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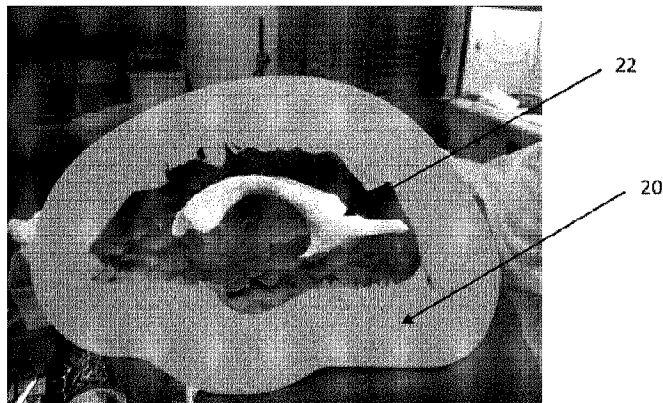
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(57) Abrégé/Abstract:

Disclosed herein are anatomical simulators produced using three dimensional (3D) printing to produce interior components of the simulator. The method of producing void structures in an anatomical phantom, includes 3D printing one or more structures of one or more desired sub- anatomical features using a dissolvable material; supporting and enclosing the one or more structures in an interior of a mold of the anatomical phantom; filling a remaining internal volume in the interior of the mold between an outer surface of the one or more structures and an inner surface of the mold with a liquid precursor of a matrix material selected to mimic anatomical tissue and processing said liquid precursor to form a tissue mimic matrix material; and dissolving the one or more structures with a fluid selected to dissolve said dissolvable material to produce one or more internal cavities within the tissue mimic matrix material.

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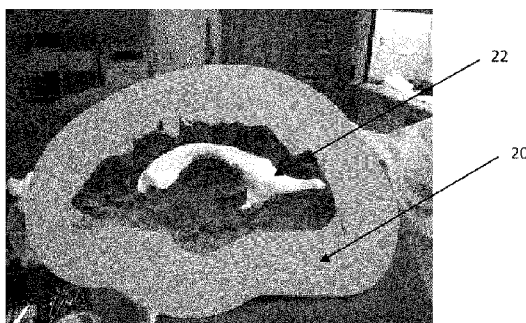


Figure 8

(57) Abstract: Disclosed herein are anatomical simulators produced using three dimensional (3D) printing to produce interior components of the simulator. The method of producing void structures in an anatomical phantom, includes 3D printing one or more structures of one or more desired sub-anatomical features using a dissolvable material; supporting and enclosing the one or more structures in an interior of a mold of the anatomical phantom; filling a remaining internal volume in the interior of the mold between an outer surface of the one or more structures and an inner surface of the mold with a liquid precursor of a matrix material selected to mimic anatomical tissue and processing said liquid precursor to form a tissue mimic matrix material; and dissolving the one or more structures with a fluid selected to dissolve said dissolvable material to produce one or more internal cavities within the tissue mimic matrix material.

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ANATOMICAL SIMULATORS PRODUCED USING 3D PRINTING

FIELD

The present disclosure relates to anatomical phantoms produced using three dimensional (3D) printing, and more particularly it relates to cerebrospinal diffusion phantoms produced using 3D printing techniques.

BACKGROUND

In the field of medicine, phantoms or simulators are very useful. Certain sub-anatomical features present a development / manufacturing challenge. For example, brain ventricles are negative spaces within the brain that allow cerebral spinal fluid (CSF) to circulate and nourish the brain and provide protection against compression. A number of currently used methods to prepare these structures have challenges. One method of creating voids or negative spaces involves using balloons. The balloons are inflated within a liquid hydrogel which is then cooled. After a freeze-thaw cycle (FTC), the balloon is removed from the hydrogel. This removal leaves a scar on the surface and may require post-processing such as back-filling with water and removal of air pockets that develop.

SUMMARY

The present disclosure discloses embodiments of methods of incorporating negative (fluid-filled) spaces as sub-anatomy features in anatomical simulators/phantoms and utilizes printing 3D structures using materials which can be dissolved once the simulator has been produced. In an embodiment the method involves a number of steps including 3D

printing of the negative space required (e.g. brain ventricles with a dissolvable material such as a PVA filament) to produce a printed 3D volume, followed by placement of the printed 3D volume within a mold of an anatomical part. A polyvinyl alcohol (PVA) formulation is then poured into the mould to surround and encapsulate an appropriate number of freeze thaw cycles (FTC) are carried out to produce a tissue phantom with the desired biomechanical properties. The printed 3D volume is then dissolved to produce a fluid filled void having the size and shape of the printed 3D volume.

The filament material used to print the 3D volume selected based on the ability of the resulting 3D volume to maintain its integrity for the course of the FTCs and be able to be dissolved completely leaving a fluid in the negative space. This can be achieved by either choosing a filament material with desirable properties or printing the 3D volume and applying a protective layer of a water resistant material to extend its life until the FTC is complete.

In an embodiment in which the anatomical phantom/simulator is mimicking the brain, to produce the ventricles and cerebral spinal fluid (CSF), the PVA filament can be printed with wall thicknesses to create a final solution of a targeted viscosity. This approach can be used to ensure that the rate of equalization of concentrations of various materials (e.g. PVA and water) is slowed so as to not cause a change in shape in the structure or impinge on the shelf/usable life of the product. Additional materials may also be added beforehand to help retain water in the spaces (such as cornstarch).

Other embodiments could include using alternative filaments such as high impact polystyrene (HIPS) that require another agent such as limonene to dissolve. In addition salt, sugar, sand, silicone may be used.

In a non-limiting embodiment, vascularity may be printed using a red plastic at high resolution with PVA filament as scaffold and placed in a silicone mold and immersed in the hydrogel formulation and a simulator produced by the usual method. The solution would dissolve the scaffold and form a cryogel supporting the printed structure.

An embodiment of a method of producing void structures in an anatomical phantom, comprises:

3D printing one or more structures of one or more desired sub-anatomical features using a dissolvable material;

supporting and enclosing the one or more structures in an interior of a mold of the anatomical phantom;

filling a remaining internal volume in the interior of the mold between an outer surface of the one or more structures and an inner surface of the mold with a liquid precursor of a matrix material selected to mimic anatomical tissue and processing said liquid precursor to form a tissue mimic matrix material; and

dissolving the one or more structures with a fluid selected to dissolve said dissolvable material to produce one or more internal cavities within the tissue mimic matrix material.

Another embodiment of a method of producing void structures in an anatomical phantom, comprises:

a) printing, using 3D printing with silicone, one or more hollow structures of one or more desired sub-anatomical features, connecting the one or more hollow structures to a proximal end of an associated fluid flow channel;

b) supporting and enclosing the one or more hollow structures and associated fluid flow channel in an interior of a mold of the anatomical phantom with a distal end of the associated fluid flow channel being located on an exterior of the mold;

c) filling a remaining internal volume in the interior of the mold between an outer surface of both the one or more hollow structures and the associated vasculature and an inner surface of the mold with a liquid precursor of a matrix material selected to mimic anatomical tissue, the liquid precursor including at least polyvinyl alcohol, and curing the polyvinyl alcohol to produce a polyvinyl alcohol-based hydrogel to form a tissue mimic matrix material; and

d) filling, through the access port, the one or more one hollow structures and their associated vasculature with liquid solutions selected to mimic preselected bodily fluids.

A further understanding of the functional and advantageous aspects of the invention can be realized by reference to the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments disclosed herein will be more fully understood from the following detailed description thereof taken in connection with the accompanying drawings, which form a part of this application, and in which:

Figure 1 is an illustration of an example port-based surgical approach. A port is inserted along the sulci to approach a tumor located deep in the brain.

Figure 2 is an illustration of an example training model in an exploded view, illustrating parts of the base component and the training component.

Figure 3 is an illustration of an example base component of the training model illustrating the tray, the head and the skull assembled together.

Figure 4 is an illustration of an example base component of the training model without the skull section, illustrating fiducials that are important for registration of images acquired using different modalities.

Figure 5 is an illustration of an example base component of the training model, shown containing the brain training component.

Figure 6 is an elevation view of an embodiment of a printed 3D human ventricle.

Figure 7 is perspective view of two human ventricles supported on a support rod.

Figure 8 is a view of the ventricle of **Figure 6** supported in one half of a cerebrospinal simulator.

Figure 9 is a cross-section view of a subanatomical element within a cerebrospinal simulator.

Figure 10 is a cross-section view of a sub-anatomical element found in the cerebrospinal simulator of **Figure 9**.

Figure 11 illustrates anatomical vascularity that would be mimicked using the technique of paramagnetic nanoparticle-doped silicone to additively manufacture (3D-print) MRI contrast-controlled sub-anatomical elements.

DETAILED DESCRIPTION

Various embodiments and aspects of the disclosure will be described with reference to details discussed below. The following description and drawings are illustrative of the disclosure and are not to be construed as limiting the disclosure. Numerous specific details are described to provide a thorough understanding of various embodiments of the present disclosure. However, in certain instances, well-known or conventional details are not described in order to provide a concise discussion of embodiments of the present disclosure.

As used herein, the terms “comprises” and “comprising” are to be construed as being inclusive and open ended, and not exclusive. Specifically, when used in the specification and claims, the terms “comprises” and “comprising” and variations thereof mean the specified features, steps or components are included. These terms are not to be interpreted to exclude the presence of other features, steps or components.

As used herein, the term “exemplary” means “serving as an example, instance, or illustration,” and should not be construed as preferred or advantageous over other configurations disclosed herein.

As used herein, the terms “about” and “approximately” are meant to cover variations that may exist in the upper and lower limits of the ranges of values, such as variations in properties, parameters, and dimensions.

As used herein, the term "patient" is not limited to human patients and may mean any organism to be treated using the planning and navigation system disclosed herein.

As used herein, "hydrogels" refer to materials that are formed by crosslinking polymer chains, through physical, ionic or covalent interactions and are known for their ability to absorb water. An example of a physical interaction that can give rise to a hydrogel is by thermal treatment of the liquid hydrogel precursor which, prior to being subjected to a freeze thaw cycle is a liquid or near liquid. The process of freezing the liquid precursor acts to freeze the water contained in the polymer/water mixture and ice particles causes the polymer strands to be topologically restricted in molecular motion by other chains thus giving rise to the “entanglement” cross linking to produce the hydrogel. Hydrogels that have been produced by a freeze that cycle are sometimes referred to as "cryogels".

Hydrogels characterized by cross linking that are produced through ionic or covalent interactions typically require a cross linking (XL) agent and/or an initiator and activation by methods such as heat or radiation.

The present disclosure provides methods for producing organ structures for embedding in anatomical simulators/phantoms which involves creating negative spaces within the simulator housing, e.g. printing structures with PVA or HIPS filament material and dissolving the structures post simulator production with water or limonene respectively to leave a negative space that corresponds to a ventricle or other void feature of the anatomical part.

In an embodiment, PVA printed structures may be used to create a cystic tumor defined by a high-cellularity boundary and containing a low-cellularity inner domain. In an embodiment, a water soluble raft or scaffold structure can be used to orientate and support a non-soluble structure such as a vascular model so that when a cryogel sets around this structure the rafting dissolves leaving the non-soluble model encapsulated and supported by the cryogel. In addition, the printed 3D structures can be coated with a thin varnish or membrane structure to simulate a pial boundary. As well as creating negative spaces, a printed 3D structure can be fabricated so that it 'softens' instead of dissolves to create a sub-anatomical feature with high precision and predictable haptic properties.

When performing surgical and / or diagnostic procedures that involve the brain, neurosurgical techniques such as a craniotomy, or a minimally invasive procedure such as an endo-nasal surgery or a port based surgical method, may be performed to provide access to the brain. In such procedures, as indicated, the medical procedure is invasive of the mammalian head. For example, in the port-based surgical method

illustrated in **Figure 1**, a port **105** is inserted along the sulci **110** of the brain **120** to access a tumor **130** located deep in the brain.

According to embodiments provided herein, the simulation of such procedures may be achieved by providing a brain model that is suitable for simulating the surgical procedure through one or more layers of the head. Such a procedure may involve perforating, drilling, boring, punching, piercing, or any other suitable methods, as necessary for an endo-nasal, port-based, or traditional craniotomy approach. For example, some embodiments of the present disclosure provide brain models comprising an artificial skull layer that is suitable for simulating the process of penetrating a mammalian skull. As described in further detail below, once the skull layer is penetrated, the medical procedure to be simulated using the training model may include further steps in the diagnosis and/or treatment of various medical conditions. Such conditions may involve normally occurring structures, aberrant or anomalous structures, and/or anatomical features underlying the skull and possibly embedded within the brain material.

In some example embodiments, the brain model is suitable for simulating a medical procedure involving a brain tumor that has been selected for resection. In such an example embodiment, the brain model is comprised of a brain material having a simulated brain tumor provided therein. This brain material simulates, mimics, or imitates at least a portion of the brain at which the medical procedure is directed or focused.

The simulation of the above described medical procedure is achieved through simulation of both the surgical procedure and the

associated imaging steps that are performed prior to surgery (pre-operative imaging) and during surgery (intra-operative imaging). Pre-operative imaging simulation is used to train surgical teams on co-registration of images obtained through more than one imaging methodology such as MR, CT and PET. Appropriate co-registration geometrically aligns images from different modalities and, hence, aids in surgical planning step where affected regions in the human body are identified and suitable route to access the affected region is selected. Another use of pre-operative imaging is to train the surgical team and radiologists on optimizing the imaging parameters so that clinically relevant images are acquired prior to the surgical procedure. For example, pre-operative MR images need to be acquired in a specific manner to ensure that the acquired data can be used to generate tractography information, such as Diffusion Tensor Imaging (DTI), which shows the location and direction of the brain tracks which are not visually observable by the surgeon. Intra-operative imaging is used to guide the surgeon through accurate surgical intervention while avoiding damaging the brain tracks if possible. Surgical intervention includes accessing a previously identified affected region in the human body and subsequent resection of affected tissue.

Referring to **Figures. 2-5**, an exploded view of an example model or phantom shown generally at **100** is provided that is suitable for use in training or simulation of a medical procedure which is invasive of a mammalian head. The training model **100** may be adapted or designed to simulate any mammalian head or a portion thereof. It is to be understood

that the person to be trained may be selected from a wide variety of roles, including, but not limited to, a medical doctor, resident, student, researcher, equipment technician, or other practitioner, professionals, or personnel. In other embodiments, the models provided herein may be employed in simulations involving the use of automated equipment, such as robotic surgical and/or diagnostic systems.

Referring now to **Figure 2**, an exploded view of an example implementation of training model **100** is shown that includes a base component and a training component. The base component is comprised of a tray component **200** and a head component. The head component is comprised of a bowl component **210** and a skull component **220**. The training component may be comprised of a brain **230** with the following layers: dura, CSF (cerebrospinal fluid), vessels, white matter, grey matter, fiber bundles or tracks, target tumors, or other anomalous structures. The training component may also include the aforementioned skull component **220** when crafted in a skull mimicking material. Optionally, the training model **100** may be also comprised of a covering skin layer (not shown). Further, the base component may include a holder **240** provided on the tray **200** to facilitate easy mounting of fiducials or reference points for navigation.

Referring to **Figures 3 to 5**, the tray component **200** forming part of the base component defines a training receptacle which includes a pedestal section **242** which is sized and configured for receipt of the bowl component **210** therein. Thus the training component is sized, configured or otherwise adapted to be compatible with, or complementary to the base

component, and particularly the training component receptacle, such that the base component and the training component may be assembled to provide the assembled training model **100**.

The base component may have any size, shape and configuration capable of maintaining the training component, mounted within the training component receptacle, in a position suitable for performing the medical procedure to be trained. This base component comprises features that enable registration, such as fiducials, touchpoint locations, and facial contours for 3D surface scanning, MR, CT, OCT, US, PET, optical registration or facial registration. Furthermore, the base component is adapted or configured to maintain the training component in a relatively stable or fixed position throughout the performance of the medical procedure to be simulated during the training procedure. The base component provides both mechanical support during the training procedure and aids in the proper orientation of the training components to mimic actual positioning of a patient's head during the surgical procedure.

Referring to **Figures 2 and 3**, as noted above, the base component may be comprised of a head component **210** and a tray component **200**. The tray component **200** is sized, configured or otherwise adapted to be compatible with, or complementary to the head component **210**. The tray component **200** is adapted or configured to maintain the head component **210** in a relatively stable or fixed position throughout the performance of the imaging or medical procedure to be simulated. This may be accomplished with the use of a mechanical feature such as a snap mechanism that exists to affix the head component **210** to the tray

component **200**. The tray component **200** may contain a trough **244** to catch liquids, and insertion points to affix hardware to aid with image registration and/or the medical procedure to be trained.

The head component **210** is sized, configured or otherwise adapted to be compatible with, or complementary to the tray component **200** and the training component. The head component **210** is adapted or configured to maintain the training component **230** (located under skull component **220** in a relatively stable or fixed position throughout the performance of the medical procedure to be simulated. This head component **210** is adapted or configured to enable anatomically correct surgical positioning. This may include affixing the head component **210** with a surgical skull clamp or headrest, for example a Mayfield skull clamp. This head component **210** is also adapted or configured to enable anatomically correct imaging positioning for any contemplated imaging modality including, but not limited to, MR, CT, OCT, US, PET, optical registration or facial registration. For example the head component **210** may be positioned in a supine position within an MRI apparatus to enable anatomically accurate coronal image acquisition.

In some embodiments, the head component **210** is shaped or configured to simulate a complete or full skull. In other words, the training component comprises bowl section **210** and skull section **220**, while the bowl section **210** comprises a further portion of a complete skull and head. In some embodiments, as shown in **Figure 2**, the head component i.e., bowl section **210** and skull section **220**, and training component **230** together provide a complete simulated skull or together provide a

simulated head including skull **220** and brain **230**. The simulated head provided by the training model **100** enhances the reality of the overall simulation training experience.

In addition, the base and training components of the training model **100**, and particularly the head component, may also include one or more external anatomic landmarks or fiducial locations **400**, as shown in **Figure 4**, such as those likely to be relied upon by the medical practitioner for image registration for example, touchpoints, the orbital surface, nasal bone, middle nasal concha, inferior nasal concha, occipital bone, nape, and nasal passage. These features will aid in registering the training component with the preoperative images, such as MR, CT, OCT, US, PET, so that the surgical tools can be navigated appropriately.

In this regard, navigation to establish the location of the hole or passage through the skull of the patient during the craniotomy procedure is often critical for the success of the medical procedure. Accordingly, external anatomic landmarks and/or touchpoints are provided by the simulated head in order to provide training on the correct registration of the training model with the acquired images. These anatomic landmarks and touchpoints may be utilized for attaching registration hardware, for example a facial registration mask or fiducial landmark. Thus, the training model, and particularly the simulated head, are sized, configured and shaped to approximate and closely resemble the size, configuration and shape of the head of a patient on which the medical procedure is to be performed. In other words, the head component may be both 'life-like' and 'life-sized'.

The base component may be comprised of any composition or material suitable for providing the training component receptacle, and may be suitable for being cast, molded or otherwise configured to provide or support the simulated head when assembled with the training component. For instance, the base component may be comprised of any suitable casting compound, casting composition or plaster. The base component may be comprised of a material that is rigid, non-reflective, non-ferrous, non-porous, cleanable, and lightweight, for example a urethane or acrylonitrile butadiene styrene (ABS). In addition, the bowl **210** and skull **220** components of the base component may be comprised of a material that is visible by the imaging procedure of interest to enable registration. The material for the bowl **210** and skull **220** components of the base may therefore be selected to be visible by MR, CT, and/or PET.

As shown in **Figure 5**, the training component **230** and the base component **210** are complementary or compatible such that when the training component **230** is mounted on the pedestal **242** in the training component receptacle in tray **200**, together they provide the training model. Furthermore, the configuration and dimensions of the training component **230** and the base component **210** are complimentary or compatible such that the training component **230** may be received and fixedly or releasably mounted in the base component **210**.

In some embodiments, in order to permit the replacement or substitution of the training component **230**, the training component is detachably or releasably mounted in the base component **210**. Any detachable or releasable fastener or fastening mechanism may be used

which is capable of securing the training component **230** in the receptacle, while also permitting the training component **230** to be readily detached, released or removed as desired or required. In one embodiment, the training component **230** is releasably or detachably mounted within the base component **210**, specifically the training component **230** is held within the base component **210** to emulate the mechanical fixation of the brain in the skull.

Thus, in the present example embodiment, the training component **230** may be removed from the base component **210** and replaced with an alternate, replacement or substitute training component as desired or required by the user of the training model. For instance, a replacement training component **230** may be required where the previous training component **230** is damaged or modified during the training of the procedure. An alternate training component **230** may be adapted or designed for use in the training of the performance of a specific medical procedure or condition of the patient, allowing for the reuse of the base component **210**.

Alternatively, as indicated, the training model **100** may not include the base component **210**. In this instance, the other components comprising the training model **100**, such as the training component **230** in isolation, may be supported directly by a supporting structure or a support mechanism (not shown) that does not look like a mammalian head. Specifically, the supporting structure may securely maintain the training component **230**, without the other components of the training model, in the desired orientation. In such an embodiment, the training component **230**

may be releasably attached or fastened with the supporting structure such that the training component **230** may be removed from the supporting structure and replaced with an alternate, replacement or substitute training component **230** as desired or required by the user of the training model.

Referring to **Figures 6**, there is shown an elevation view of a printed 3D volume printed in the shape and size of a human ventricle **22**. **Figure 7** shows a perspective view of two such ventricles **22** supported on a support member **24**. **Figure 8** shows one half of a human brain simulator mold **20** with one of the printed ventricles **22** supported in the simulator half. Once the one or more ventricles **22** are supported, the two halves of the simulator are joined and sealed together and then filled with a matrix material used to mimic brain tissue. The process of manufacturing simulator **20** is further explained in international application PCT/CA2014/050975 entitled "**PHANTOM PRODUCTION TOOL**".

In an embodiment, the assembled brain simulator may be filled with a matrix material which is chosen to be magnetic resonance (MR) compatible and give MR signals including signals in the range of human tissue. The matrix material can be a polyvinyl alcohol (PVA) cryogel that is subjected to freeze thaw cycles, PVA solution, water, mineral oil or a solution of salt such as copper sulfate or similar materials. Exemplary formulations are disclosed in international application **WO/2015/003271** entitled: "**SURGICAL TRAINING AND IMAGING BRAIN PHANTOM**", corresponding to **US Patent Publication US2017291359**. Once assembled and the brain tissue mimic material established, the 3D

ventricle volumes are then dissolved leaving a fluid filled void having the size and shape of the human brain ventricles.

Figure 9 is a cross-section view of a sub-anatomical element within a cerebrospinal simulator contained in a mold housing **36** used during the method of casting the simulator anatomical part, with mold **36** configured for producing a brain simulator. In **Figure 9**, the negative (fluid-filled) space is generated through the use of silicone additive manufacturing technology. In this embodiment, sub-anatomical features of the body are constructed using micro-layers of silicone. Silicone is an elastomeric material that is effective as a tissue simulator. The silicone layers are built up by multitudes of silicone droplets that are UV cross-linked into an elastomeric material.

The left image of **Figure 9** shows silicon mold **20** housing a cavity or negative space **32**. Suspended within the cavity **32** by a filling port **34** is a silicone sub-anatomical element **30**. Sub-anatomical element **30** may be designed to mimic ventricles **22** as shown in **Figures 6, 7 and 8**.

The image on the right hand side of **Figure 9** is a section view of section taken along line **A-A** on the image on the left hand side. This image is cross-hatched to show different materials. Mold casing **36** may be constructed of aluminum or other machined light alloys or it can also be laser sintered via additive manufacturing. Mold **20** is preferably made of silicone, however, other materials such as plastic or rubber which have similar ductility could also be used. Filling port **34** is also illustrated in detail here. Filling port **34** is preferably a cylindrical rod or straw that is additively manufactured (i.e., 3D-printed) via layering of ultra-violet (UV) cured

silicone. Filling port **34** connects to sub-anatomical element **30** to enable filling of element **30** with various mediums at various stages of the production process (e.g. pre or post- FTC).

Figure 10 is a cross-section view of a sub-anatomical element found in the cerebrospinal simulator of **Figure 9**. The sub-anatomical element **30** is connected to filling port **34** and is designed to include internal cavities and feature wall thicknesses appropriate to simulate the tactile response of respective tissues to surgical instrumentation. These features are constructed with linked tubular structures that link the internal cavity structures (or network thereof) to the exterior of the mold. For example, in another embodiment, a sub-anatomical element **30** may be linked to other sub-anatomical elements (e.g. ventricles **22** as seen in **Figure 8**) via a tubular structure similar to the filling port **34** to enable filling with various liquids. As a further example, constructed feature in **Figure 10** can be used to create a simulator with a network of sub-anatomical structures which can be filled with a multitude of materials (e.g., hematoma structure filled with simulated blood clotting material connected to a vein structure filled with simulated blood).

In addition with regards to commonly found tumors in the brain such as GBMs there exist a multitude of materials that may be employed to mimic not only the tensile and tactile properties of the tumors but also their infusion properties. This may be useful when employed in a cerebro-spinal simulator in that it may facilitate the user to simulate infusion of various therapeutic agents directly into a tumor mimicking material allowing them to perform a mock procedure and potentially demonstrate results.

Intraparenchymal drug and cell delivery using catheters is one potential example. An embodiment of a material that may mimic the infusion properties of the brain includes agarose gels of varying concentrations such as those described by the paper [Chen, Zhi-Jian, et al. "**A realistic brain tissue phantom for intraparenchymal infusion studies.**" *Journal of neurosurgery* 101.2 (2004): 314-322.].

Furthermore, integrating the capability of variable-density printing within these networks of sub-anatomical features enables high resolution simulation of tissue structures. This is useful because biomaterials do not typically exhibit consistent densities, thus creating a simulation tool that exhibits variable densities or variable diffusive properties such as commonly used to mimic the fluidic diffusion properties of brain tissue such as grey matter or commonly found glioblastomas. As an example, Wacker Chemie has created a new silicone 3D printing technology that would enable production of constructed features of **Figures 9 and 10**.

In further embodiments (not shown), the use of bi-photon polymerization to create nano / micro scale structures can be considered. As an example, a silicone sub-anatomical structure can be 3D printed that includes cavities for filling with fluid. Other micro structures that may be 3D printed using the bi-photon polymerization may be embedded into the sub-anatomical structure. The other micro structures may also have micro grooves appropriate for generating diffusion.

Halfway through printing of the silicone sub-anatomical structure, the 3D printing is paused, a plurality of bi-photon polymerized micro-structures **38** in **Figure 10** are inserted into the sub-anatomical structure. Then the

silicone printing is completed. This process of inserting the bi-photon polymerized micro structures is repeated to create a pattern array of tractography within the scanned simulator that accurately depicts diffusion in the anatomical region of interest. Using this combined methodology, one can accurately simulate micro structures (e.g., axons) and macro structures (e.g., hematomas, ventricles) within the brain, vascularity, tumours, diseased white matter cartilage, bone, or neuro sub-anatomical structures.

The visibility of internal body structures in MRI is often improved through the use of contrast media, specifically, through the use of ultra-small superparamagnetic and paramagnetic particles. These particles work by shortening (in some cases increasing) the T_1/T_2 relaxation time of water protons via interactions with the particle. Thermally driven motion of the strongly paramagnetic metal ions in the contrast agent generate oscillating magnetic fields that provide the relaxation mechanisms that enhance the rate decay of the induce polarization.

In another embodiment, the additive manufacturing (3D-printing) of UV-cured silicone sub-anatomical structures may be supplemented through addition of superparamagnetic/paramagnetic nanoparticles into the UV-curable silicone. There are various nanoparticles that could be integrated into the silicone to generate this effect. Gadolinium (III) is often used for MR contrast enhancement of vessels in MR angiography or brain tumours. Iron oxide, manganese are used as well. Novel carbon nanohybrids (graphene oxide/ metallofullerenes) have also been successfully utilized as efficient MRI contrast agents and are an

improvement to Gadolinium due to there reduced toxicity, (see Cui, R, et al. Novel carbon nanohybrids as highly efficient magnetic resonance imaging contrast agents. Nano Research 2015, 8 (4): 1259-1268.)

The paramagnetic nanomaterials would be mixed with the silicone in before UV-curing. The ratio of nanoparticles to silicone would fluctuate according to the biomaterial and/or disease state being mimicked. A person skilled in the art would be able to determine which particles and which concentrations are most appropriate for the biomaterial and/or disease state being mimicked.

Through combining the method explained in this embodiment with those previously described, a surgical simulator may be produced that includes various fluid-filled, sub-anatomical elements, each with MRI characteristics and tactile response characteristics that accurately mimic biological tissues at various states. This may include, but is not limited to, vascularity, tumours, cartilage, bone, and sub-anatomy of the brain.

Figure 11 illustrates the anatomical vascularity **40** that would be mimicked using the technique of paramagnetic nanoparticle-doped silicone to additively manufacture (3D-print) MRI contrast-controlled sub-anatomical elements. This embodiment would add an additional level of realism and therefore training utility to the simulator. Should a surgical trainee incise the silicone fluid-filled cavity with a blade it could 'bleed' simulated blood.

Incorporating this embodiment with the "**SURGICAL TRAINING AND IMAGING BRAIN PHANTOM**" disclosed in PCT WO 2015/003271 the product would enable surgical trainees to have a visual reference for

anatomical regions of interest (e.g. fluid-filled vascularity) during their pre-operative trajectory planning as well as during navigation-guided surgical port cannulation, and tumour resection.

While the Applicant's teachings described herein are in conjunction with various embodiments for illustrative purposes, it is not intended that the applicant's teachings be limited to such embodiments. On the contrary, the applicant's teachings described and illustrated herein encompass various alternatives, modifications, and equivalents, without departing from the embodiments, the general scope of which is defined in the appended claims.

Except to the extent necessary or inherent in the processes themselves, no particular order to steps or stages of methods or processes described in this disclosure is intended or implied. In many cases the order of process steps may be varied without changing the purpose, effect, or import of the methods described.

The specific embodiments described above have been shown by way of example, and it should be understood that these embodiments may be susceptible to various modifications and alternative forms. It should be further understood that the claims are not intended to be limited to the particular forms disclosed, but rather to cover all modifications, equivalents, and alternatives falling within the spirit and scope of this disclosure.

WHAT IS CLAIMED IS:

1. A method of producing void structures in an anatomical phantom, comprising:

a) printing, using 3D printing with silicone, one or more hollow structures and associated vasculature of one or more desired sub-anatomical features, connecting the one or more hollow structures to a proximal end of an associated fluid flow channel;

b) supporting and enclosing the one or more hollow structures and the associated fluid flow channel in an interior of a mold of the anatomical phantom with a distal end of the associated fluid flow channel being located on an exterior of the mold;

c) filling a remaining internal volume in the interior of the mold between an outer surface of both the one or more hollow structures and associated vasculature and an inner surface of the mold with a liquid precursor of a matrix material selected to mimic anatomical tissue, the liquid precursor including at least polyvinyl alcohol, and curing the polyvinyl alcohol to produce a polyvinyl alcohol-based hydrogel to form a tissue mimic matrix material; and

d) filling, through an access port, the one or more one hollow structures and the associated vasculature and inner surface of the mold with liquid solutions selected to mimic preselected bodily fluids.

e) producing one or more microstructure, using bi-photon polymerization, in one or more positions in a wall of the one or more hollow structures that restrict radial water diffusion in order to generate DTI tractography.

2. The method according to claim 1, wherein the associated fluid flow channel is configured to mimic the associated vasculature connected to the one or more hollow structures.

3. The method according to claim 1, wherein curing the polyvinyl alcohol includes subjecting the polyvinyl alcohol to a preselected number of freeze-thaw cycles.

4. The method according to claim 1 wherein the one or more microstructures is produced partway through the step of 3D printing of the one or more hollow structures such that the 3D printing is paused and then the one or more microstructures is produced in the one or more positions using bi-photon polymerization, after which the 3D printing is resumed to completion, wherein a pattern array of DTI tractography within the wall of the one or more hollow structures is produced which depicts diffusion in an anatomical region of interest.

5. The method according to claim 4 wherein the pattern array of DTI tractography is configured to simulate any one or combination of one or more microstructure within the anatomical region of interest.

6. The method according to claim 5 wherein the anatomical region of interest is a human brain.

7. The method according to claim 5 wherein the one or more microstructures is selected from a group consisting of axons, hematomas, ventricles, vascularity, tumours, diseased white matter cartilage, bone, or neuro sub-anatomical structures.
8. The method according to claim 1 wherein the 3D printing is paused substantially midway through the 3D printing of the one or more hollow structure such that the microstructure is produced substantially in a middle of the wall of said one or more hollow structures.
9. The method according to claim 1 wherein any one or combination of paramagnetic and superparamagnetic nanoparticles are incorporated into the silicone to provide T_1/T_2 contrast manipulation.
10. The method according to claim 9 wherein the any one or combination of paramagnetic and superparamagnetic nanoparticles comprise any one or combination of gadolinium (III), iron oxide, and carbon nanohybrids.
11. The method according to claim 10 wherein the carbon nanohybrids are any one or combination of graphene oxide and metallofullerenes.

REPLACEMENT SHEET

1/9

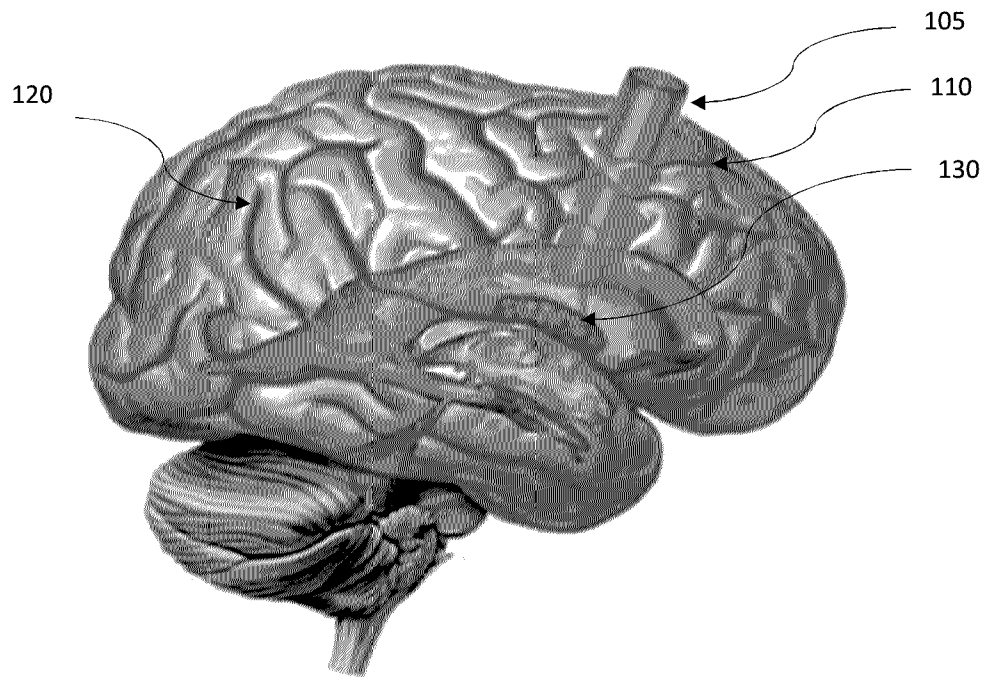
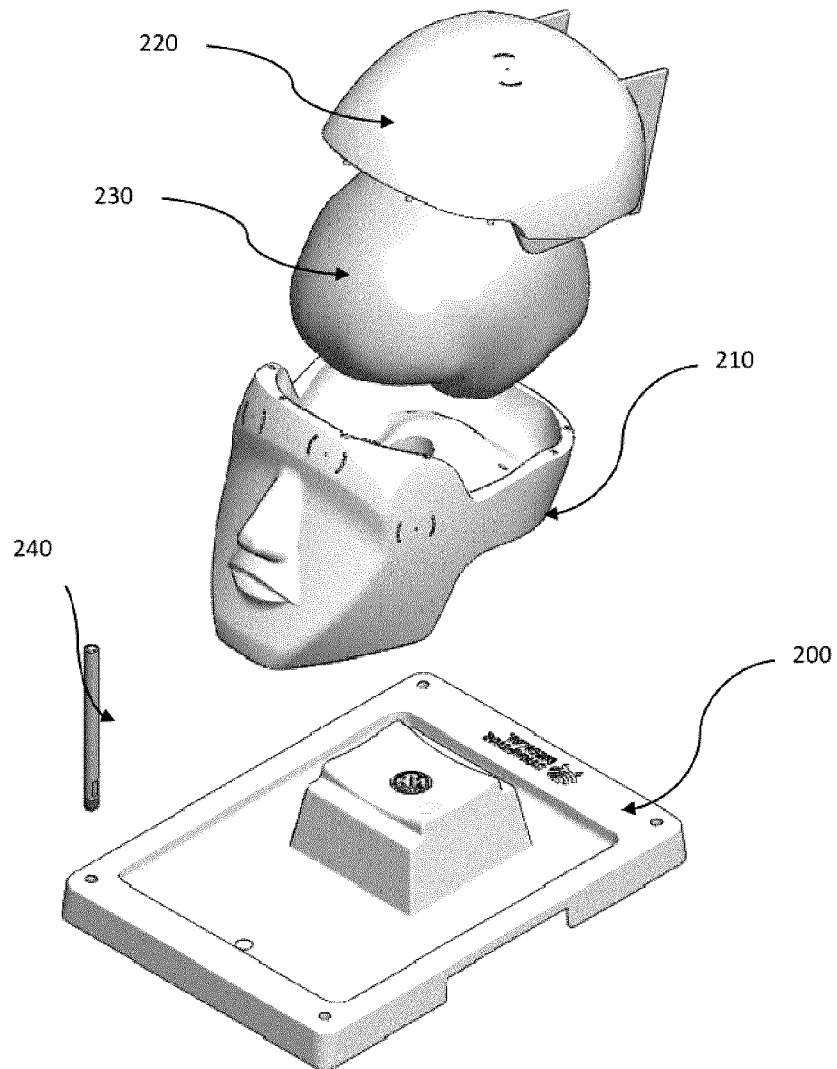


Figure 1

2/9**Figure 2**

REPLACEMENT SHEET

3/9

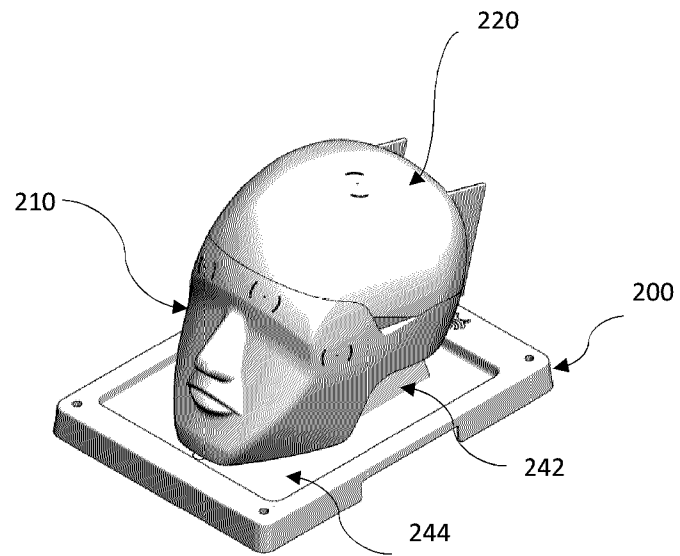


Figure 3

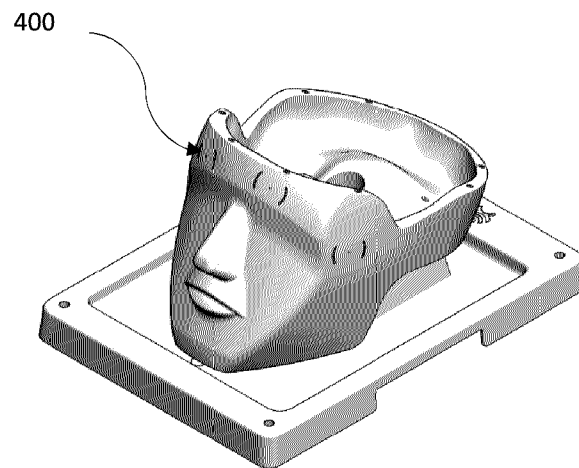


Figure 4

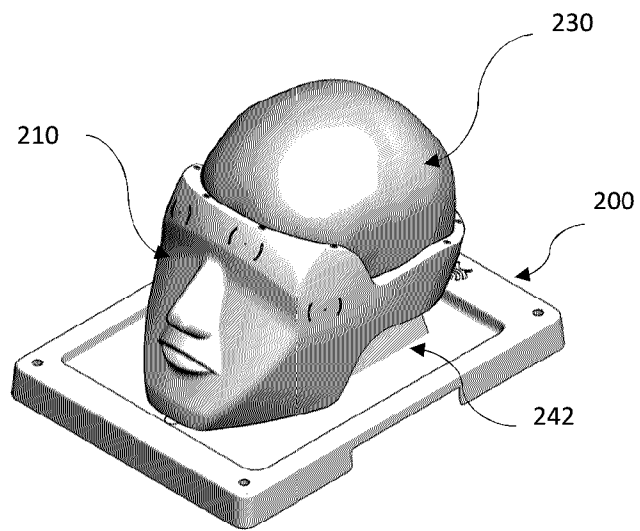
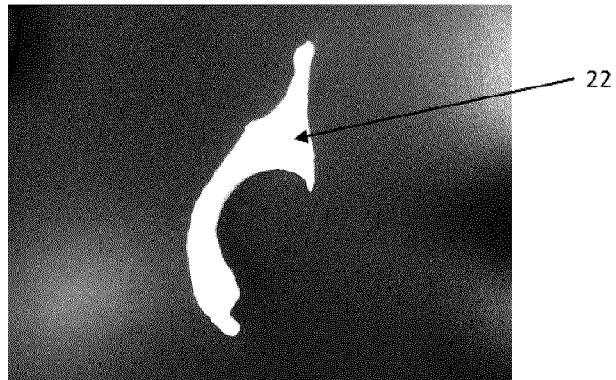
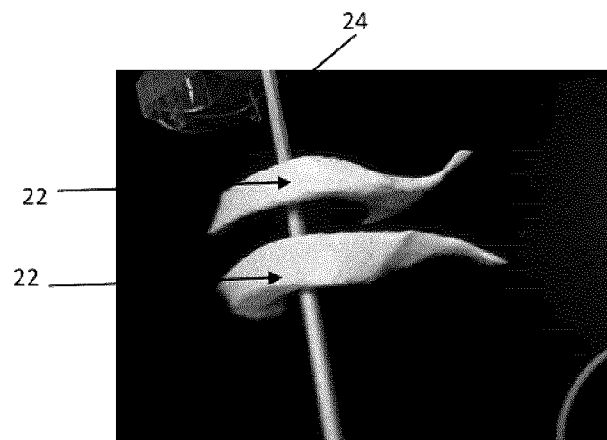


Figure 5

5/9**Figure 6****Figure 7**

6/9

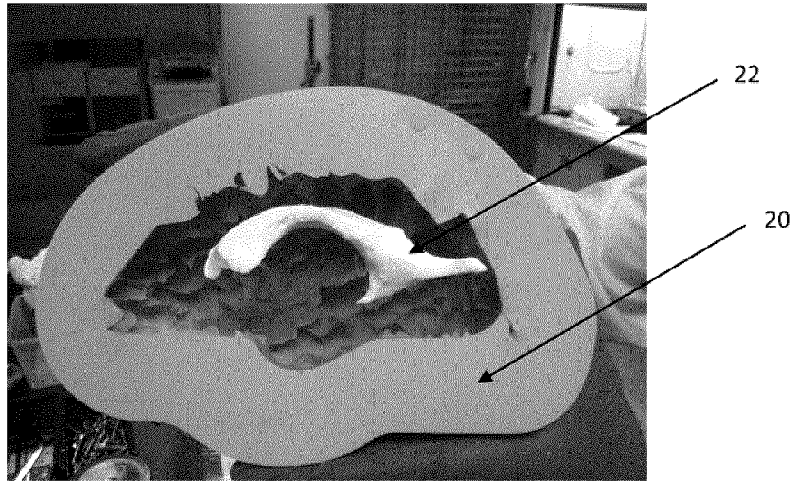


Figure 8

7/9

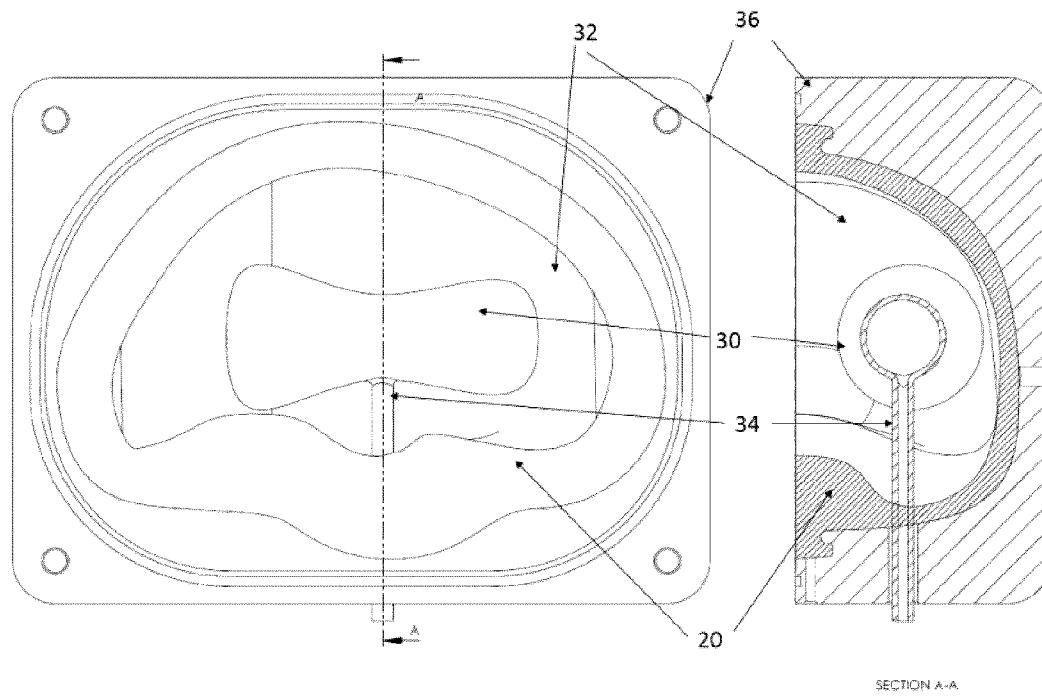


Figure 9

8/9

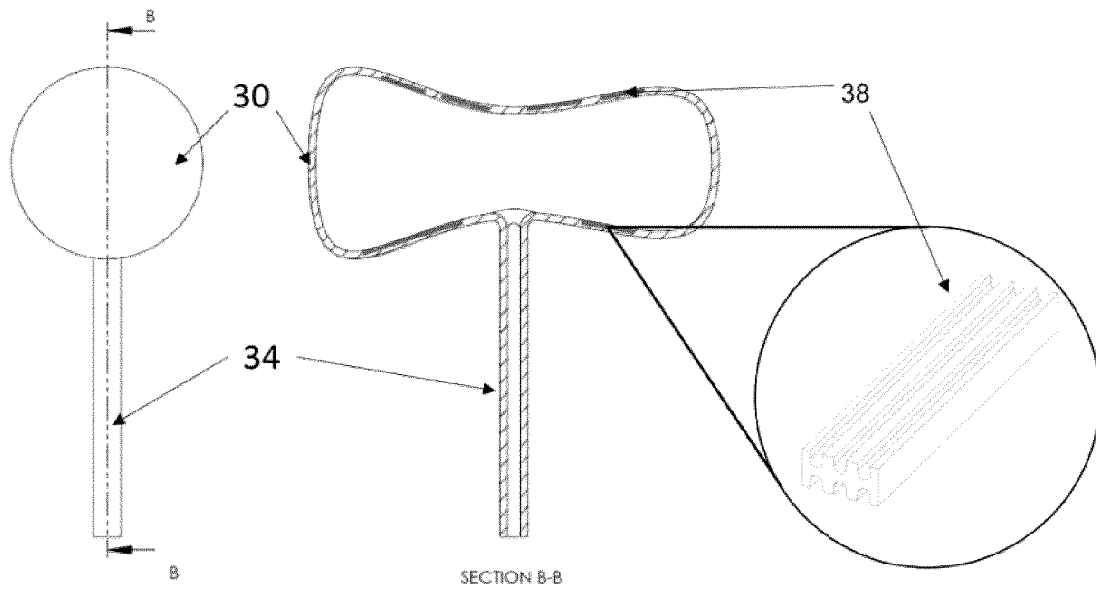


Figure 10

9/9

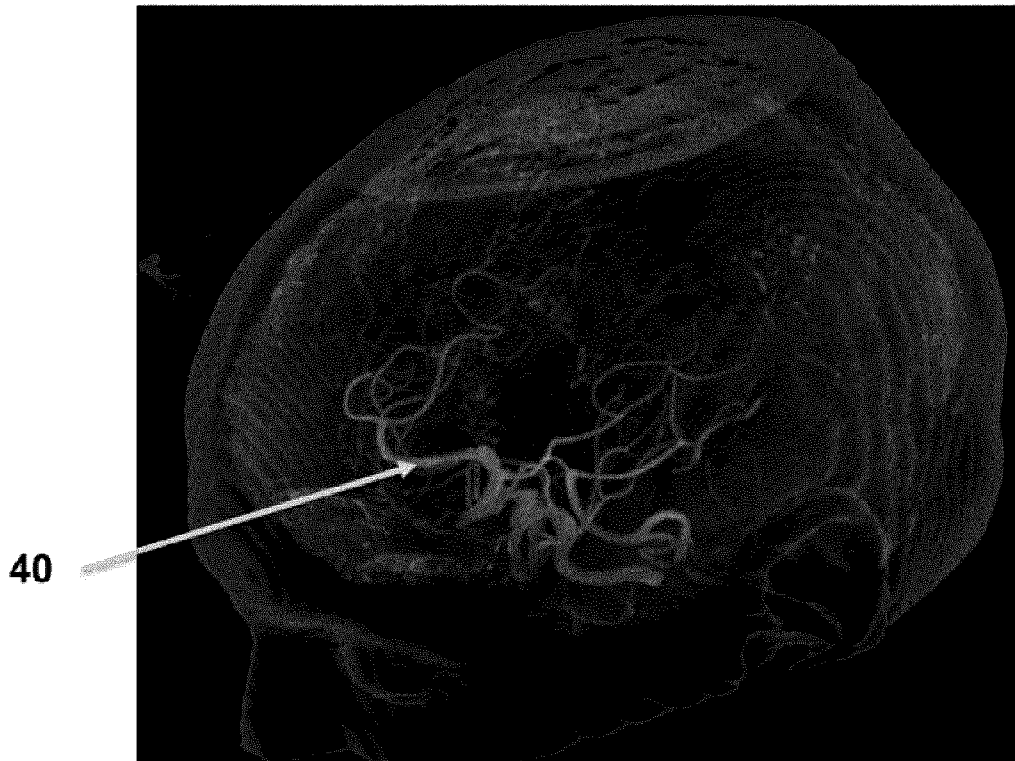


Figure 11

