Perfusion Of A Semi-Permeable Tissue-Containing Block By Means Of A Pressure Gradient In A Circulatory Bioreactor

Tech ID: 34885 / UC Case 2026-592-0

BACKGROUND

Problem 1: In conventional static or rocking 3D culture systems, nutrients and oxygen reach cells mainly by diffusion, which is too slow to penetrate thick tissues (>200 µm). This leads to necrotic cores and poor viability or maturation. By generating a controlled pressure gradient across the tissue, the invention drives convective perfusion (bulk flow) through the tissue block or hydrogel. This allows continuous exchange of nutrients, gases, and signaling molecules deep inside, extending viable tissue thickness and lifespan.

Problem 2: In certain tissues, fluidic cues also shape tissue organization and function. Most organoid or 3D culture systems lack physiologically relevant interstitial flow, an important mechanical cue for morphogenesis, endothelial alignment, and extracellular matrix remodeling. The pressure-driven perfusion creates interstitial shear forces and gradients similar to those in living tissues, improving differentiation and structural organization.

Problem 3: Many bioreactors rely on imprecise or uncontrolled flow rates and pressures that do not guarantee a stable or known pressure difference across the tissue. For example, gravity fed microfluidic apparatuses which generate pressure differentials have their pressure gradient constantly changing because the difference in fluidic column height changes as the fluid equilibrates. Rocker based "perfusion" systems have a similar problem because rocking is inherently oscillatory and causes the involved forces to be constantly changing.

Problem 4: Capillary to tissue pressure gradients in vivo are on the order of 10-15 mmHg. This is 10 or more times higher than generated by gravity fed or rocker perfusion systems. We anticipate needing a larger pressure gradient for perfusion in thicker tissues as well, since we seek to perfuse tissues much thicker than normal intercapillary distances. In our system, we have successfully generated gradients as high as 200 mmHg (limited by tissue integrity, not by our fluidic actuators.)

Problem 5: Surgical specimens or organ slices can’t easily be perfused with microfluidic chips, which are typically designed for engineered scaffolds. By using two fluidic compartments sandwiching any tissue-containing block or hydrogel, the system can adapt to irregular natural tissue samples, not just engineered constructs.

Problem 6: Self-contained culture systems with pressure gradient generation within a closed device (such as gravity and rocker devices) often make it difficult to monitor metabolites, oxygen, or pH dynamically. Because fluid continuously circulates through defined compartments, it can integrate inline sensors (e.g., pressure, oxygen, conductivity, FTIR) for real-time monitoring and feedback control.

Problem 7: Traditional perfusion systems often require high media volumes or continuous replacement, increasing reagent costs and diluting secreted factors of interest. This design allows for a closed fluidic loop circulation system minimizes media consumption while maintaining exchange efficiency. The ability to adjust flow and pressure allows optimization for either steady-state homeostasis or

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OTHER INFORMATION

KEYWORDS

fluid pressure, tissue block, organoid, tissue perfusion, bioreactor, sealed bioreactor

CATEGORIZED AS

- **Engineering**
  - Engineering
- **Sensors & Instrumentation**
  - Process Control
  - Scientific/Research

RELATED CASES

2026-592-0

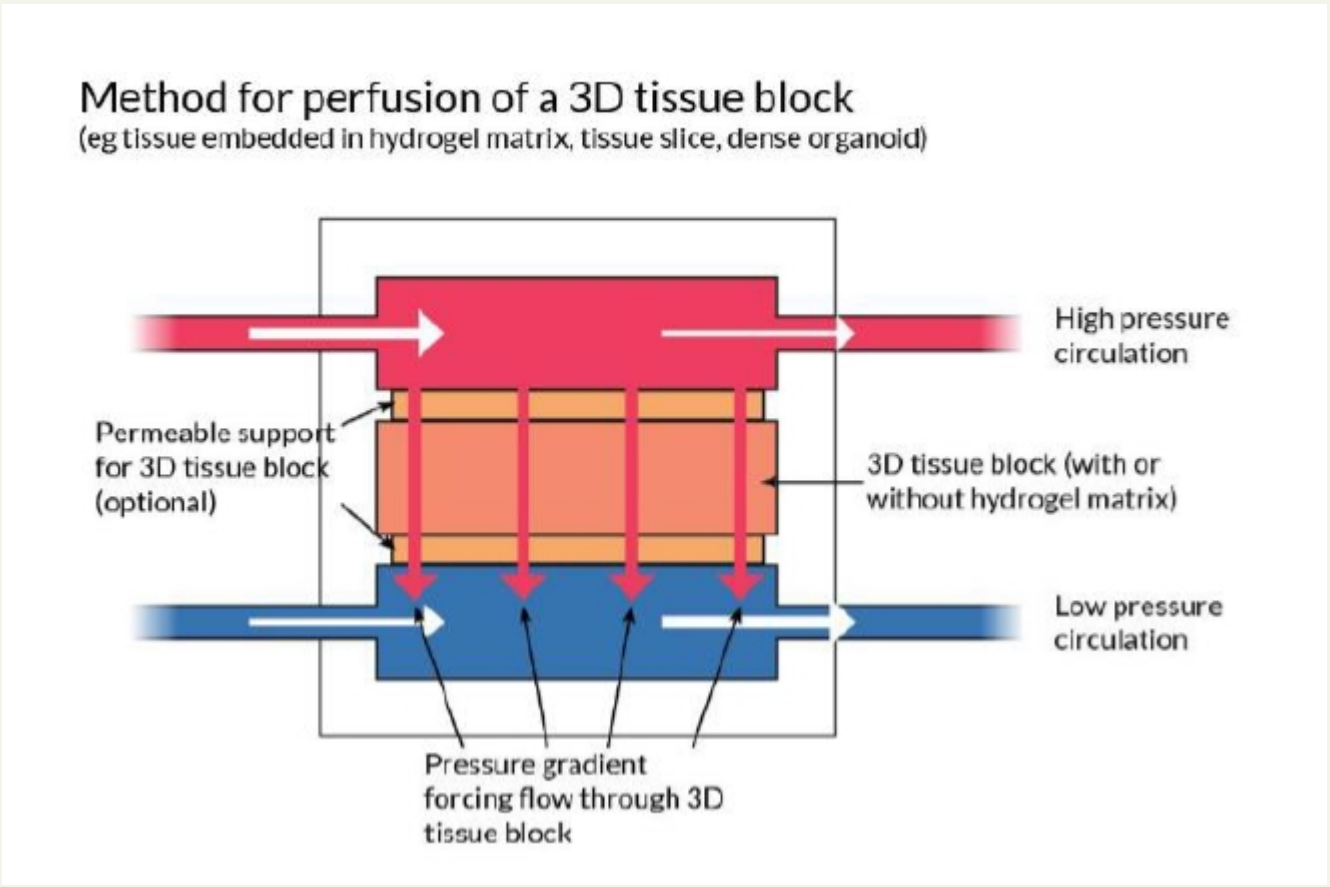
accumulation of secreted products.

TECHNOLOGY DESCRIPTION

Perfusion of a semi-permeable tissue-containing block by means of a pressure gradient in a circulatory bioreactor

This invention is the method of using a bioreactor which has two media filled fluidic compartments separated by a block of tissue (e.g. flattened organoid, 3D layered cells, surgical specimen) or a hydrogel which contains tissue. The two media filled compartments have circulating media flowing through them, supplied by a fluidic apparatus which circulates fluid using a pump. In one case, the two compartments are in series with respect to fluid circulation, and a variable orifice valve (e.g. an IV stopcock, needle valve or ball valve) is placed in between the two, such that an elevated pressure is generated in the upstream compartment relative to the downstream compartment, establishing a pressure gradient across the tissue containing block.

In a secondary aspect, the two compartments are in parallel, and a shunting pump from the low pressure compartment to the high pressure compartment generates the pressure gradient. In both cases, the outcome is to generate a pressure gradient from one side of the tissue containing block to the other, providing a motivating force for perfusion through the tissue containing block.



Our invention relates to methods, devices, and compositions for generating a controlled pressure gradient across a tissue-containing block, thereby enabling convective perfusion through three-dimensional biological tissues, organoids, or tissue-mimetic hydrogels. The invention provides a compact, sealed, and tunable bioreactor system capable of maintaining physiologically relevant flow and pressure conditions without requiring an external incubator or complex pneumatic equipment.

In one embodiment, the invention provides a bioreactor apparatus comprising two media-filled fluidic compartments separated by a tissue-containing block. The tissue-containing block may include a biological specimen such as a flattened organoid, multicellular layer, hydrogel embedded with cells, or excised tissue sample. The block serves as a semipermeable barrier between the compartments, allowing media to flow through interstitial spaces, hydrogel pores or engineered or grown capillary blood vessels while maintaining structural separation. The compartments are fluidically connected to one another and to a circulation circuit containing at least one pump configured to drive liquid media flow.

The system is sealed from the external environment to preserve aseptic conditions and to permit buildup of hydrostatic pressure. In a series-flow configuration, the upstream and downstream compartments are arranged sequentially in the circulation loop. The outlet of the upstream compartment is connected to the inlet of the downstream compartment through a variable orifice valve such as a stopcock, needle valve, or microfluidic constriction. Operation of the pump generates circulation of the culture medium through the system, and adjustment of the variable orifice produces a controlled pressure drop across the valve. This in turn elevates the pressure in the upstream compartment relative to the downstream compartment, thereby generating a defined pressure gradient across the tissue-containing block.

The magnitude of the gradient can be tuned by adjusting pump speed or valve resistance, permitting physiological interstitial pressures to be established across the tissue. In an alternative parallel-flow configuration, the two compartments are positioned in separate but fluidically linked loops, each receiving medium from a common pump or reservoir. A shunting pump or equivalent pressure-elevating mechanism transfers fluid from the downstream (low-pressure) compartment back to the upstream (high-pressure) compartment. The rate of this shunting flow defines the steady-state pressure differential between compartments, which again results in a trans-tissue pressure gradient across the tissue-containing block. This configuration enables independent control of the pressure and flow rate within each compartment and may be advantageous for maintaining asymmetric or bidirectional perfusion conditions.

The system includes pressure and flow sensors placed upstream and downstream of the tissue block to measure and regulate the pressure differential. Data from these sensors can be used for closed-loop feedback control of the pump or valve, ensuring constant perfusion parameters over extended periods. The entire fluidic circuit may be constructed from biocompatible, sterilizable materials such as polycarbonate, glass, silicone, or polytetrafluoroethylene (PTFE). Tubing may include sterile sampling ports. The medium may be oxygenated by a gas-permeable membrane module, maintained in an incubator using an open reservoir or gas permeable tubing or maintained under sealed, pre-equilibrated conditions.

In preferred embodiments, the system is operated as a closed-loop recirculatory circuit, allowing long-term culture without manual media exchanges. The sealed design maintains sterility and also enables safe containment of hazardous, infectious, or genetically modified biological materials. Because gas exchange, temperature regulation, and perfusion are maintained internally, the device can operate independently of an external incubator, providing a portable and self-contained culture environment.

The tissue-containing block positioned between the two fluidic compartments may include a natural or synthetic hydrogel, a decellularized tissue scaffold, or an intact tissue slice. In some embodiments, the tissue block comprises a composite of biological tissue and hydrogel matrix. The matrix composition is selected to provide permeability suitable for interstitial flow under modest pressure differentials. The matrix stiffness and porosity are tuned to resist compression under flow while maintaining structural integrity and viable cellular microenvironments. The block may be held in place by a compressible gasket, porous support ring (eg a porous PTFE or glass filter element on a support), or clamping frame that seals the perimeter while allowing flow through the interior volume.

The invention further encompasses a method of using the described bioreactor to perfuse biological tissues. The method includes the steps of (a) positioning a tissue-containing block between two fluidic compartments, (b) filling the compartments with liquid culture medium, (c) circulating the medium through the compartments using a pump, and (d) establishing a controllable pressure differential between the compartments using a flow restriction or shunting pump. The pressure gradient thus produced drives interstitial perfusion through the tissue-containing block, resulting in improved oxygenation, nutrient delivery, waste removal, and mechanical stimulation. The method may include monitoring the pressure differential and adjusting flow parameters to maintain physiological interstitial flow conditions.

The method can be applied to organoid cultures, engineered tissues, or explanted specimens for purposes including long-term culture, drug screening, toxicology testing, and disease modeling. In some embodiments, the invention further includes a tissue-hydrogel composite composition specifically designed for use in the described pressure-gradient bioreactor. The composition comprises a biological component, such as living cells or tissue fragments, dispersed within a porous, biocompatible hydrogel matrix. The composite exhibits sufficient permeability to permit interstitial flow and sufficient mechanical stability to withstand pressure-driven perfusion without deformation. The material properties of the composite, including porosity, compressive modulus, and permeability, are selected to yield stable convective flow and oxygen transport at physiologically relevant pressures. The composite may also incorporate biomolecular gradients, embedded sensors, or structural reinforcements to enhance reproducibility and analytical performance.

Collectively, the above-described features produce several synergistic advantages. The application of a controlled pressure gradient across the tissue-containing block overcomes diffusion limitations that restrict the thickness of viable 3D tissues in static culture, while reproducing the interstitial flow and mechanical cues found in vivo. The sealed recirculatory design reduces contamination risk and simplifies aseptic maintenance. The incorporation of standard valves, tubing, and pumps minimizes fabrication complexity and cost, enabling broad adoption. The system can be scaled from single-unit benchtop reactors to multiplexed arrays for high-throughput experiments.

The invention provides a novel combination of structural and functional elements—a dual-compartment bioreactor, a pressure-modulating fluidic circuit, and a perfusable tissue composition—that together enable controlled, sterile, and physiologically relevant perfusion of three-dimensional biological tissues. This configuration allows precise generation of interstitial pressure gradients through natural or engineered tissue blocks, achieving improved viability, biological realism, and experimental accessibility relative to existing culture systems.

APPLICATIONS

Producing organoids, engineered tiessues, explanted specimens

Long term culture

Disease modeling

ADVANTAGES

WO2022226405A1 - "Fluidic platforms for perfusable vascular tissues" includes an embodiment involving a microfluidic chip which contains a tissue containing block separating two perfusable fluidic compartments, but uses gravity columns to provide pressure. This does not allow integration into a circulating culture loop. This does not allow for dynamic (e.g. computer driven actuator) control over pressure gradients. This does not allow for a stable pressure gradient due to changes in the gravity column heights. This does not allow for physiological pressure gradients, since a constant column height in excess of 10cm would be needed.

US11680241B2 - "Perfusion enabled bioreactors", in its main design, also uses a gravity column to force fluid through a tissue containing block in a similar way to WO2022226405A1. It has two additional methods of providing a pressure gradient, one of which is to attach the outflow to a vacuum line, and the other is to use a screw mechanism on a lid to distract the lid, causing a relative vacuum. This device integrates sealed, noncirculating fluidic chambers into the device, where either a gravity column difference or applied vacuum provides pressure gradient, and this design prevents media changes without having to disassemble portions of the device. Without vacuum, a constant column height in excess of 10cm would be needed, which is not provided for in the design. With vacuum, access to the culture

device is impeded, furthermore, failure to cease vacuum before all media has been pulled through the device would lead to a catastrophic failure through aspiration of air through the sample.

https://doi.org/10.3390/bioengineering11111147 - "An Arteriovenous Bioreactor Perfusion System for Physiological In Vitro Culture of Complex Vascularized Tissue Constructs" describes a similar two-compartment system with circulatory flow however, it requires separate arterial and venous pressure control, increasing system complexity.

https://research.utoronto.ca/technology-opportunities/db/microfluidic-device-and-pump-system-vascularization-organoids "Microfluidic Device and Pump System for Vascularization of Organoids" has a similar arterio-venous design, but is a monolithic miniature microfluidic chip, where there is no ability to manipulate the fluidic resistance, and the mixed nonocclusive impeller design and fixed resistance would struggle to generate physiological pressure gradients. Furthermore, this depends on the use of an incubator, which ours does not.

Within our group, we have also created a version of this where there is no circulation outflow of the chamber on either side, therefore making it difficult to control pressure gradient -- small changes in actuator force can cause large changes in compartment pressure on either side, without a recourse for outflow of fluid. Overpressure events thereby often rupture the intervening tissue containing block. We note that US11680241B2 likely has this same problem for the same reason, though it is not discussed.

INTELLECTUAL PROPERTY INFORMATION

Patent Pending

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Dual Gasket System For Gas-Tight But Biocompatible Cell Culture Vessel Sealing
- "Incubator-Free" Vessels For Cell Culture Which Do Not Use An Air Intermediate For Gas Regulation
- Fiber Optic Light Source Scheme For Modular Remote Illumination Of Incubator-Based Live-Cell Microscopy

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