attaching to the separator surface, resisting droplet impacting and forming liquid or solid layers on surfaces such as
20 resisting ice formation on aircraft, and others. Accordingly, it can be appreciated that the principles described herein may be extrapolated to apply to structures and devices used in the processing, segregation and handling of complex fluids other than blood.

Embodiments of micro-textured surfaces described herein may be used to assess the pressure in a fluid flowing across such a textured surface, orthogonal to the
25 direction of fluid flow. Fig. 7 shows a computational fluid dynamics simulation employing Navier-Stokes governed concepts to predict the orthogonal pressure from a fluid flowing across a micro-textured surface (i.e., pressure acting in a direction substantially perpendicular to the direction of fluid flow).

Fig. 7 depicts a simulation of a smooth wall moving in close proximity to and
30 past a micro-textured stationary surface, with fluid located therebetween. Above each micro-textured unit cell, for both two and three dimensional unit cells, the normal

gauge pressure was observed to increase toward the center of the cell. Similar results were observed for a fluid flowing across the micro-textured features, absent the moving smooth wall. Given a suitable combination of patterned geometries and particle containing fluid flow, for some embodiments, such effects may be generated on any surface independent of the geometry or the direction of flow, and are not limited to flow within tubes or channels.

With respect to blood, the folded or pleated endothelium lining of constricting arteries provides guidance in specifying the type of pattern and associated dimensions for two dimensional elongated ridge structures and three dimensional grid-like patterns for tubular and non-tubular structures and surfaces, which may allow for selective segregation of red and white blood cells, platelets and other large molecules away from a surface. Accordingly, patterned structures in accordance with the present disclosure may also accommodate for suitable blood flow or contact with a surface without giving rise to clotting or thrombosis in and/or on artificial tubular devices in an undesirable manner.

For blood, it is noted that only small arteries, arterioles and capillaries have sufficiently small diameters, as shown in the tables depicted in Fig. 8, to be compatible with the Fahraeus-Lindquist and Segré-Silberberg effects, which are driven by particle (blood cell) induced lateral flow of the plasma to the arterial walls, with the red and other blood cells being focused to specific axial laminar flow lines. However, it is apparent that arteries also have additional structures for segregating red and other blood cells away from their walls, for instance, by way of surface tension effects, normal hydrodynamic pressure and/or a pulsatile radial channel plume flow.

Notably, the endothelial lining of an artery does not contract, so when an artery constricts after a systolic pressure pulse, its endothelium forms into folds that give the inner arterial wall an axial pleated appearance, as shown in Fig. 9. When not opposed by blood pressure pulse, the elastic fibers in the walls of muscular arteries recoil (vasoconstriction), constricting the lumen in response to the passing pulse which creates a pulsatile flow of blood along the artery.

In accordance with aspects of the present disclosure, the pleated structure of the endothelium creates a linear 2D ridge-based micro-texture driven surface tension

and normal hydrodynamic pressure in response to axial flow that causes red and other blood cells to be repelled therefrom, helping to avoid injury or rupture of the red blood cells by the constricting artery. As with the Fahraeus-Lindquist and Segré-Silberberg effects, this surface texture segregates the plasma to the arterial wall so as to reduce the apparent viscosity, which facilitates flow.

The endothelium folds of a constricted artery are further observed to form elongated pleats or riblets that extend along the axial direction of the artery wall, as shown in Fig. 10. The width of these ridges are generally larger than the diameter of red blood cells, and the width of the gaps between these ridges are typically smaller than the diameter of red blood cells. This structure is consistent with the dimensions of patterned structures in accordance with embodiments of the present disclosure. For example, embodiments of patterned structures described herein may be substantially similar in structure to the inner lining of a wall of a blood vessel, such as that depicted in Fig. 10.

Consequently, with this appreciation for the surface tension philic/phobic and fluid dynamic normal pressure functionality of the endothelium folds in the artery wall, embodiments of the present disclosure now make it possible to fabricate similar micro-structures on the surfaces of various devices to achieve similar segregation function with blood and other complex fluids. This enables the expansion of the Fahraeus-Lindquist and Segré-Silberberg like segregation effects to beyond the limitation of micro tubes, and so accommodates for a range of functions with complex fluids in larger diameter tubes and with surfaces functionalized with an engineered surface tension and/or fluid dynamic normal pressure. Such functionalities may be achieved using patterned structures in accordance with the present disclosure.

Accordingly, in applications where blood is processed, blood cells and other particles within the blood may be kept away from surfaces that employ embodiments of patterned structures described herein. Thus, damage to blood cells and initiation of clotting may be substantially eliminated for flow of blood across embodiments of such surfaces. That is, the tendency for blood that flows over such surfaces to clot or coagulate on the surface(s) is substantially reduced as compared to flow of blood over other surfaces, such as smooth surfaces.

In some embodiments, when blood is flowed (e.g., perfused for 5 minutes at 37 degrees C) over a patterned structure according to the present disclosure, the clotting time of the blood, as determined by those of skill in the art, is greater than 1 minute, greater than 2 minutes, greater than 3 minutes, greater than 4 minutes, greater than 5 minutes, or greater than 10 minutes.

The ability of various components of the blood (e.g., platelets, lymphocytes, monocytes, and polymorphonuclear leukocytes (PMNs), amongst others) that is flowed over and on the patterned structures to bind or otherwise adhere to the respective surfaces may be assessed, via quantification methods of immunostaining and confocal microscopy, as known to those skilled in the art. In various embodiments, surfaces with certain patterned structures may result in adhesion of significantly fewer cells and other components of blood thereto, as compared to the degree of adhesion to smooth surfaces, or other types of surfaces.

In some embodiments, flow of blood over a surface having a suitable patterned structure may give rise to less than 10.0%, less than 8.0%, less than 6.0%, less than 5.0%, less than 4.0%, less than 3.0%, less than 2.0%, less than 1.0%, between 0.1% and 10.0%, between 0.5% and 5.0%, between 0.5% and 3.0%, or between 0.8% and 3.0% of the platelets and/or lymphocytes of the blood becoming activated or otherwise adhering to the surface.

In some embodiments, flow of blood over a surface having a suitable patterned structure may give rise to less than 50.0%, less than 40.0%, less than 30.0%, less than 25.0%, less than 20.0%, less than 18.0%, less than 15.0%, between 0.1% and 50.0%, between 1.0% and 40.0%, between 5.0% and 40.0%, between 15.0% and 30.0%, or between 20.0% and 25.0% of the monocytes of the blood becoming activated or otherwise adhering to the surface.

In some embodiments, flow of blood over a surface having a suitable patterned structure may give rise to less than 80.0%, less than 70.0%, less than 60.0%, less than 55.0%, less than 50.0%, less than 45.0%, less than 40.0%, less than 35.0%, less than 30.0%, between 1.0% and 80.0%, between 10.0% and 70.0%, between 20.0% and 60.0%, between 30.0% and 60.0%, between 35.0% and 55.0%, or between

40.0% and 50.0% of the polymorphonuclear leukocytes of the blood becoming activated or otherwise adhering to the surface.

It can be appreciated that other percentages of platelets, lymphocytes, monocytes, and/or polymorphonuclear leukocytes of blood perfused over a surface
5 having a patterned structure in accordance with various embodiments may adhere thereon.

In general, the surfaces having patterned structures in accordance with various embodiments may be found to result in between 20.0% and 95.0%, between 25.0% and 90.0%, between 30.0% and 80.0%, or between 40.0% and 70.0% reduction in
10 cell/platelet attachment or activation on to the surface as compared to surfaces without a suitable patterned structure (e.g., smooth surface).

As discussed herein, the degree of thrombus formation on embodiments of surfaces with patterned structures when blood is flowed overhead may be significantly reduced, as compared to other types of surfaces. For example, as
15 examined by light and/or fluorescence microscopy, thrombus formation on surfaces with patterned structures in accordance with the present disclosure may be reduced as compared to surfaces without a suitable patterned structure (e.g., smooth surface) by greater than 20%, greater than 40%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 95%, or greater than 99%.

As discussed above, various embodiments of patterned structures may
20 substantially avert or reduce the formation of clots when blood is flowed overhead. Though, in some embodiments, blood that flows over or is otherwise exposed to the patterned structure may still undergo the process of clotting, yet based on the flow profile(s) that arise from exposure to the patterned structure, the clots themselves that
25 are formed may be suitably repelled therefrom. Accordingly, any such clots may be unable to stick to the surface of the patterned structure(s), resulting in minimal or significantly reduced clot accumulation than would otherwise be observed. That is, by being repelled from the surface, the clot(s) would continue to flow forward without substantial coagulation.

It is further thought that the repulsive force(s) that may be caused by the
30 patterned structures on the particles of the blood results in mutual separation of the

platelets and the red blood cells. In general, for the clotting process to run its course, platelets, red blood cells and other components within the blood are in intimate contact. However, when such components (e.g., platelets and red blood cells) are separated, such as by flow patterns that arise from embodiments of patterned structures according to the present disclosure, clotting is significantly reduced.

Taking dialysis as another example where micro-textured surfaces in accordance with aspects of the present disclosure may be employed, a patterned structure may be formed on a membrane dialyser surface. The patterned structure may facilitate the segregation of uremic waste rich plasma and water in blood toward the micro-textured surface while pushing red and other blood cells away from the wall. In some cases, the surface energy of the patterned structures may render the surface of the membrane wall philic to plasma and water while being phobic to the red and other large cells/molecules found in blood.

As described above, membrane separation is a physical process that results in the separation of a mixed solution or complex fluid into useful fractions of permeate and retentate. Isothermal membrane separation processes are used in a number of industries, such as food, beverage, biotechnology, pharmaceutical, medical and environmental industries, and others. In artificial kidney dialysis, membrane separation is useful to remove toxins by hemodialysis and excess water by hemofiltration, and for use in an artificial lung, for bubble-free supply of oxygen to blood. Embodiments of patterned structures may be applicable to any of the applications discussed herein.

A semipermeable membrane allows certain molecules and/or ions to pass through its body or pore structure by diffusion and/or convection. The rate of passage or flux through the membrane is largely determined by the pressure, concentration and temperature of the molecules and/or solutes on either side of the membrane, as well as the permeability of the membrane to each molecule, particle, solute or other component in the fluid. The membrane can be constructed with various interconnected pore structures to be selective in its permeability.

Mass transfer across the membrane can be by solution diffusion or hydrodynamic convection, or a combination thereof. During the filtration process, a

boundary layer or concentration gradient of retentate molecules can form at the surface of the membrane creating a concentration polarization that can reduce the trans-membrane flow or flux. Accordingly, it may be preferable to maintain fluid flow substantially parallel to the membrane surface so as to lower the formation and effect of fouling.

In accordance with aspects of the present disclosure, micro-textured surfaces having a suitable patterned structure may be employed to the inner surface of a dialyser tube. For various embodiments, the micro-texture based surface tension and/or normal gauge pressure may accommodate any appropriate tube with a suitable diameter or shape.

The flux of permeate across a permeable membrane may be driven by the concentration or pressure gradient of permeate across the membrane, or a combination thereof. Consequently, it may be preferable for a relatively high concentration and/or pressure of permeate be maintained at the membrane surface.

The Fahraeus-Lindquist and/or Segré-Silberberg effects may apply to blood dialysis by segregating uremic waste and water carrying plasma at the membrane wall as it flows through an appropriately sized micro-tube. However, such a micro-tube maintains a laminar flow under steady pressure-driven flow conditions. As a result, the concentration of uremic waste and water in the plasma at the membrane wall at the entrance to the tube may decline steadily as the segregated blood and plasma undergo laminar flow along the dialyser tube. Under these laminar flow conditions, uremic waste and water can only migrate from the core of the steady laminar flow stream to the membrane wall via lateral diffusion. It would be advantageous to be able to use turbulent or pulsatile flow in dialysis, as well as other filtration processes, to accommodate mixing across the core channel of the flow and thereby facilitate lateral convective flow of mixing to refresh the permeate to the membrane wall.

Surface tension driven segregation at the surface of a suitably micro-textured membrane surface may be independent of the bulk flow conditions of the complex fluid. For example, in the case of blood, pulsatile flow may result in alternating steady laminar and turbulent (possibly reversing) flow resulting in mixing of the core flow stream and thereby refreshing the concentration of the uremic waste and water in

the plasma segregated at the membrane wall. The surface tension driven phobic and gauge pressure/force created by the micro-textured surface may serve to repel the red and other blood cells from contact with the membrane surface. The eddy currents, generated by the patterned structures, which may create the normal pressure, may also
5 serve to circulate and refresh the phobic plasma component of blood that is in wetted contact with the surface. The flow channel can be tubular, rectangular or otherwise shaped and, as discussed previously, is not limited to certain micron dimensions and/or shapes.

In various embodiments, the combined substrate and patterned structure
10 provided on the surface of the substrate may be suitable not only to cause repulsion of particles therefrom, the substrate and patterned structure may behave as a filter for the carrier fluid (e.g., composed of a membrane filter material). For example, in the context of dialysis, cell-free plasma carrying uremic waste and water may effectively be segregated toward the micro-textured surface having the patterned structure(s). In
15 some embodiments, the permeate component(s) may be forced or otherwise caused to interface with and/or pass through the membrane/filter, for example, by a concentration gradient, applied pressure, centrifugal force, mechanical vibrations, etc. While permeate fluid may be directed toward the underlying filtration surface, particles may be suitably repelled therefrom so as to mitigate against particles/cells
20 from fouling and/or clogging the surface. Accordingly, the motive force that causes cell-free plasma/fluid to move toward the surface may be balanced with the motive force that causes particles (e.g., red/white blood cells, platelets, etc.) to be repulsed from the surface.

Given the repulsive surface tension force and normal gauge pressure on
25 particles, such as droplets and biological cells, it is possible to segregate the carrier fluid and any droplet, biological cell or other particle as a function of its density relative to the other particles in the fluid at the wall of a vessel or tube using centrifugal force. In the case of blood dialysis, since urea is 30 percent more dense than both plasma and whole blood, centrifugal force may be particularly effective for
30 segregating various components therein. The centrifugal force on the components of the complex fluid can be created by rotating the system or device at a suitable

rotational velocity, for example, using a coiled membrane tube, employing spiral flow or other arrangements.

Fig. 11 shows an illustrative embodiment where the centrifugal force of spiral laminar blood flow, balanced with the phobic surface tension and gauge pressure on
5 larger blood cells provided by embodiments of patterned structures described herein, may be used to further segregate the phobic plasma at the inner membrane wall and suitably concentrate uremic waste and water at the membrane wall. This increases the concentration gradient of the uremic waste and water across the permeable membrane, and thereby increases the flux and filtration efficiency of the process of dialysis.

10 Accordingly, cell-free plasma or other liquid may be concentrated at the surface of the patterned structures where filtration occurs, while the larger particles (e.g., cells, platelets) are kept away from the surface. In various embodiments, the centrifugal effect on the dialyser may be driven by any suitable system, for example, using a coiled membrane tube which provides a spiral pattern into the inner wall of the tube
15 or channel, or other system.

Once permeate enters the membrane, its passage across the thickness of the membrane may be controlled by diffusion and/or convective flow. Another method of enhancing flux and/or assisting convective flow across the membrane may be by imposing a pulsed or steady mechanical vibration along the length of the membrane
20 tube or channel. Such mechanical vibrations may be provided by an acoustically driven and/or agitation device, coupled with the membrane. In some embodiments, the membrane wall may have an interconnected porosity that increases in pore density and size radially across the membrane. This increasing radial pore density may act to divert part of the longitudinal vibration radially outward in the direction of increasing
25 porosity across and through the membrane wall, as illustratively shown in Fig. 12.

The above described vibrational wave energy may enhance uremic waste and water mixing with dialysate in the membrane and increase outward convection through the membrane. By employing a surface having patterned structures, which may cause cells and other particles to be repelled from the inner membrane wall, by
30 being kept away from the membrane wall, such cells and particles may remain undamaged from the vibration. In addition, this longitudinal and radial vibration may

also serve to enhance mixing, radial flow and circulation of plasma with the patterned structures of the inner and/or outer surfaces of the permeable membrane.

As shown in Fig. 13, it is possible to further enhance mixing in and convective flow through the permeable membrane by imposing a pulsed or steady hydrostatic pressure on the complex fluid across the membrane, to facilitate water and solute exchange, mixing and convection within and through the membrane. This may serve to enhance uremic waste and water mixing with the dialysate in the membrane and increase overall radial convection.

Accordingly, the soft spongy core of the membrane may contract and expand in response to a suitable pulsed pressure and act like a pump in the radial direction of increasing porosity. The pressure of the complex fluid and/or external fluid, or both can be pulsed, resulting in contraction and expansion of the membrane wall. Such contraction and expansion of the wall may serve to radially pump plasma away from the surface to both refresh and enhance mixing with a micro-textured surface while also moving red and other blood cells away from the wall. In addition, red and other blood cells and platelets may remain undamaged due to the repulsive effects of the patterned structures therefrom.

In further embodiments, further active separation mechanisms may be employed, such as electro-dialysis, iontophoresis, etc., where patterned structures on the surface of a device or graft may provide for surface tension driven segregation and radial flow to isolate specific permeates from complex fluids such as blood and other fluids.

In a further embodiment, a short cycle dialysis treatment where cycle collection and reinfusion of previously purified and stored plasma may be employed. Dialysis treatments typically involve a 3-4 hour dialysis cycle of whole blood three or more times per week with the patient continuously attached to the unit during the dialysis treatment.

Given that it is possible to segregate plasma from red and other blood cells at a permeable membrane using surface tension, gauge pressure, and/or with the combined Fahraeus-Lindquist and/or Segré-Silberberg effects as extended to more general surface structures, it is possible to selectively pass the plasma rapidly through an

- 29 -

appropriate membrane. This plasma may be collected relatively quickly while a previously collected and purified plasma is simultaneously infused, after which the patient disconnects from the dialysis unit. The collected plasma may subsequently be purified by the dialysis machine independent of the patient and properly stored for reinfusion during the next plasma dialysis cycle. This procedure could be repeated several times per day at the convenience of the patient, in their own home, and may be portable in nature. Such a treatment plan would free the patient from the constraints of the current dialysis clinic and cycle times.

Accordingly, the exchange of 0.5 liters of plasma twice a day for 7 days a week would be equivalent to the current 3-4 hour cycle 3 times per week. If the patient increases the proposed plasma purification process to 3 times per day, then they would receive the equivalent of 1.5 more treatments per week, which would result in substantial benefits to the patient.

EXAMPLES

Fig. 14 illustrates the results of a number of examples where a micro-textured surface was shown to exhibit desirable properties. Results of this study are also shown in Fig. 5. In this example, silicone rubber patterned structures were fabricated with a mold using manufacturing methods known in the art. Here, the patterned structures were created by lithography techniques known in the art for etching a silicon wafer, and the silicon wafer was used as a mold to fabricate the patterns on polydimethyl siloxane (PDMS).

In Example A), an unpatterned silicone rubber surface was fabricated. As shown in Fig. 14, example A) is provided as a comparative example, having a relatively smooth surface without protrusions.

To demonstrate the beneficial results arising from patterned structures in accordance with the present disclosure, examples of two patterned structures are presented here.

In example B), a silicone rubber surface was fabricated to have a patterned structure that includes a periodic arrangement of protrusions shaped as pillars approximately 25 microns in height, approximately 10 microns in width and

- 30 -

approximately 10 microns in pitch. The pillars are shown to have a substantially square cross-sectional shape that is generally constant along their height. Here, the patterned structure covers approximately 25% of the underlying surface of the substrate. As further shown in Fig. 14, the patterned structure of example B) has a
5 single phase of protrusions distributed uniformly along the substrate surface. Though, it can be appreciated that other embodiments of patterned structures in accordance with the present disclosure may have protrusions having other shapes and configurations that are suitable to achieve the desired philic or phobic effects.

As discussed above, for some embodiments, patterned structures may have
10 multiple phases, such as in example C), also shown in Fig. 14. In example C), a silicone rubber surface was fabricated to have a patterned structure that includes a periodic arrangement of pillars having two phases superimposed on one another. Here, the first phase is similar to that shown in example B), including pillars having a shape with a square cross-section that are approximately 25 microns in height,
15 approximately 10 microns in width and approximately 10 microns in pitch. The second phase is superimposed over the first phase, also having pillars with a square cross-sectional shape that are approximately 25 microns in height, yet the width of the pillars are approximately 50 microns and the pitch between pillars is approximately 50 microns. In this example, the patterned structure covers approximately 37% of the
20 underlying surface of the substrate.

For each of examples A), B) and C), fresh porcine blood (within 4 hours of slaughter without additives or cooling) at room temperature was applied thereon and wiped across the respective surface using either non-absorbent or absorbent methods. The non-absorbent method involved pipetting blood on to the surface and wiping the
25 blood across the surface with a metal spatula. A visual view of each of the surfaces after wiping with the metal spatula (left side of a dish) is labeled in Fig. 14 as "After spatula wipe." The absorbent method involved dipping a paper towel in the blood and wiping the blood containing portion of the paper towel across the surface, shown on the right side of Fig. 14. A visual view of the surface after wiping with the paper
30 towel (right side of the surface) is labeled in Fig. 14 as "After fabric wipe."

It was observed that the patterned structures of Examples B) and C) exhibited favorable results where, upon application and wiping of the porcine blood across the respective surfaces, the blood would not remain thereon, indicating a lack of clotting, partial clotting or clot accumulation of the blood on the surface. This indication was evidenced by a lack of red color from the blood. That is, both surfaces were observed to be repelling some components of the blood. It was further observed that the two phase patterned structure of Example C) exhibited more favorable blood repelling characteristics than the single phase patterned structure of Example B). The surfaces were characterized by macroscopically observing the lack of red color, and, by microscopically observing the lack of blood cells, clots or partial clots trapped within the patterned structure(s) of the surface.

In another example (not shown in Fig. 14), a silicone rubber surface was fabricated to have a single phase patterned structure similar to Example B), having a periodic arrangement of protrusions shaped as pillars approximately 25 microns in height, except the pillars were approximately 3 microns in width (rather than 10 microns in width, as in Example B)) and approximately 10 microns in pitch. When the porcine blood was wiped across the surface of this patterned structure, results similar to those demonstrated for Example B) were observed.

In yet another comparative example (also not shown in Fig. 14), a silicone rubber surface was fabricated to have a single phase patterned structure having a periodic arrangement of substantially larger protrusions than what was fabricated for the above examples. These protrusions were shaped as pillars approximately 150 microns in height, approximately 100 microns in width and approximately 200 microns in pitch. When the porcine blood was wiped across the surface of this patterned structure, results similar to those demonstrated for the smooth surface of Example A) were observed.

Similar results were achieved when the above structured surfaces were tested using materials other than silicone rubber; in particular, high density polyethylene, low density polyethylene and polypropylene.

In addition, human blood was perfused over the surfaces of Example A) and Example C) in vitro for 5 minutes at 37 degrees C, so as to assess the ability of human

platelets, lymphocytes, monocytes, and polymorphonuclear leukocytes (PMNs) to bind to the respective surfaces. Adherent cells were immunostained and quantified using confocal microscopy.

It was observed that significantly fewer cells were attached to the textured surface of Example C) as compared to the smooth surface of Example A). In particular, the flow of the human blood over the smooth surface of Example A) was observed to induce activation of between 6% and 20% of the platelets, between 5% and 18% of the lymphocytes, between 40% and 80% of the monocytes, and between 70% and 98% of the PMNs. However, the flow of the human blood over the textured surface of Example C) was observed to induce significantly less amounts of activation, between 0.8% and 3% of the platelets, between 0.8% and 3% of the lymphocytes, between 16.8% and 28% of the monocytes, and between 36.7% and 55% of the PMNs. In general, the textured surfaces of Example C) were found to give rise to between 25% and 90% reduction in cell attachment as compared to the smooth surfaces of Example A).

The degree of thrombus formation (i.e., adhesion of multiple cell types and deposition of proteins to the surface) on the smooth and textured surfaces after 1-24 hours was also observed via light microscopy and fluorescence microscopy.

In particular, as visualized by light microscopy, it was observed that thrombus formation and platelet adhesion to the textured surface of Example C) (between the patterned surface structures and immediately at the patterned surface structures) was reduced by between 80% and 99%, as compared to the observed thrombus formation and platelet adhesion to the smooth surface of Example A). Further, as visualized by fluorescence microscopy, it was observed that the fibrin-network formation at the textured surface of Example C) was reduced by between 70% and 99%, as compared to the observed the fibrin-network formation at the smooth surface of Example A).

Fig. 15 shows a simulation of a particle containing fluid flowing past a patterned surface having protrusions arranged in a configuration similar to that of Example C). Employing a Navier-Stokes model for fluid flow, it was observed that the pressure arising from a flow stream over the patterned surface causes a particle flowing therein to be pushed away from the patterned structures. As discussed above,

this flow behavior is thought to be due to upward moving currents generated by the interaction between the fluid flow and patterned structures, causing a normal pressure on the particles contained within the fluid.

5 It should be understood that the foregoing description is intended merely to be illustrative thereof and that other embodiments, modifications, and equivalents are within the scope of the present disclosure recited in the claims appended hereto. Further, although each embodiment described above includes certain features, the present disclosure is not limited in this respect. Thus, one or more of the above-
10 described features or methods of use, may be employed singularly or in any suitable combination, as the present disclosure and the claims are not limited to a specific embodiment.

What is claimed is:

- 34 -

CLAIMS

1. An apparatus for manipulating particle flow, comprising:
an artificial substrate; and
5 a patterned structure having a plurality of protrusions that extend from the substrate and are configured to cause movement of at least one particle away from the patterned structure, upon flow of a fluid containing the at least one particle over the patterned structure.
- 10 2. An apparatus for manipulating particle flow, comprising:
an artificial substrate; and
a patterned structure having a plurality of protrusions that extend from the substrate, wherein an average height of the plurality of protrusions, or holes formed by the protrusions, is between 5 microns and 50 microns, an average width of the
15 plurality of protrusions or holes is between 5 microns and 50 microns, and an average spacing between the protrusions or holes is between 5 microns and 50 microns.
3. An apparatus for manipulating particle flow, comprising:
an artificial substrate; and
20 a patterned structure having a plurality of protrusions that extend from the substrate and are configured such that, upon flow of blood over the patterned structure, less than 6% of platelets of the blood, less than 5.0% of lymphocytes of the blood, less than 40% of monocytes of the blood, or less than 70% of
polymorphonuclear leukocytes of the blood adhere to the patterned structure.
25
4. An apparatus for manipulating particle flow, comprising:
an artificial substrate; and
a patterned structure having a plurality of protrusions that extend from the substrate, wherein the plurality of protrusions comprises a first plurality of protrusions
30 and a second plurality of protrusions, wherein the first plurality of protrusions are

arranged to form a plurality of elongate ridges and the second plurality of protrusions are arranged to form a grid-like pattern of posts or holes.

- 5 5. The apparatus of one of the preceding claims, wherein an average height of the plurality of protrusions, or holes formed by the protrusions, is between 500 nm and 50 microns, between 5 microns and 50 microns, or between 2 microns and 10 microns.
- 10 6. The apparatus of one of the preceding claims, wherein an average spacing between the protrusions, or holes formed by the protrusions, is between 500 nm and 50 microns, between 5 microns and 50 microns, or between 2 microns and 10 microns.
- 15 7. The apparatus of one of the preceding claims, wherein an average width of the plurality of protrusions, or holes formed by the protrusions, is between 500 nm and 100 microns, or between 5 microns and 50 microns.
- 20 8. The apparatus of one of the preceding claims, wherein a space occupied by the patterned structure covers between 20% and 95%, between 20% and 50%, or between 50% and 95% of an underlying surface of the substrate.
- 25 9. The apparatus of one of the preceding claims, wherein an average angle formed between the plurality of protrusions or holes and a lower surface of the substrate is between 20 degrees and 90 degrees, or between 60 degrees and 90 degrees.
- 30 10. The apparatus of one of the preceding claims, wherein each of the plurality of protrusions or holes includes at least one branch having an average width of less than 1 micron.
11. The apparatus of one of the preceding claims, wherein the plurality of protrusions or holes are arranged in a grid-like pattern or other geometric pattern.

12. The apparatus of one of the preceding claims, wherein each of the plurality of protrusions or holes have a cross-sectional shape comprising at least one of a polygon, rectangle, circle and ellipse.

5

13. The apparatus of one of the preceding claims, wherein the protrusions or holes of the patterned structure comprise a plurality of sizes and shapes.

14. The apparatus of one of the preceding claims, wherein the plurality of protrusions or holes are arranged to form a plurality of elongate ridges, or elongated ridges in combination with a plurality of posts or holes.

15. The apparatus of one of the preceding claims, wherein the plurality of protrusions comprises a first plurality of protrusions, or first holes formed by the protrusions, and a second plurality of protrusions, or second holes formed by the protrusions, wherein an average width of the first plurality of protrusions or holes is less than an average width of the second plurality of protrusions or holes.

16. The apparatus of claim 15, wherein the average width of the first plurality of protrusions or holes is less than the average width of the second plurality of protrusions holes by approximately 5 times.

17. The apparatus of one of claims 15 or 16, wherein an average height of the first plurality of protrusions or holes is approximately the same as an average height of the second plurality of protrusions.

18. The apparatus of one of the preceding claims, wherein the at least one particle includes biological material.

19. The apparatus of one of the preceding claims, wherein the at least one particle includes at least one of a red blood cell, white blood cell and platelet.

20. The apparatus of claim 19, wherein the at least one particle has a particle size of between 1 micron and 25 microns, between 2 microns and 5 microns, between 8 microns and 12 microns, or between 15 microns and 25 microns.

5

21. The apparatus of one of the preceding claims, the patterned structure is configured such that, upon flow of blood over the patterned structure, clotting time of the blood is greater than 1 minute.

10 22. The apparatus of one of the preceding claims, wherein the apparatus is constructed as a dialysis tube, artificial blood graft or artificial bladder.

23. The apparatus of one of the preceding claims, wherein the fluid is at least one of a biological fluid, food, beverage and petroleum.

15

24. The apparatus of one of the preceding claims, wherein the artificial substrate includes a membrane adapted to filter a portion of the fluid therethrough.

25. The apparatus of one of the preceding claims, wherein the patterned structure is configured such that, upon flow of blood over the patterned structure, between 20 0.5% and 6.0% of platelets of the blood, between 0.5% and 5.0% of lymphocytes of the blood, between 15.0% and 40.0% of monocytes of the blood, or between 35.0% and 70.0% of polymorphonuclear leukocytes of the blood adhere to the patterned structure.

25

26. The apparatus of claim 25, wherein the patterned structure is configured such that, upon flow of blood over the patterned structure, between 0.5% and 3.0% of platelets of the blood, between 0.5% and 3.0% of lymphocytes of the blood, between 15.0% and 30.0% of monocytes of the blood, or between 35.0% and 55.0% of 30 polymorphonuclear leukocytes of the blood adhere to the patterned structure.

27. A method for manipulating particle flow, comprising:
flowing a fluid containing at least one particle over a patterned structure
having a plurality of protrusions that extend from an artificial substrate resulting in
movement of the at least one particle away from the patterned structure.

5

28. A method for manipulating particle flow, comprising:
contacting blood with a patterned structure having a plurality of protrusions
that extend from an artificial substrate resulting in less than 6% of platelets of the
blood, less than 5.0% of lymphocytes of the blood, less than 40% of monocytes of the
10 blood, or less than 70% of polymorphonuclear leukocytes of the blood adhering to the
patterned structure.

29. The method of one of the preceding claims, wherein flowing the fluid
comprises flowing the fluid at a velocity of between 0.1 cm/s and 50 cm/s.

15

30. The method of one of the preceding claims, wherein flowing the fluid
comprises flowing blood over the patterned structure resulting in movement of at least
one red blood cell away from the patterned structure.

20 31. The method of one of the preceding claims, wherein flowing the fluid
comprises flowing blood over the patterned structure resulting in a clotting time of the
blood of greater than 1 minute.

25 32. The method of one of the preceding claims, further comprising filtering a
portion of the fluid through the artificial substrate.

33. The method of claim 32, wherein filtering the portion of the fluid through the
artificial substrate comprises causing movement of the portion of the fluid toward the
patterned structure.

30

34. The method of claim 33, wherein causing movement of the portion of the fluid toward the patterned structure comprises at least one of forming a concentration gradient, applying a centrifugal force and applying mechanical vibrations to the fluid.

5 35. The method of claim 34, wherein contacting blood with the patterned structure comprises flowing blood over the patterned structure resulting in movement of at least one red blood cell away from the patterned structure.

36. The method of one of the preceding claims, wherein contacting blood with the
10 patterned structure results in between 0.5% and 6.0% of platelets of the blood, between 0.5% and 5.0% of lymphocytes of the blood, between 15.0% and 40.0% of monocytes of the blood, or between 35.0% and 70.0% of polymorphonuclear leukocytes of the blood adhering to the patterned structure.

15 37. The method of claim 36, wherein contacting blood with the patterned structure results in between 0.5% and 3.0% of platelets of the blood, between 0.5% and 3.0% of lymphocytes of the blood, between 15.0% and 30.0% of monocytes of the blood, or between 35.0% and 55.0% of polymorphonuclear leukocytes of the blood adhering to the patterned structure.

20

38. The method of one of the preceding claims, wherein the patterned structure comprises the patterned structure of one of the preceding claims.

39. An apparatus for manipulating particle flow, comprising:
25 an artificial substrate;
a patterned structure that is configured to cause movement of at least one particle of biological material away from the patterned structure, upon flow of blood containing the at least one particle of biological material over the patterned structure, wherein the patterned structure includes:

30 a first plurality of protrusions, or holes formed by the protrusions, having an average height of between 5 microns and 50 microns, an average width of between 2

- 40 -

microns and 30 microns and an average spacing between the protrusions of between 2 microns and 10 microns, and

5 a second plurality of protrusions, or holes formed by the protrusions, having an average height of between 5 microns and 50 microns, an average width of between 20 microns and 100 microns and an average spacing between the protrusions of between 2 microns and 10 microns,

wherein the average width of the first plurality of protrusions or holes is less than the average width of the second plurality of protrusions or holes.

10 40. The apparatus of claim 39, wherein the patterned structure is configured such that, upon flow of blood over the patterned structure, between 0.5% and 6.0% of platelets of the blood, between 0.5% and 5.0% of lymphocytes of the blood, between 15.0% and 40.0% of monocytes of the blood, or between 35.0% and 70.0% of polymorphonuclear leukocytes of the blood adhere to the patterned structure.

15

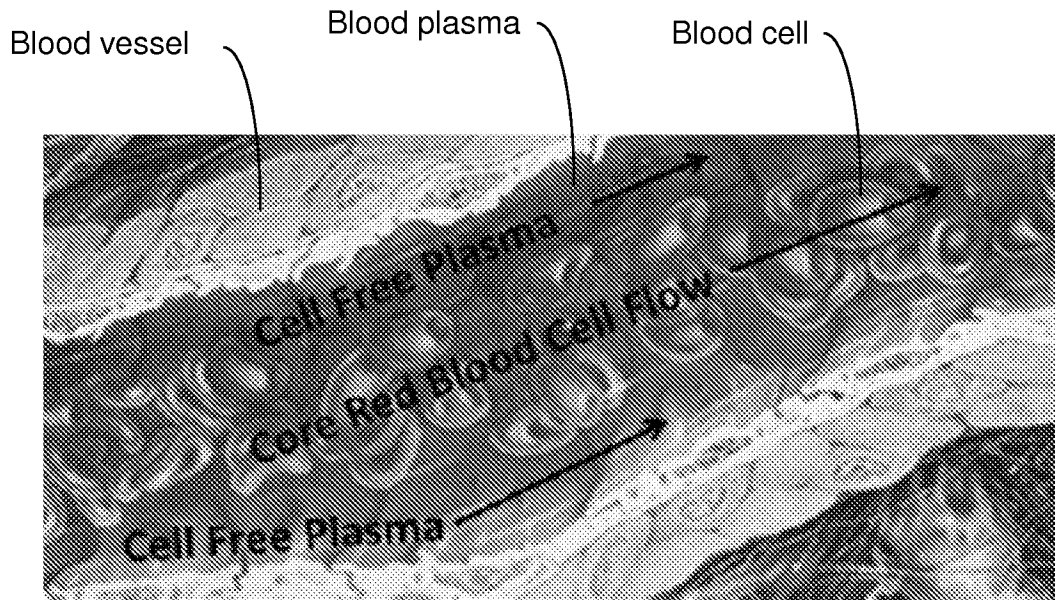


Fig. 1

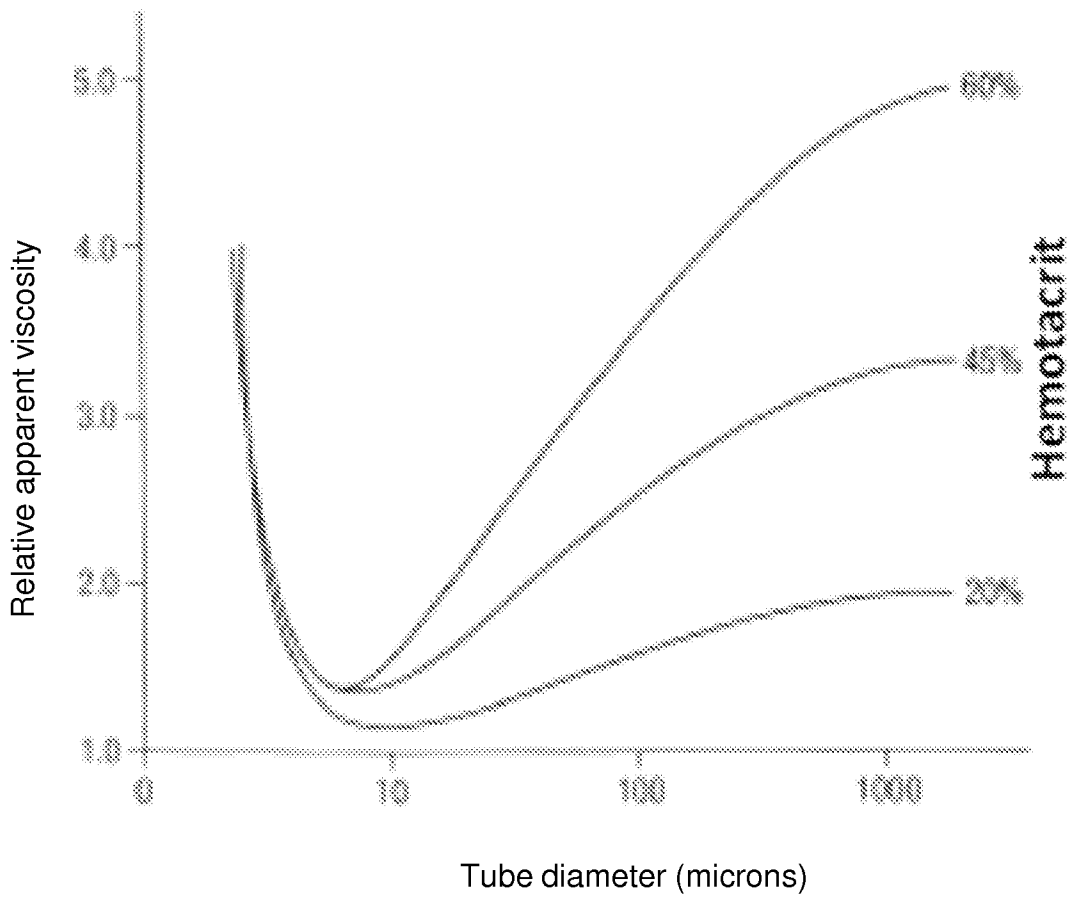


Fig. 2

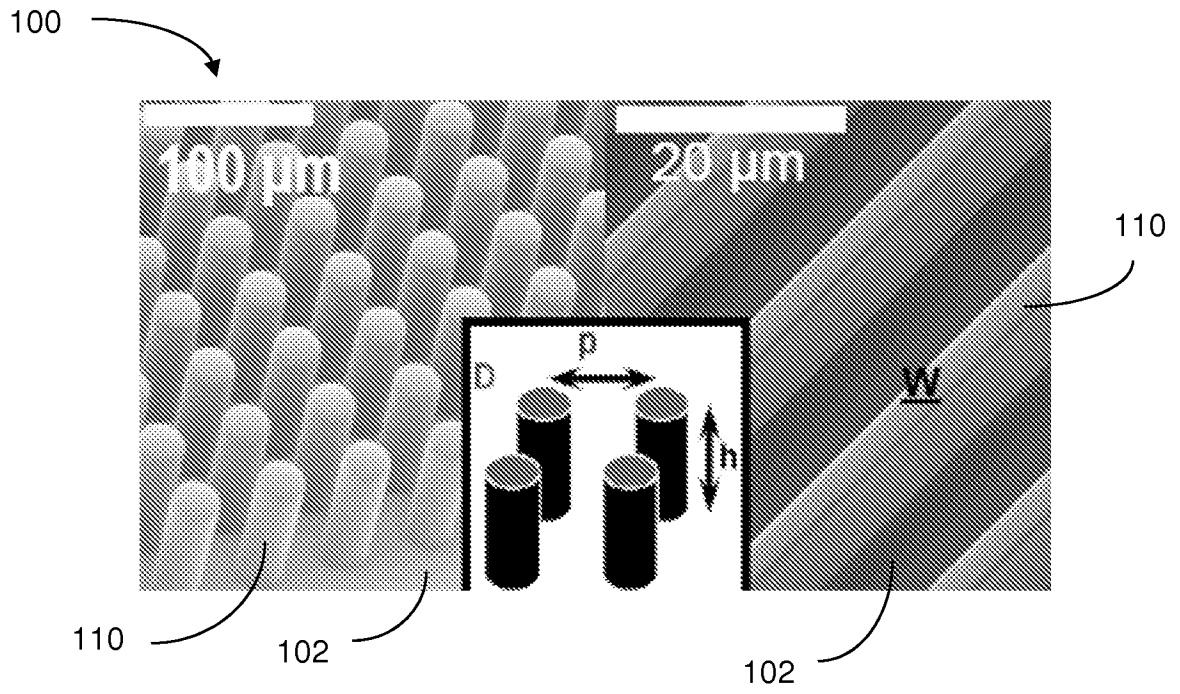


Fig. 3

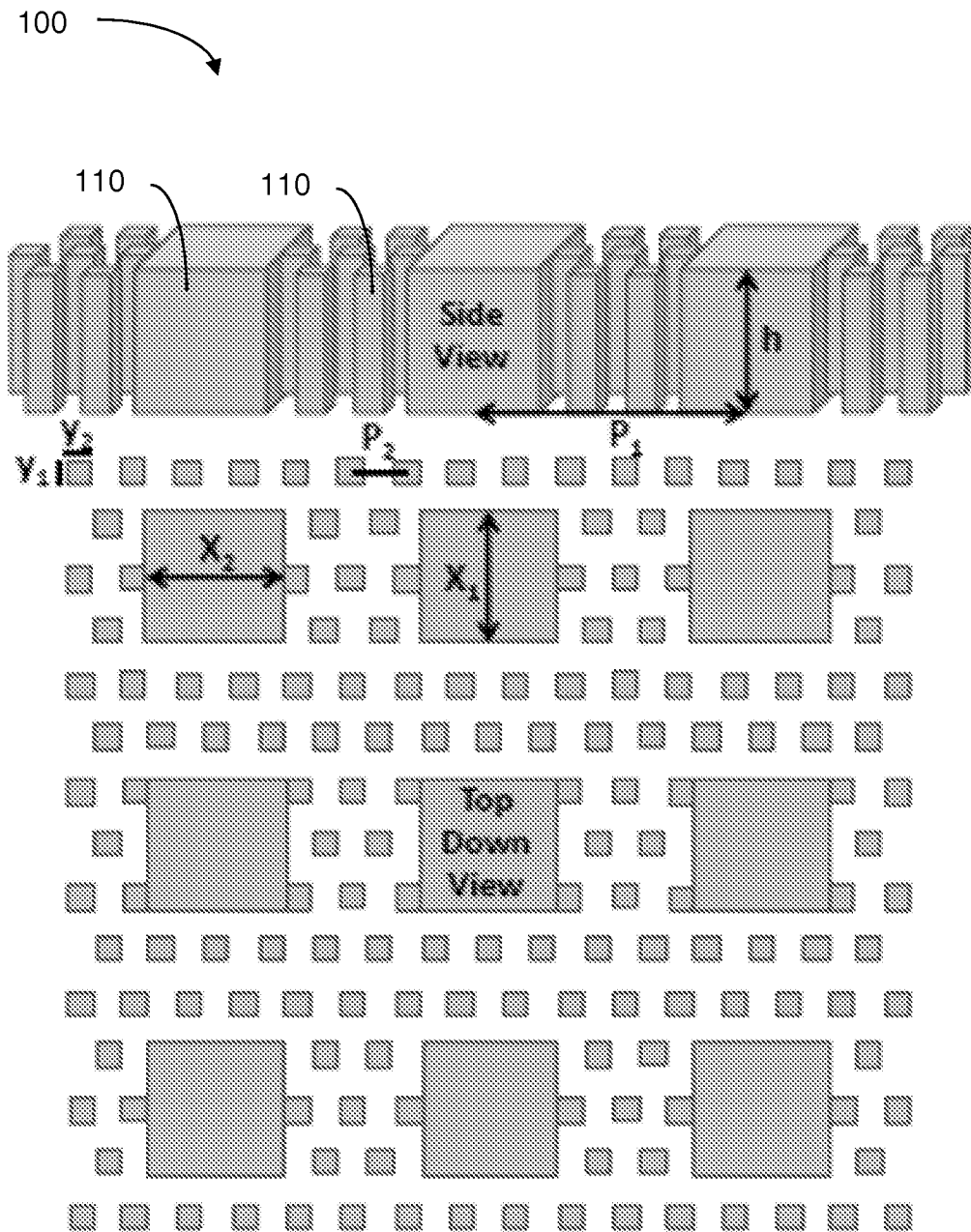


Fig. 4

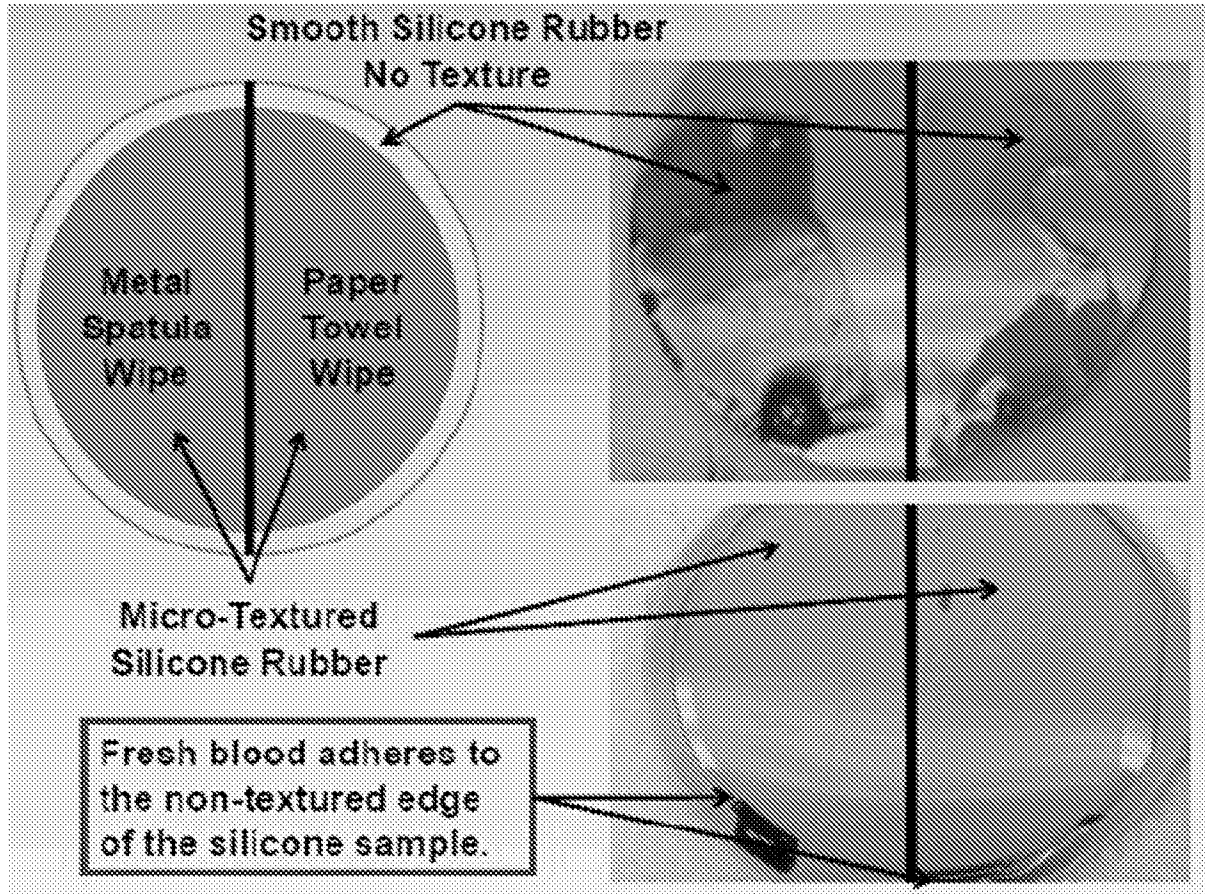


Fig. 5

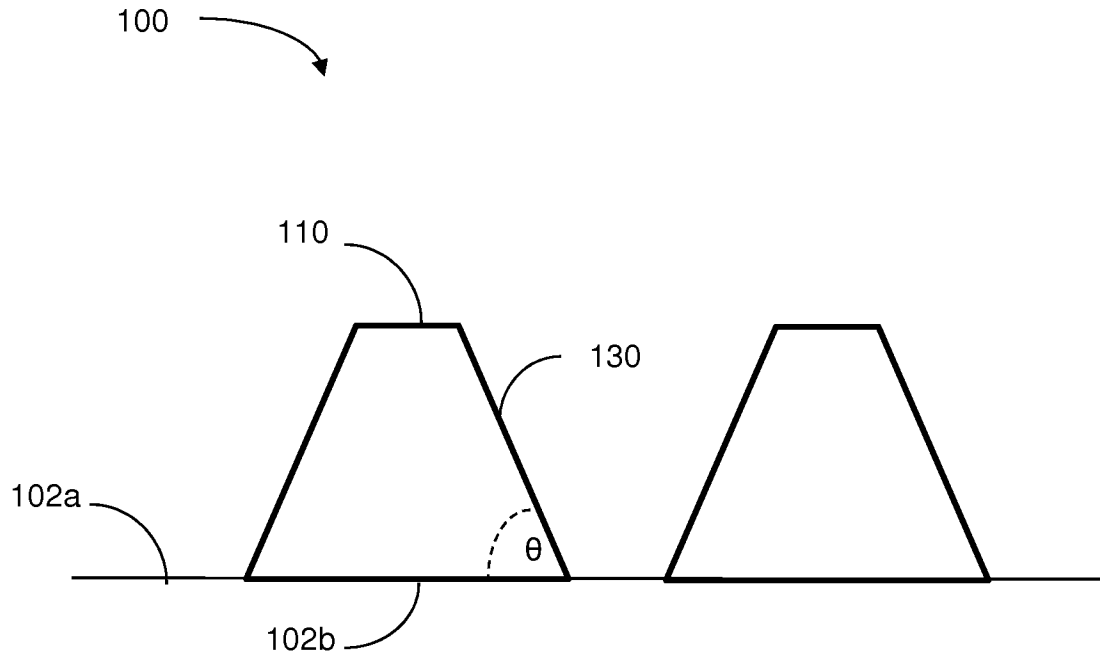


Fig. 6

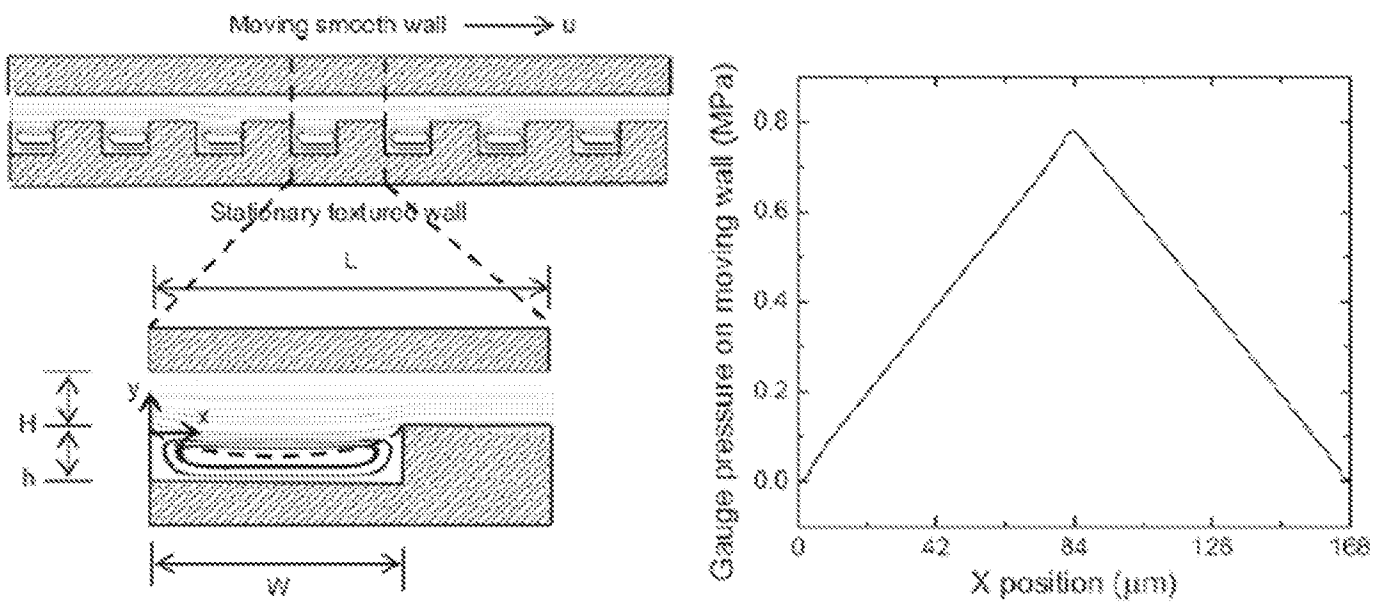


Fig. 7

<u>Vessel</u>	<u>(cm/s)</u>	<u>Dia</u> <u>(cm)</u>	<u>Mean wall</u> <u>Shear</u> <u>Rate</u>	<u>Reynolds</u> <u>Number</u>
Aorta	48	2.5	155	3,400
Artery	45	0.4	900	500
Arteriole	5	0.005	8,000	0.7
Capillary	0.1	0.0008	1,000	0.002
Venule	0.2	0.002	800	0.01
Vein	10	0.5	160	140
Vena Cava	38	3.0	100	3,300
		<i>mean diameter</i> <i>[mm]</i>		<i>number of</i> <i>vessels</i>
aorta		10 - 4.5		1
arteries		4 - 0.15		110,000
arterioles		0.05		$2.7 \cdot 10^6$
capillaries		0.008		$2.8 \cdot 10^9$

Fig. 8

Artery Vein Pair

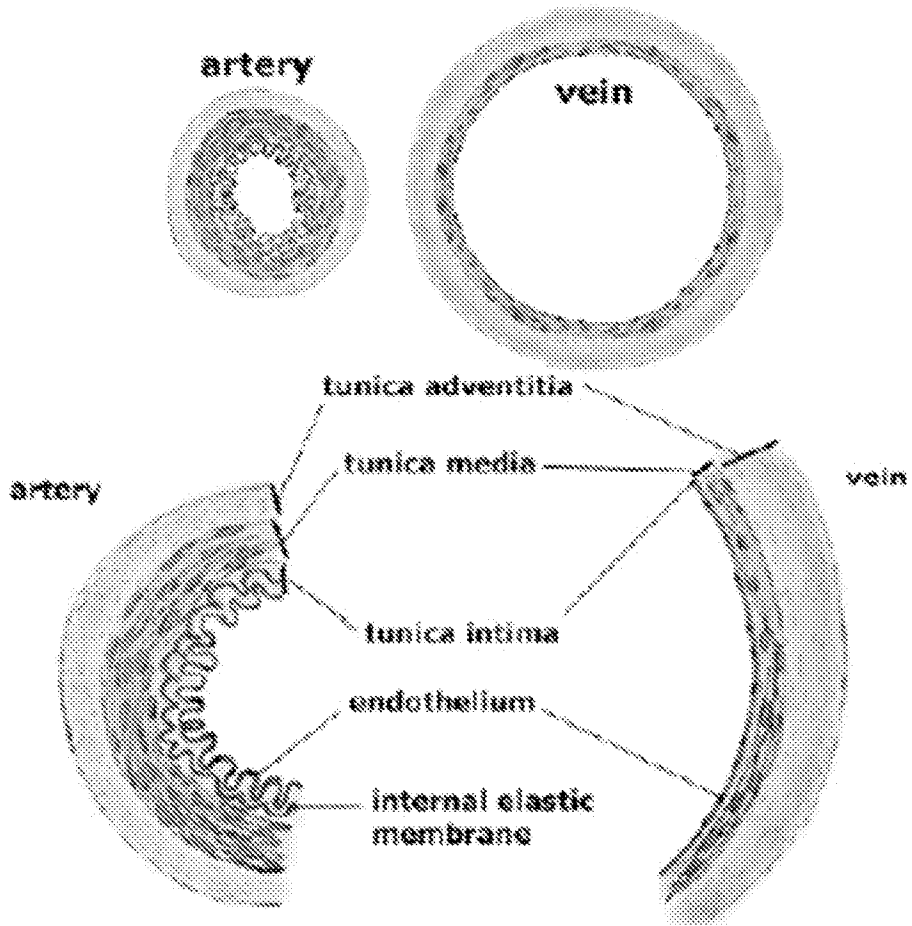


Fig. 9

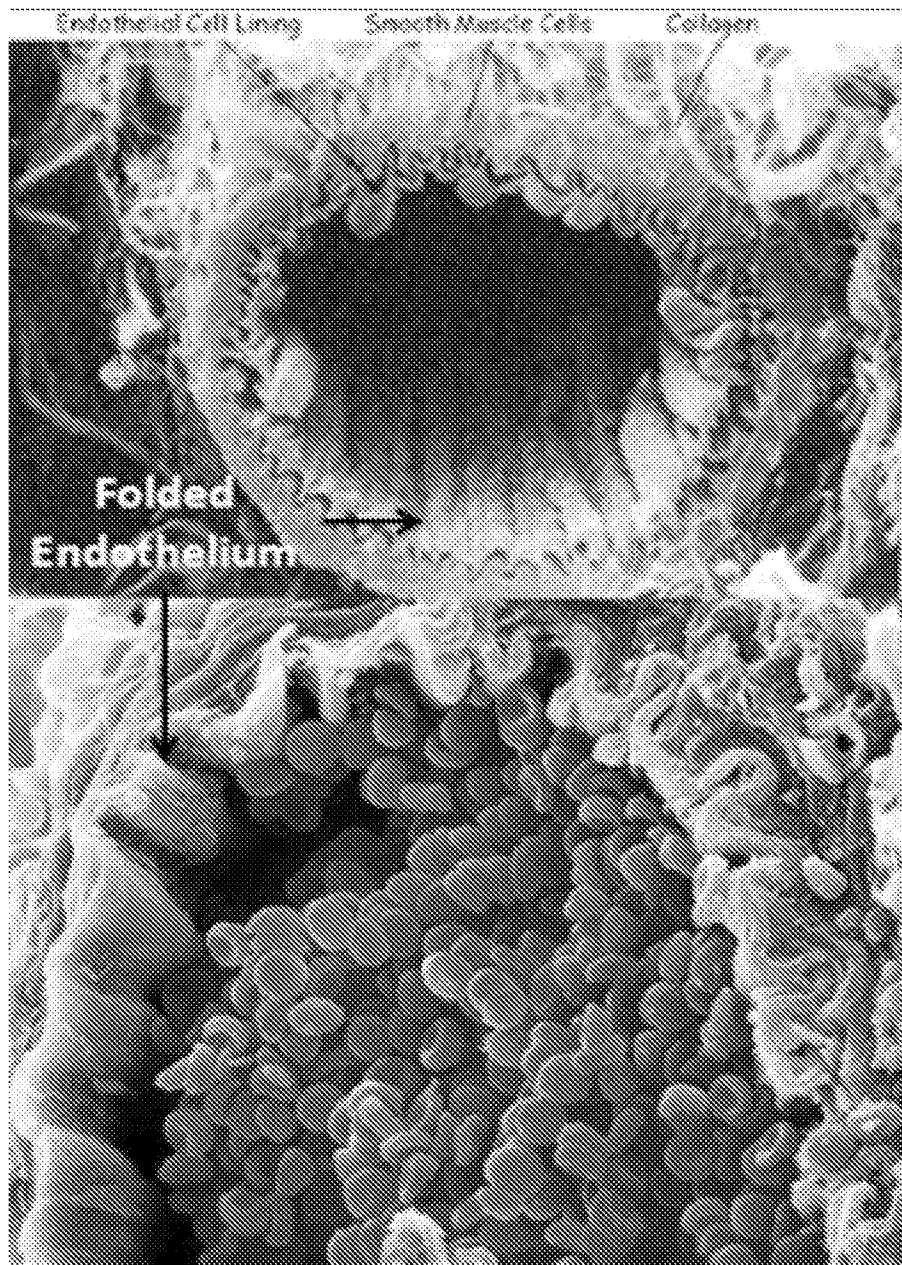


Fig. 10

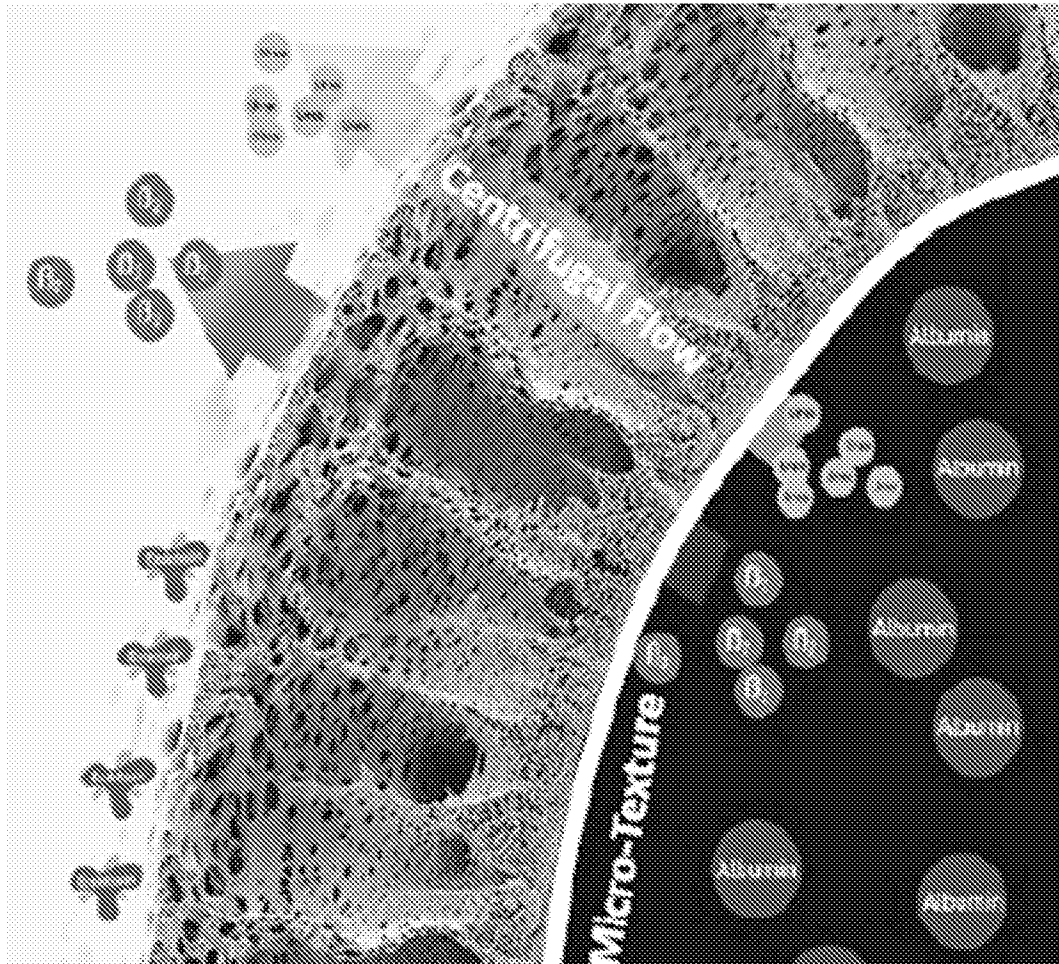


Fig. 11

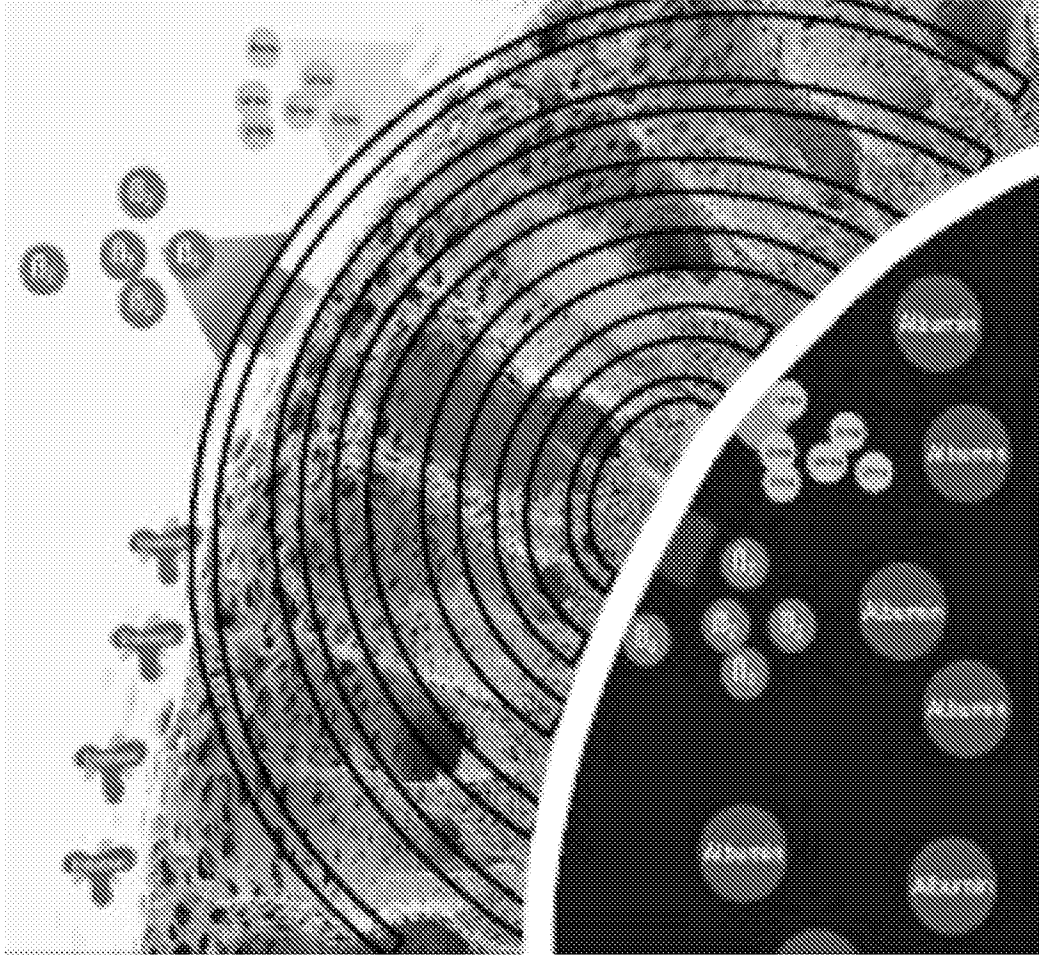


Fig. 12

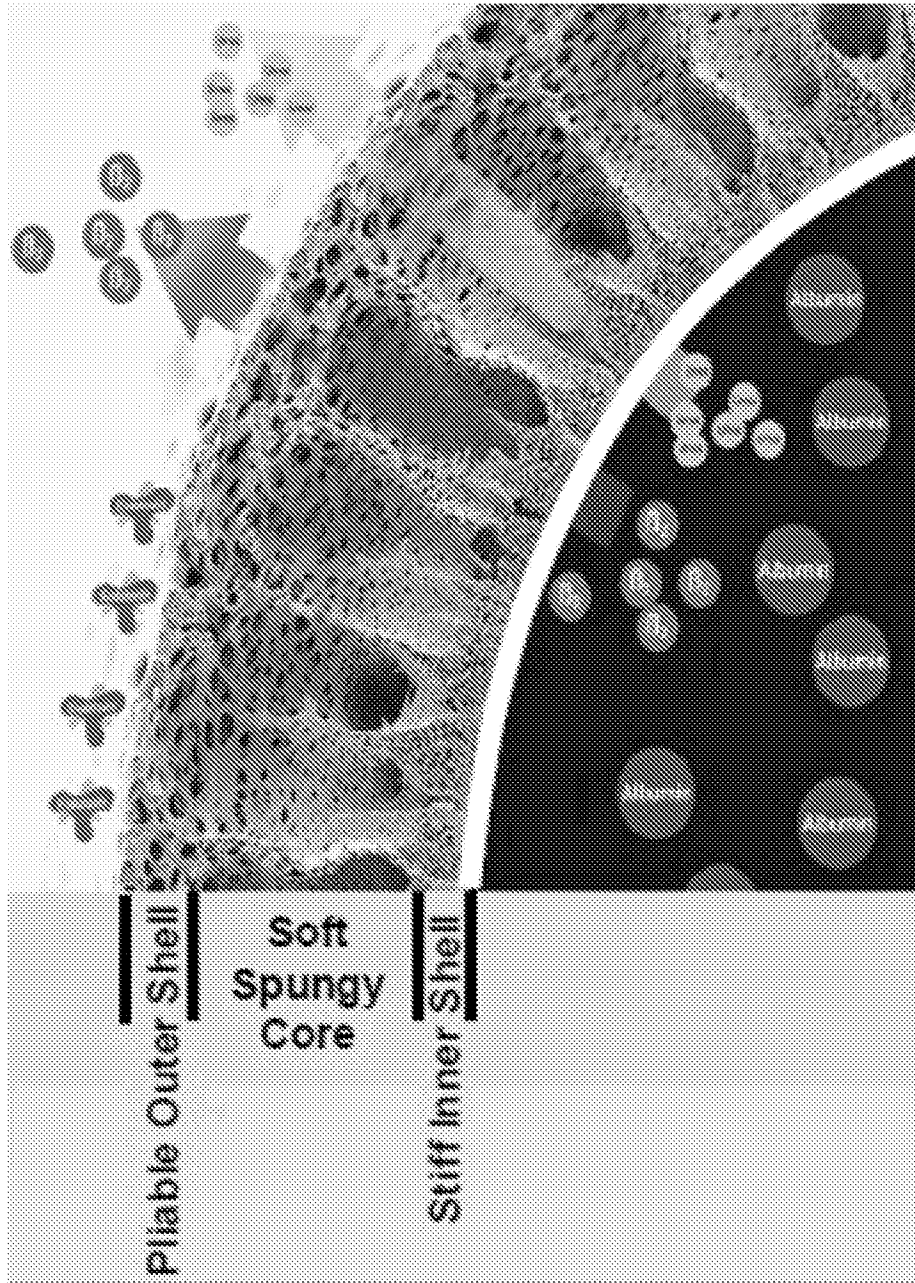


Fig. 13

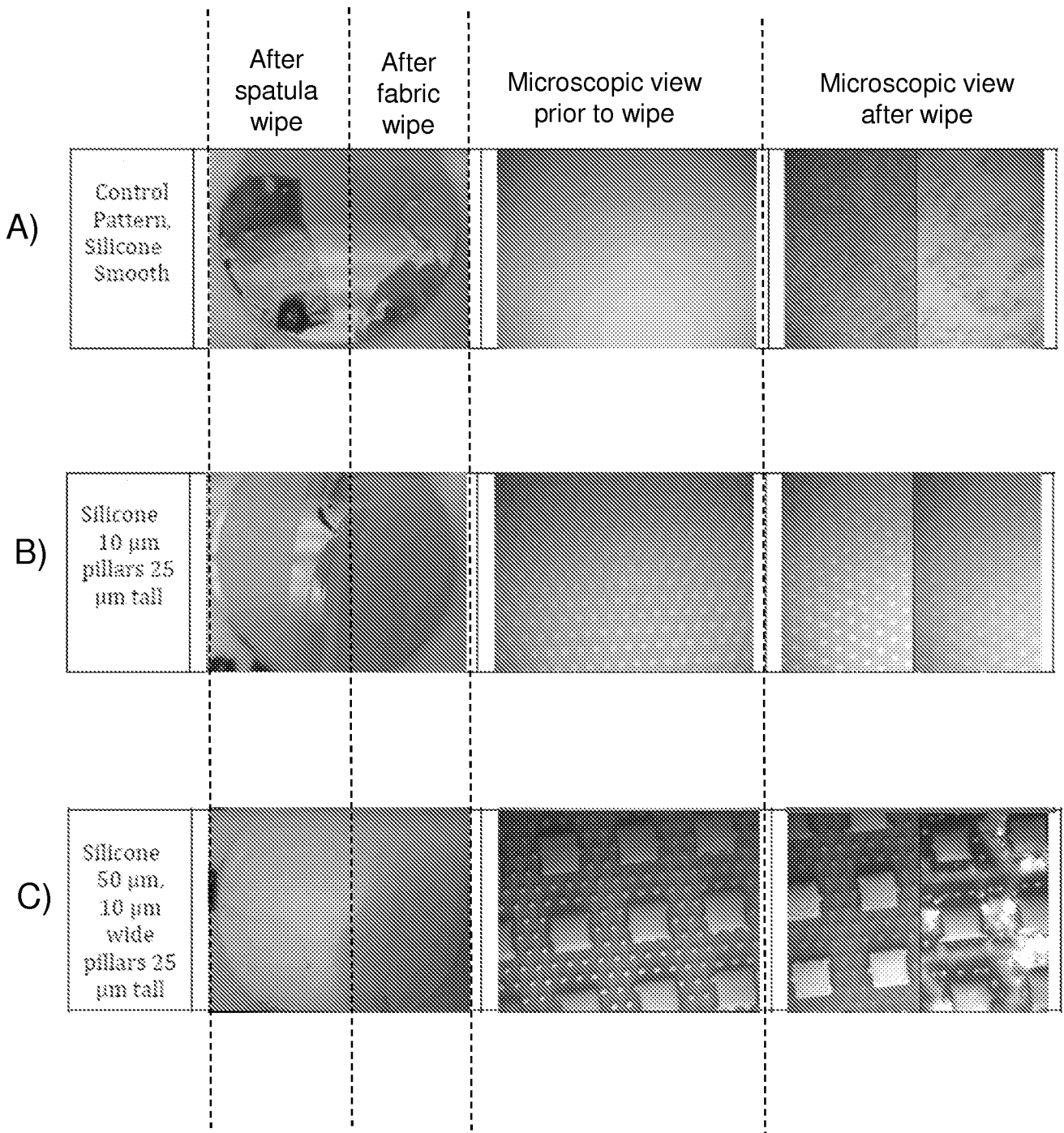


Fig. 14

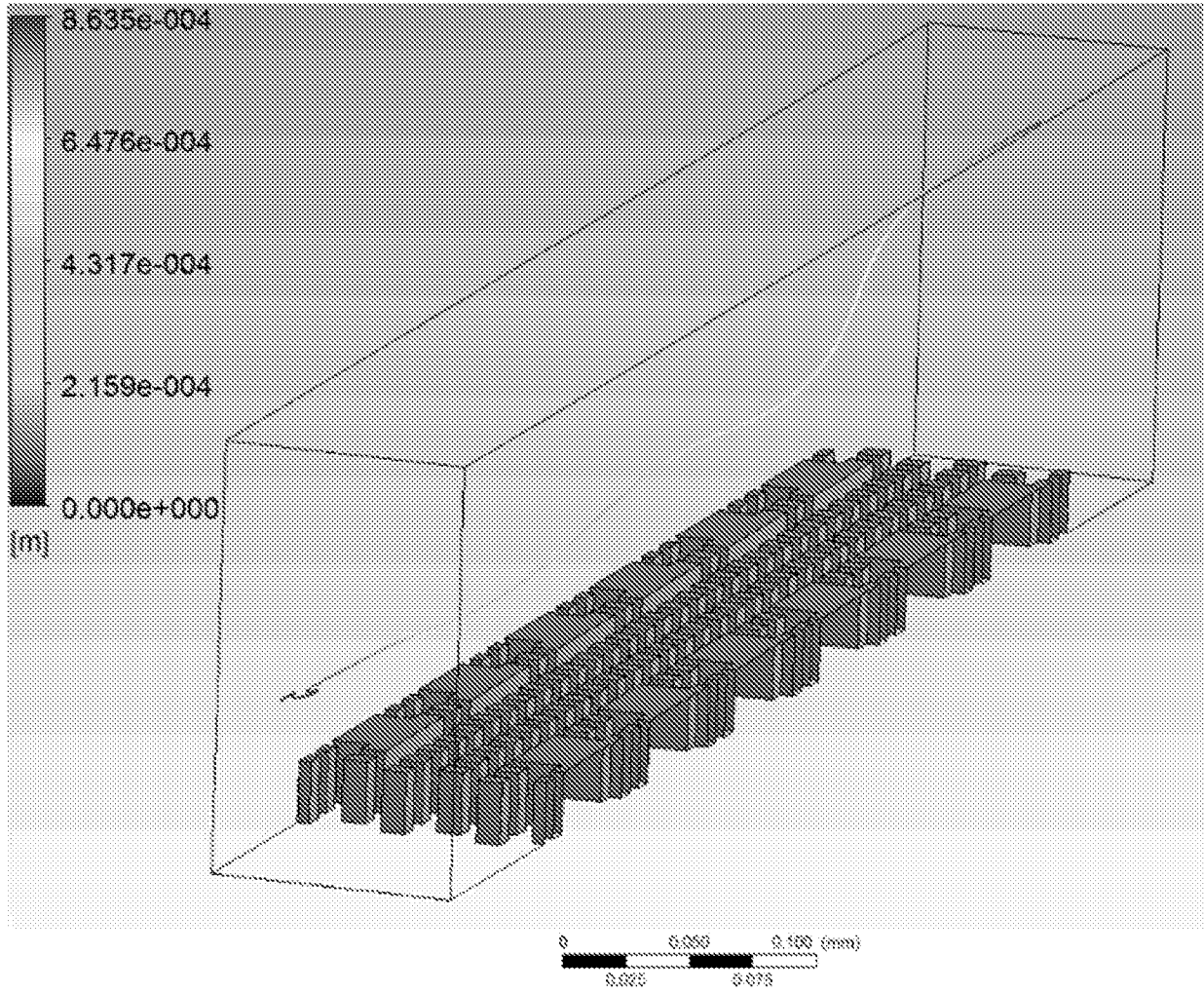


Fig. 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/29961

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12M 3/00; G01N 33/487; B07B 1/00 (2014.01) USPC - 435/7.21; 209/273; 428/131 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8): C12M 3/00; G01N 33/487; B07B 1/00; G06F 19/00; B32B 3/00 (2014.01) USPC: 435/7.21; 209/273; 428/131, 141; 702/19; 264/219 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C.B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Patent; Google; Google Scholar; ProQuest; manipulate, particle, flow, substrate, pattern, protrusion, post, hydrodynamic, sort, separate, direct, blood, leukocyte		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2007/0059781 A1 (KAPUR, R et al.) 15 March 2007; figures 1, 3, 5; paragraphs [0028], [0050]-[0051], [0067], [0070]-[0079], [0095], [0212]-[0213]	1-4, 5/1-4, 27-28 39-40
Y	US 8,076,127 B2 (TANG, Z et al.) 13 December 2011; column 3, lines 48-67; column 11, lines 36-62	39-40
A	US 2007/0026381 A1 (HUANG, LR et al.) 01 February 2007; entire document	1-4, 5/1-4, 27-28, 39-40
A	US 2009/0286300 A1 (LEVOT, S et al.) 19 November 2009; entire document	1-4, 5/1-4, 27-28, 39-40
A	US 2010/0167337 A1 (TSINBERG, P et al.) 01 July 2010; entire document	1-4, 5/1-4, 27-28, 39-40
A	US 2012/0006728 A1 (HUANG, LR et al.) 12 January 2012; entire document	1-4, 5/1-4, 27-28, 39-40
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 28 June 2014 (28.06.2014)		Date of mailing of the international search report 17 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/29961

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 6-26, 29-38
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.