feed across the filtration element as is done in the alternating tangential flow (ATF) technology, by backwashing the permeate through the filter, and/or by periodic washing of the filter.

[05] Advancements in filtration have been made (see e.g., Tim Sewerin et al., "Advances and Applications of Hollow Fiber Nanofiltration Membranes: A Review. *Membranes,* 2021, *11*, 890). One such advancement includes Hollow Fiber (HF) filters (HFF), which may be operated in tangential flow mode, an example of which are tangential flow depth filtration® (TFDF®) filters. Such TFDF® filters combine the benefits of tangential flow with depth filtration. However, certain HF filters can be considered expensive and/or relatively bulky, and during the transition between bioreactors for cell growth phase and harvest phase, cell culture is prone to contamination and associated loss of product.

[06] Thus, it is desirable to have assemblies, systems, and methods capable of improving these processes.

SUMMARY

[07] Described herein are assemblies, systems, and methods suitable for production of biologics. Disclosed herein are bioreactor systems, comprising: a) a bioreactor including an input port and an output port; b) a feed stream conduit operably connected to the output port and inlet of a Hollow Fiber (HF) filter, the feed stream conduit operable to carry fluid from the bioreactor to the HF filter; c) a retentate stream conduit operably connected to the input port of the bioreactor and an outlet of the HF filter, the retentate stream conduit operable to carry fluid to the bioreactor from the HF filter; and d) a multi-purpose assembly operably connected to the HF filter, the multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluid from the HF filter and a flow meter operable to measure flow rate of fluid in the first flowpath; wherein the second flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are configured to have different pump capacities. In one aspect, the disclosure provides a bioreactor system, comprising: a) a bioreactor including an input port and an output port; b) a feed stream conduit operably connected to the output port and inlet of a Hollow Fiber (HF) filter, the feed stream conduit operable to carry fluid from the bioreactor to the HF filter; c) a retentate stream conduit operably connected to the input port of the bioreactor and an outlet of the HF filter, the retentate stream conduit operable to carry fluid to the bioreactor from the HF filter; and d) a multi-purpose assembly operably connected to the HF filter, the multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluid from the HF filter and a flow meter operable to measure flow rate of fluid in the first flowpath; wherein the second flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are configured to have different pump capacities.

[08] In some examples, the HF filter is operable for tangential flow. In some examples, the HF filter is a tangential flow depth filtration® (TFDF®) filter. In some examples, the first and second pump are configured to have different accuracy ratings. In some examples, the system further includes: one or more clarification filter(s) in the first and/or second flow path. In some examples, the first and second pumps are selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™ (e.g., positive displacement rotary pumps), gear,

diaphragm, syringe, and piston pumps. In some examples, the first pump and second pumps are peristaltic pumps. In some examples, the feed stream conduit comprises a feed stream pump selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™, gear, diaphragm, syringe, and piston pumps, is operable to carry unfiltered fluid from the bioreactor to the HF filter. In some examples, the retentate stream conduit is operable to carry cell culture fluid to the bioreactor from the HF filter.

[09] In some examples, the first flowpath including a first pump operable to draw fluid from the HF filter, draws perfusion permeate stream fluid from the HF filter. In some examples, the second flowpath including a second pump operable to draw fluid from the HF filter, draws harvest permeate stream fluid from the HF filter. In some examples, the first flowpath and the second flowpath have different internal diameters. In some examples, the first flowpath and the second flowpath have the same internal diameters. In some examples, the second flowpath is capable of conducting fluids at a higher flowrate than the first flowpath.

[010] In some examples, the first pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 liters per min (LPM) and 5 LPM, between about 0.01 LPM to about 10 LPM, and/or between about 0.01 LPM to about 15 LPM. In some examples, the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.2 liters per fiber per minute (L/fiber/min). In some examples, the first pump is operable to draw fluid from the HF filter while maintaining a viable cell density (VCD) of greater than about 75 x 10^6 cells/mL, greater than about 50 x 10^6 cells/mL, and/or greater than about 25 x 10^6 cells/mL. In some examples, the first pump is operable to draw fluid from the HF filter at a rate of between about 0.1 and about 5 bioreactor vessel volumes per day (VVD), at a rate of between about 0.5 and about 4.3 bioreactor VVD, at a rate of between about 1 and about 4.3 bioreactor VVD, and/or at a rate up to about 5 bioreactor VVD. In some examples, the first pump is operable to draw fluid from the HF filter at a filter flux rate of between about 50 and about 800 liters per square meter per hour (LMH), and/or between about 100 and about 600 LMH.

[011] In some examples, the flow meter operable to measure flow rate of fluid in the first flowpath continuously monitors the VVD rate and is in communication with the first pump to adjust the first pump rate to maintain a desired VVD rate. In some examples, the flow meter operable to measure flow rate of fluid in the first flowpath is capable of accurately

monitoring a flow rate of about 0 to about 8 LPM, or about 0.5 LPM to about 6 LPM. In some examples, the first pump is operable to draw fluid from the HF filter at a throughput equal to between about 10,000 liters per square meter (L/m^2) to about 30,000 L/m^2, between about 10,000 liters per square meter (L/m^2) to about 50,000 L/m^2, and/or between about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2. In some examples, the first pump is operable to draw fluid from the HF filter while maintaining a shear rate (s-1) of less than about 5,000 s-1, less than about 3,500 s-1, and/or less than about 2,500 s-1.

[012] In some examples, the bioreactor has a volume less than or equal to about 15 liters, less than or equal to about 50 liters, less than or equal to about 100 liters, or less than or equal to about 500 liters. In some examples, the bioreactor has a volume greater than or equal to about 500 liters, about 1,000 liters, about 1,500 liters, and/or about 3,500 liters. In some examples, the bioreactor has a volume equal to between about 2,000 liters and about 7,000 liters. In some examples, the bioreactor has at least two input ports and at least two output ports, and at least two of b), c), and d).

[013] In some examples, the bioreactor system is capable of operating in a perfusion process. In some examples, the bioreactor system is capable of operating in a harvest process. In some examples, the bioreactor system is capable of operating in a perfusion process, an in-between perfusion and harvest process, and a harvest process. In some examples, the bioreactor system is capable of operating in a continuous harvest process. In some examples, the bioreactor system further comprises a human machine interface (HMI) control unit. In some examples, the HMI control unit is programmed and can display perfusion process controls, in-between perfusion and harvest process controls, or harvest process controls.

[014] In some examples, the bioreactor system further comprises one or more sensors. In some examples, the bioreactor system further comprises one or more of a feed stream or retentate stream fluid pump. In some examples, the bioreactor system further comprises at least one component capable of facilitating at least one process intensification parameter. In some examples, the process intensification parameter is one or more of increased cell number, increased cell density, provision of rich cell culture growth media, rapid cell number expansion, or increased biologic production. In some examples, the bioreactor system is further capable of backflushing the HF filter with permeate fluid.

[015] In some examples, the bioreactor system further comprises a second flow meter operable to measure flow rate of fluid in the second flowpath and accurately monitoring a flow

rate of about 0 to about 10 LPM, or about 0.5 LPM to about 8 LPM. In some examples, the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 36,000 L/m^2, between about 12,000 liters per square meter (L/m^2) to about 60,000 L/m^2, and/or between about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2. In some examples, the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 150 and about 900 liters per square meter per hour (LMH), and/or between about 200 and about 700 LMH.

[016] In some examples, the second flowpath and pump are operable to draw a feed flow rate from the HF filter of about 1 to about 3 liters per fiber per minute (L/fiber/min). In some examples, the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 8 LPM, between about 0.01 LPM to about 13 LPM, and/or between about 0.01 LPM to about 18 LPM.

[017] In some examples, the first flowpath comprises a connection system with 3/8″ ID tubing, and/or 1/8″ ID tubing. In some examples, the second flowpath comprises a connection system with 1/2″ ID tubing and/or 1/8″ ID tubing. In some examples, the first flowpath has an accuracy requirement of about 1%. In some examples, the second flowpath has an accuracy requirement of about 3%.

[018] In some examples, the HF filter is constructed of and/or comprises polypropylene, and/or polyethylene terephthalate. In some examples, the HF filter comprises isotropic pore structures. In some examples, the HF filter has an average pore size diameter of between about 0.65 μm to about 8 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm to about 5 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm.

[019] In some examples, the bioreactor system is operable for use with shear sensitive cells. In some examples, the bioreactor system is operable for use with animal cells. In some examples, the bioreactor system is operable for use with mammalian cells. In some examples, the bioreactor system is operable for use with Chinese Ovarian Hamster (CHO) cells. In some examples, the bioreactor system is operable for use with human embryonic kidney 293 (HEK293) cells. In some examples, the bioreactor system is operable for use with cells for the production of a biologic. In some examples, the biologic comprises an antibody, peptide, and/or virus.

[020] Also disclosed herein are multi-purpose filter assemblies, comprising: a) a Hollow Fiber (HF) filter; and b) a multi-purpose assembly operably connected to the HF filter, the

multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluids from the HF filter and a flow meter operable to measure flow rate of fluid in the first flowpath; wherein the second flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are capable of having different pump capacities and accuracy ratings. In one aspect, the disclosure provides a multi-purpose filter assembly, comprising: a) a Hollow Fiber (HF) filter; and b) a multi-purpose assembly operably connected to the HF filter, the multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluids from the HF filter and a flow meter operable to measure flow rate of fluid in the first flowpath; wherein the second flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are capable of having different pump capacities and accuracy ratings. In some examples, the HF filter is operable for tangential flow.

[021] In some examples, the HF filter is a tangential flow depth filtration® (TFDF®) filter. In some examples, the multi-purpose filter assembly further comprises one or more clarification filter(s) in the first and/or second flow path. In some examples, the first and second pumps are selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™, gear, diaphragm, syringe, and piston pumps. In some examples, the first pump and second pumps are peristaltic pumps. In some examples, the first flowpath and pump are operable to draw fluids from the HF filter at a throughput greater than or equal to about 10,000 liters per square meter (L/m^2) to about 30,000 L/m^2. In some examples, the first flowpath and pump are operable to draw fluids from the HF filter at a throughput greater than or equal to about 10,000 liters per square meter (L/m^2) to about 50,000 L/m^2. In some examples, the first flowpath and pump are operable to draw fluids from the HF filter at a throughput greater than or equal to about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2. In some examples, the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.2 liters per fiber per minute (L/fiber/min). In some examples, the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.0 L/fiber/min, and/or about 1 to about 1.8 L/fiber/min. In some examples, the first flowpath and pump are operable to draw fluids from the HF filter at a filter flux of about 50 to about 800 LMH, and/or about 100 to about 600 LMH. In some examples, the first flowpath and pump are operable to maintain a packed cell volume (PCV) of about 2 to about 40%, about 8 to about 40%, and/or about 12 to about 35%. In some examples, the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 25 x 10^6 cells/mL, about 50 x 10^6 cells/mL, about 75 x 10^6 cells/mL, about 100 x 10^6 cells/mL, and/or about 25 x 10^7 cells/mL. In some examples, the first flowpath and pump are operable to draw fluid from the HF filter at a shear rate of less than about 5,000 s-1, about 3,500 s-1, and/or about 2,500 s-1. In some examples, the first flowpath and pump are operable to draw fluid from

the HF filter at a flow rate of between about 0.01 LPM to about 5 LPM, about 0.01 LPM to about 10 LPM, and/or about 0.01 LPM to about 15 LPM.

[022] In some examples, the flow meter operable to measure flow rate of fluid in the first flowpath continuously monitors the LPM rate and is in communication with the first pump to adjust the first pump rate to maintain a desired LPM rate. In some examples, the flow meter operable to measure flow rate of fluid in the first flowpath is capable of accurately monitoring a flow rate of about 0 to about 8 LPM, and/or about 0.01 LPM to about 6 LPM. In some examples, the first flowpath has an accuracy requirement of about 1%. In some examples, the second flowpath has an accuracy requirement of about 3%.

[023] In some examples, the first flowpath and the second flowpath have different internal diameters. In some examples, the first flowpath and the second flowpath have the same internal diameters. In some examples, the second flowpath and pump are operable to draw fluid from the HF filter at a higher flowrate than the first flowpath and first pump. In some examples, the second flowpath and pump are operable to draw fluid from the HF filter as a continuous harvest process. In some examples, the HF filter is not replaced when the multi-purpose assembly directs fluids through one flowpath and pump and then directs fluid through the other flowpath and pump. In some examples, the HF filter is not replaced when the multi-purpose assembly directs fluids first through the first flowpath and pump, and subsequently through the second flowpath and pump. In some examples, the first flowpath and second flowpath of the multi-purpose assembly are connected by a T connector, a Y connector, or a valve.

[024] In some examples, the multi-purpose filter assembly further comprises a second flow meter operable to measure flow rate of fluid in the second flowpath and accurately monitoring a flow rate of about 0 to about 10 LPM, or about 0.5 LPM to about 8 LPM. In some examples, the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 36,000 L/m^2, between about 12,000 L/m^2 to about 60,000 L/m^2, and/or between about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2. In some examples, the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 150 and about 900 liters per square meter per hour (LMH), and/or between about 200 and about 700 LMH. In some examples, the second flowpath and pump are operable to draw a feed flow rate from the HF filter of about 1 to about 3 liters per fiber per minute (L/fiber/min). In some examples, the second pump

is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 8 LPM, about 0.01 LPM to about 13 LPM, and/or about 0.01 LPM to about 18 LPM.

[025] In some examples, the HF filter is constructed of and/or comprises polypropylene, and/or polyethylene terephthalate. In some examples, the HF filter comprises isotropic pore structures. In some examples, the HF filter has an average pore size diameter of between about 0.65 μm to about 8 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm to about 5 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm.

[026] In some examples, the multi-purpose filter assembly is operable for use with shear sensitive cells, animal cells, mammalian cells, CHO cells, and/or HEK293 cells. In some examples, the multi-purpose filter assembly is operable for use with cells for the production of a biologic. In some examples, the biologic comprises an antibody, peptide, and/or virus.

[027] Also disclosed herein are methods of producing biologics from cells, comprising: a) expanding cells in a cell culture fluid in a bioreactor, b) during cell expansion, perfusing cell culture fluid through a Hollow Fiber (HF) filter to remove spent cell culture media while retaining the expanding cells, and adding an appropriate replacement volume of cell culture media to the bioreactor to maintain a desired cell culture fluid level in the bioreactor, wherein the spent cell culture media is perfused through the HF filter at a first flow rate to enter a first flowpath, and c) following cell expansion, harvesting cell culture fluid through a HF filter to obtain the biologics, and adding an appropriate replacement volume of cell culture media to the bioreactor to maintain a desired cell culture fluid level in the bioreactor during different phases of harvest, wherein the cell culture media is harvested through the HF filter at a second flow rate to enter a second flowpath, wherein the second flow rate is greater than the first flow rate. In one aspect, the disclosure provides a method of producing biologics from cells, comprising: a) expanding cells in a cell culture fluid in a bioreactor, b) during cell expansion, perfusing cell culture fluid through a Hollow Fiber (HF) filter to remove spent cell culture media while retaining the expanding cells, and adding an appropriate replacement volume of cell culture media to the bioreactor to maintain a desired cell culture fluid level in the bioreactor, wherein the spent cell culture media is perfused through the HF filter at a first flow rate to enter a first flowpath, and c) following cell expansion, harvesting cell culture fluid through a HF filter to obtain the biologics, and adding an appropriate replacement volume of cell culture media to the bioreactor to maintain a desired cell culture fluid level in the bioreactor during different phases of harvest, wherein the cell culture media is harvested through the HF filter at a second flow rate to enter a second flowpath, wherein the second flow rate is greater than the first flow rate. In some examples, the HF filter is operable for tangential flow. In some examples, the HF filter is a tangential flow depth filtration® (TFDF®) filter. In some examples, the replacement volume of cell culture media in b) and/or c) is the same amount of spent cell culture media as is removed. In some examples, the replacement volume of cell culture media in b) and/or c) is greater than the amount of spent cell culture media removed. In some examples, the replacement volume of cell culture media in b) and/or c) is less than the amount of spent cell culture media removed. In some examples, the replacement volume of cell culture media is fresh cell culture media. In some examples, the first flow rate is less than or equal to about 5 LPM, and a second flow rate is greater than about 5 LPM. In some examples, the HF filter is constructed of and/or comprises polypropylene, and/or

polyethylene terephthalate. In some examples, the HF filter comprises isotropic pore structures. In some examples, the HF filter has an average pore size diameter of between about 0.65 μm to about 8 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm to about 5 μm. In some examples, the HF filter has an average pore size diameter of about 2 μm. In some examples, the cells are shear sensitive cells. In some examples, the cells are animal cells, mammalian cells, CHO cells, and/or HEK293 cells. In some examples, the biologic comprises an antibody, peptide, and/or virus.

[028] Also disclosed herein are methods of producing biologics from cells, comprising use of a bioreactor system and/or multi-purpose filter assembly disclosed herein.

[029] Also disclosed herein are uses of a multi-purpose filter assembly disclosed herein in a bioreactor system. In one aspect, the disclosure provides use of a multi-purpose filter assembly as disclosed herein in a bioreactor system. In some examples, the bioreactor system is a bioreactor system of the disclosure.

[030] Also disclosed herein are uses of a bioreactor system disclosed herein for the culturing of cells. In one aspect, the disclosure provides use of a bioreactor system as disclosed herein for the culturing of cells. In some examples, the cells produce biologics and the use may further comprise harvesting cell culture fluid through the HF filter to obtain the biologics.

[031] Also disclosed herein are methods of producing biologics from cells, comprising use of a bioreactor system or multi-purpose filter assembly disclosed herein. In one aspect, the disclosure provides a method of producing biologics from cells, comprising use of a bioreactor system or multi-purpose filter assembly as disclosed herein. Also disclosed herein are methods of use of a system, assembly, or method disclosed herein to improve productivity, improve performance, improve efficiency, reduce contamination rates, reduce capital investment, reduce physical footprint, reduce consumables attrition, and/or reduce operation costs for a facility comprising a biologics production process.

[032] Certain examples of the present disclosure are characterized through the following.

[033] Example 1 is a bioreactor system, comprising: a) a bioreactor including an input port and an output port; b) a feed stream conduit operably connected to the output port and inlet of a Hollow Fiber (HF) filter, the feed stream conduit operable to carry fluid from the bioreactor to the HF filter; c) a retentate stream conduit operably connected to the input port of the bioreactor and an outlet of the HF filter, the retentate stream conduit operable to carry fluid to the bioreactor from the HF filter; and d) a multi-purpose assembly operably connected to the HF filter, the multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluid from the HF filter and a flow meter operable to measure flow rate of fluid in the first flowpath; wherein the second

flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are configured to have different pump capacities.

[034] Example 2 is the bioreactor system of example 1, wherein the HF filter is operable for tangential flow.

[035] Example 3 is the bioreactor system of examples 1 or 2, wherein the HF filter is a tangential flow depth filtration® (TFDF®) filter.

[036] Example 4 is the bioreactor system of any one of examples 1-3, wherein the first and second pump are configured to have different accuracy ratings.

[037] Example 5 is the bioreactor system of any one of examples 1-4, further including: one or more clarification filter(s) in the first and/or second flow path.

[038] Example 6 is the bioreactor system of any one of examples 1-5, wherein the first and second pumps are selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™, gear, diaphragm, syringe, and piston pumps.

[039] Example 7 is the bioreactor system of any one of examples 1-6, wherein the first pump and second pumps are peristaltic pumps.

[040] Example 8 is the bioreactor system of any one of examples 1-7, wherein the feed stream conduit comprises a feed stream pump selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™, gear, diaphragm, syringe, and piston pumps, is operable to carry unfiltered fluid from the bioreactor to the HF filter.

[041] Example 9 is the bioreactor system of any one of examples 1-8, wherein the retentate stream conduit is operable to carry cell culture fluid to the bioreactor from the HF filter.

[042] Example 10 is the bioreactor system of any one of examples 1-9, wherein the first flowpath including a first pump operable to draw fluid from the HF filter, draws perfusion permeate stream fluid from the HF filter.

[043] Example 11 is the bioreactor system of any one of examples 1-10, wherein the second flowpath including a second pump operable to draw fluid from the HF filter, draws harvest permeate stream fluid from the HF filter.

[044] Example 12 is the bioreactor system of any one of examples 1-11, wherein the first flowpath and the second flowpath have the same or have different internal diameters.

[045] Example 13 is the bioreactor system of any one of examples 1-12, wherein the second flowpath is capable of conducting fluids at a higher flowrate than the first flowpath.

[046] Example 14 is the bioreactor system of any one of examples 1-13, wherein the first pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 liters per min (LPM) and 5 LPM.

[047] Example 15 is the bioreactor system of any one of examples 1-13, wherein the first pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 10 LPM.

[048] Example 16 is the bioreactor system of any one of examples 1-13, wherein the first pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 15 LPM.

[049] Example 17 is the bioreactor system of any one of examples 1-16, wherein the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.2 liters per fiber per minute (L/fiber/min).

[050] Example 18 is the bioreactor system of any one of examples 1-17, wherein the first pump is operable to draw fluid from the HF filter while maintaining a viable cell density (VCD) of greater than about 75 x 10^6 cells/mL.

[051] Example 19 is the bioreactor system of any one of examples 1-17, wherein the first pump is operable to draw fluid from the HF filter while maintaining a viable cell density (VCD) of greater than about 50 x 10^6 cells/mL.

[052] Example 20 is the bioreactor system of any one of examples 1-17, wherein the first pump is operable to draw fluid from the HF filter while maintaining a VCD of greater than about 25 x 10^6 cells/mL.

[053] Example 21 is the bioreactor system of any one of examples 1-20, wherein the first pump is operable to draw fluid from the HF filter at a rate of between about 0.1 and about 5 bioreactor vessel volumes per day (VVD).

[054] Example 22 is the bioreactor system of any one of examples 1-21, wherein the first pump is operable to draw fluid from the HF filter at a rate of between about 0.5 and about 4.3 bioreactor vessel volumes per day (VVD).

[055] Example 23 is the bioreactor system of any one of examples 1-22, wherein the first pump is operable to draw fluid from the HF filter at a filter flux rate of between about 50 and about 800 liters per square meter per hour (LMH).

[056] Example 24 is the bioreactor system of any one of examples 1-23, wherein the first pump is operable to draw fluid from the HF filter at a filter flux rate of between about 100 and about 600 LMH.

[057] Example 25 is the bioreactor system of any one of examples 1-24, wherein the flow meter operable to measure flow rate of fluid in the first flowpath continuously monitors the VVD rate and is in communication with the first pump to adjust the first pump rate to maintain a desired VVD rate.

[058] Example 26 is the bioreactor system of any one of examples 1-25, wherein the flow meter operable to measure flow rate of fluid in the first flowpath is capable of accurately monitoring a flow rate of about 0 to about 8 LPM, or about 0.5 LPM to about 6 LPM.

[059] Example 27 is the bioreactor system of any one of examples 1-26, wherein the first pump is operable to draw fluid from the HF filter at a throughput equal to between about 10,000 liters per square meter (L/m^2) to about 30,000 L/m^2.

[060] Example 28 is the bioreactor system of any one of examples 1-26, wherein the first pump is operable to draw fluid from the HF filter at a throughput equal to between about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2.

[061] Example 29 is the bioreactor system of any one of examples 1-28, wherein the first pump is operable to draw fluid from the HF filter while maintaining a shear rate (s-1) of less than about 5,000 s-1.

[062] Example 30 is the bioreactor system of any one of examples 1-29, wherein the first pump is operable to draw fluid from the HF filter while maintaining a shear rate (s-1) of less than about 3,500 s-1.

[063] Example 31 is the bioreactor system of any one of examples 1-30, wherein the first pump is operable to draw fluid from the HF filter while maintaining a shear rate (s-1) of less than about 2,500 s-1.

[064] Example 32 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume less than or equal to about 15 liters, less than or equal to about 50 liters, less than or equal to about 100 liters, or less than or equal to about 500 liters.

[065] Example 33 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume greater than or equal to about 500 liters.

[066] Example 34 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume greater than or equal to about 1,000 liters.

[067] Example 35 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume greater than or equal to about 1,500 liters.

[068] Example 36 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume equal to between about 2,000 liters and about 3,500 liters.

[069] Example 37 is the bioreactor system of any one of examples 1-31, wherein the bioreactor has a volume equal to between about 2,000 liters and about 7,000 liters.

[070] Example 38 is the bioreactor system of any one of examples 1-37, wherein the bioreactor has at least two input ports and at least two output ports, and at least two of b), c), and d).

[071] Example 39 is the bioreactor system of any one of examples 1-38, wherein the bioreactor system is capable of operating in a perfusion process.

[072] Example 40 is the bioreactor system of any one of examples 1-39, wherein the bioreactor system is capable of operating in a harvest process.

[073] Example 41 is the bioreactor system of any one of examples 1-40, wherein the bioreactor system is capable of operating in a perfusion process, an in-between perfusion and harvest process, and a harvest process.

[074] Example 41.1 is the bioreactor system of any one of examples 1-41, wherein the bioreactor system is capable of operating in more than one perfusion process.

[075] Example 41.2 is the bioreactor system of any one of examples 1-41.1, wherein the bioreactor system is capable of operating in more than one perfusion process, an in-between perfusion and harvest process, and a harvest process.

[076] Example 42 is the bioreactor system of any one of examples 1-41.2, wherein the bioreactor system is capable of operating in a continuous harvest process.

[077] Example 43 is the bioreactor system of any one of examples 1-42, further comprising a human machine interface (HMI) control unit.

[078] Example 44 is the bioreactor system of example 43, wherein the HMI control unit is programmed and can display perfusion process controls, in-between perfusion and harvest process controls, or harvest process controls.

[079] Example 45 is the bioreactor system of any one of examples 1-44, further comprising one or more sensors.

[080] Example 46 is the bioreactor system of any one of examples 1-46, further comprising one or more of a feed stream or retentate stream fluid pump.

[081] Example 47 is the bioreactor system of any one of examples 1-46, further comprising at least one component capable of facilitating at least one process intensification parameter.

[082] Example 48 is the bioreactor system of example 47, wherein the process intensification parameter is one or more of increased cell number, increased cell density, provision of rich cell culture growth media, rapid cell number expansion, or increased biologic production.

[083] Example 49 is the bioreactor system of any one of examples 1-48, further capable of backflushing the HF filter with permeate fluid.

[084] Example 50 is the bioreactor system of any one of examples 1-49, further comprising a second flow meter operable to measure flow rate of fluid in the second flowpath and accurately monitoring a flow rate of about 0 to about 10 LPM, or about 0.5 LPM to about 8 LPM.

[085] Example 51 is the bioreactor system of any one of examples 1-50, wherein the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 36,000 L/m^2.

[086] Example 52 is the bioreactor system of any one of examples 1-50, wherein the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 60,000 L/m^2, or equal to between about 12,000 liters per square meter (L/m^2) to about 70,000 L/m^2.

[087] Example 53 is the bioreactor system of any one of examples 1-52, wherein the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 150 and about 900 liters per square meter per hour (LMH).

[088] Example 54 is the bioreactor system of any one of examples 1-53, wherein the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 200 and about 700 LMH.

[089] Example 55 is the bioreactor system of any one of examples 1-54, wherein the second flowpath and pump are operable to draw a feed flow rate from the HF filter of about 1 to about 3 liters per fiber per minute (L/fiber/min).

[090] Example 56 is the bioreactor system of any one of examples 1-55, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 8 LPM.

[091] Example 57 is the bioreactor system of any one of examples 1-55, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 13 LPM.

[092] Example 58 is the bioreactor system of any one of examples 1-55, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 18 LPM.

[093] Example 59 is the bioreactor system of any one of examples 1-58, wherein the first flowpath comprises a connection system with 3/8″ ID tubing.

[094] Example 60 is the bioreactor system of any one of examples 1-58, wherein the first flowpath comprises a connection system with 1/8″ ID tubing.

[095] Example 61 is the bioreactor system of any one of examples 1-60, wherein the second flowpath comprises a connection system with 1/2″ ID tubing.

[096] Example 62 is the bioreactor system of any one of examples 1-60, wherein the second flowpath comprises a connection system with 1/8″ ID tubing.

[097] Example 63 is the bioreactor system of any one of examples 1-62, wherein the first flowpath has an accuracy requirement of about 1%.

[098] Example 64 is the bioreactor system of any one of examples 1-63, wherein the second flowpath has an accuracy requirement of about 3%.

[099] Example 65 is the bioreactor system of any one of examples 1-64, wherein the HF filter is constructed of and/or comprises polypropylene, and/or polyethylene terephthalate.

[0100] Example 66 is the bioreactor system of any one of examples 1-65, wherein the HF filter comprises isotropic pore structures, and/or comprises an average pore lumen diameter of about 0.65 μm to about 8 μm, or about 2 μm to about 5 μm.

[0101] Example 67 is the bioreactor system of any one of examples 1-66, operable for use with shear sensitive cells.

[0102] Example 68 is the bioreactor system of any one of examples 1-67, operable for use with animal cells.

[0103] Example 69 is the bioreactor system of any one of examples 1-68, operable for use with mammalian cells.

[0104] Example 70 is the bioreactor system of any one of examples 1-69, operable for use with Chinese Ovarian Hamster (CHO) cells.

[0105] Example 71 is the bioreactor system of any one of examples 1-69, operable for use with human embryonic kidney 293 (HEK293) cells.

[0106] Example 72 is the bioreactor system of any one of examples 1-71, operable for use with cells for the production of a biologic.

[0107] Example 73 is the bioreactor system of example 72, wherein the biologic comprises an antibody, peptide, and/or virus.

[0108] Example 74 is a multi-purpose filter assembly, comprising: a) a Hollow Fiber (HF) filter; and b) a multi-purpose assembly operably connected to the HF filter, the multi-purpose assembly including a first flow path and a second flowpath: wherein the first flowpath includes a first pump operable to draw fluids from the HF filter and a flow meter operable to measure

flow rate of fluid in the first flowpath; wherein the second flowpath includes a second pump operable to draw fluid from the HF filter; and wherein the first pump and the second pump are capable of having different pump capacities and accuracy ratings.

[0109] Example 75 is the multi-purpose filter assembly of example 74, wherein the HF filter is operable for tangential flow.

[0110] Example 76 is the multi-purpose filter assembly of examples 74 or 75, wherein the HF filter is a tangential flow depth filtration® (TFDF®) filter.

[0111] Example 77 is the multi-purpose filter assembly of any one of examples 74-76, further including: one or more clarification filter(s) in the first and/or second flow path.

[0112] Example 78 is the multi-purpose filter assembly of any one of examples 74-77, wherein the first and second pumps are selected from the groups consisting of peristaltic, centrifugal, magnetic drive, positive displacement, membrane, pressure-based, quantex™, gear, diaphragm, syringe, and piston pumps.

[0113] Example 79 is the multi-purpose filter assembly of any one of examples 74-78, wherein the first pump and second pumps are peristaltic pumps.

[0114] Example 80 is the multi-purpose filter assembly of any one of examples 74-79, wherein the first flowpath and pump are operable to draw fluids from the HF filter at a throughput greater than or equal to about 10,000 liters per square meter (L/m^2) to about 30,000 L/m^2.

[0115] Example 81 is the multi-purpose filter assembly of any one of examples 74-79, wherein the first flowpath and pump are operable to draw fluids from the HF filter at a throughput greater than or equal to about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2.

[0116] Example 82 is the multi-purpose filter assembly of any one of examples 74-81, wherein the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.2 liters per fiber per minute (L/fiber/min).

[0117] Example 83 is the multi-purpose filter assembly of any one of examples 74-82, wherein the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 0.8 to about 2.0 L/fiber/min.

[0118] Example 84 is the multi-purpose filter assembly of any one of examples 74-83, wherein the first flowpath and pump are operable to draw a feed flow rate from the HF filter of about 1 to about 1.8 L/fiber/min.

[0119] Example 85 is the multi-purpose filter assembly of any one of examples 74-84, wherein the first flowpath and pump are operable to draw fluids from the HF filter at a filter flux of about 50 to about 800 LMH.

[0120] Example 86 is the multi-purpose filter assembly of any one of examples 74-85, wherein the first flowpath and pump are operable to draw fluids from the HF filter at a filter flux of about 100 to about 600 LMH.

[0121] Example 87 is the multi-purpose filter assembly of any one of examples 74-86, wherein the first flowpath and pump are operable to maintain a packed cell volume (PCV) of about 2 to about 40%.

[0122] Example 88 is the multi-purpose filter assembly of any one of examples 74-87, wherein the first flowpath and pump are operable to maintain a PCV of about 8 to about 40%.

[0123] Example 89 is the multi-purpose filter assembly of any one of examples 74-88, wherein the first flowpath and pump are operable to maintain a PCV of about 12 to about 35%.

[0124] Example 90 is the multi-purpose filter assembly of any one of examples 74-89, wherein the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 25 x 10^6 cells/mL.

[0125] Example 91 is the multi-purpose filter assembly of any one of examples 74-90, wherein the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 50 x 10^6 cells/mL.

[0126] Example 92 is the multi-purpose filter assembly of any one of examples 74-91, wherein the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 75 x 10^6 cells/mL.

[0127] Example 93 is the multi-purpose filter assembly of any one of examples 74-92, wherein the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 100 x 10^6 cells/mL.

[0128] Example 94 is the multi-purpose filter assembly of any one of examples 74-93, wherein the first flowpath and pump are operable to draw fluid from the HF filter while maintaining a VCD of greater than about 25 x 10^7 cells/mL.

[0129] Example 95 is the multi-purpose filter assembly of any one of examples 74-94, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a shear rate of less than about 5,000 s-1.

[0130] Example 96 is the multi-purpose filter assembly of any one of examples 74-95, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a shear rate of less than about 3,500 s-1.

[0131] Example 97 is the multi-purpose filter assembly of any one of examples 74-96, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a shear rate of less than about 2,500 s-1.

[0132] Example 98 is the multi-purpose filter assembly of any one of examples 74-97, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 5 LPM.

[0133] Example 99 is the multi-purpose filter assembly of any one of examples 74-97, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 10 LPM.

[0134] Example 100 is the multi-purpose filter assembly of any one of examples 74-97, wherein the first flowpath and pump are operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 15 LPM.

[0135] Example 101 is the multi-purpose filter assembly of any one of examples 74-100, wherein the flow meter operable to measure flow rate of fluid in the first flowpath continuously monitors the LPM rate and is in communication with the first pump to adjust the first pump rate to maintain a desired LPM rate.

[0136] Example 102 is the multi-purpose filter assembly of any one of examples 74-101, wherein the flow meter operable to measure flow rate of fluid in the first flowpath is capable of accurately monitoring a flow rate of about 0 to about 8 LPM.

[0137] Example 103 is the multi-purpose filter assembly of any one of examples 74-102, wherein the flow meter operable to measure flow rate of fluid in the first flowpath is capable of accurately monitoring a flow rate of about 0.01 LPM to about 6 LPM.

[0138] Example 104 is the multi-purpose filter assembly of any one of examples 74-103, wherein the first flowpath has an accuracy requirement of about 1%.

[0139] Example 105 is the multi-purpose filter assembly of any one of examples 74-104, wherein the second flowpath has an accuracy requirement of about 3%.

[0140] Example 106 is the multi-purpose filter assembly of any one of examples 74-105, wherein the first flowpath and the second flowpath have the same or have different internal diameters.

[0141] Example 107 is the multi-purpose filter assembly of any one of examples 74-106, wherein the second flowpath and pump are operable to draw fluid from the HF filter at a higher flowrate than the first flowpath and first pump.

[0142] Example 108 is the multi-purpose filter assembly of any one of examples 74-107, wherein the second flowpath and pump are operable to draw fluid from the HF filter as a continuous harvest process.

[0143] Example 109 is the multi-purpose filter assembly of any one of examples 74-108, wherein the HF filter is not replaced when the multi-purpose assembly directs fluids through one flowpath and pump and then directs fluid through the other flowpath and pump.

[0144] Example 110 is the multi-purpose filter assembly of example 109, wherein the HF filter is not replaced when the multi-purpose assembly directs fluids first through the first flowpath and pump, and subsequently through the second flowpath and pump.

[0145] Example 111 is the multi-purpose filter assembly of any one of examples 74-110, wherein the first flowpath and second flowpath of the multi-purpose assembly are connected by a T connector, a Y connector, or a valve.

[0146] Example 112 is the multi-purpose filter assembly of any one of examples 74-111, further comprising a second flow meter operable to measure flow rate of fluid in the second flowpath and accurately monitoring a flow rate of about 0 to about 10 LPM, or about 0.5 LPM to about 8 LPM.

[0147] Example 113 is the multi-purpose filter assembly of any one of examples 74-112, wherein the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 36,000 L/m^2.

[0148] Example 114 is the multi-purpose filter assembly of any one of examples 74-112, wherein the second pump is operable to draw fluid from the HF filter at a throughput equal to between about 12,000 liters per square meter (L/m^2) to about 60,000 L/m^2, and/or between about 10,000 liters per square meter (L/m^2) to about 70,000 L/m^2.

[0149] Example 115 is the multi-purpose filter assembly of any one of examples 74-114, wherein the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 150 and about 900 liters per square meter per hour (LMH).

[0150] Example 116 is the multi-purpose filter assembly of any one of examples 74-115, wherein the second pump is operable to draw fluid from the HF filter at a filter flux rate of between about 200 and about 700 LMH.

[0151] Example 117 is the multi-purpose filter assembly of any one of examples 74-116, wherein the second flowpath and pump are operable to draw a feed flow rate from the HF filter of about 1 to about 3 liters per fiber per minute (L/fiber/min).

[0152] Example 118 is the multi-purpose filter assembly of any one of examples 74-117, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 8 LPM.

[0153] Example 119 is the multi-purpose filter assembly of any one of examples 74-117, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 13 LPM.

[0154] Example 120 is the multi-purpose filter assembly of any one of examples 74-117, wherein the second pump is operable to draw fluid from the HF filter at a flow rate of between about 0.01 LPM to about 18 LPM.

[0155] Example 121 is the multi-purpose filter assembly of any one of examples 74-120, wherein the HF filter is constructed of and/or comprises polypropylene, and/or polyethylene terephthalate.

[0156] Example 122 is the multi-purpose filter assembly of any one of examples 74-121, wherein the HF filter comprises isotropic pore structures, and/or comprises an average pore lumen diameter of about 0.65 µm to about 8 µm, or about 2 µm to about 5 µm.

[0157] Example 123 is the multi-purpose filter assembly of any one of examples 74-122, operable for use with shear sensitive cells.

[0158] Example 124 is the multi-purpose filter assembly of any one of examples 74-123, operable for use with animal cells.

[0159] Example 125 is the multi-purpose filter assembly of any one of examples 74-124, operable for use with mammalian cells.

[0160] Example 126 is the multi-purpose filter assembly of any one of examples 74-125, operable for use with Chinese Ovarian Hamster (CHO) cells.

[0161] Example 127 is the multi-purpose filter assembly of any one of examples 74-125, operable for use with human embryonic kidney 293 (HEK293) cells.

[0162] Example 128 is the multi-purpose filter assembly of any one of examples 74-127, operable for use with cells for the production of a biologic.

[0163] Example 129 is the multi-purpose filter assembly of example 128, wherein the biologic comprises an antibody, peptide, and/or virus.

[0164] Example 130 is a method of producing biologics from cells, comprising: a) expanding cells in a cell culture fluid in a bioreactor, b) during cell expansion, perfusing cell culture fluid through a Hollow Fiber (HF) filter to remove spent cell culture media while retaining the expanding cells, and adding an appropriate replacement volume of cell culture media to the

bioreactor to maintain a desired cell culture fluid level in the bioreactor, wherein the spent cell culture media is perfused through the HF filter at a first flow rate to enter a first flowpath, and c) following cell expansion, harvesting cell culture fluid through a HF filter to obtain the biologics, and adding an appropriate replacement volume of cell culture media to the bioreactor to maintain a desired cell culture fluid level in the bioreactor during different phases of harvest, wherein the cell culture media is harvested through the HF filter at a second flow rate to enter a second flowpath, wherein the second flow rate is greater than the first flow rate.

[0165] Example 131 is the method of example 130, wherein the HF filter is operable for tangential flow.

[0166] Example 132 is the method of any one of examples 130-131, wherein the HF filter is a tangential flow depth filtration® (TFDF®) filter.

[0167] Example 133 is the method of any one of examples 130-132, wherein replacement volume of cell culture media in b) and/or c) is about the same amount of spent cell culture media as is removed.

[0168] Example 134 is the method of any one of examples 130-132, wherein the replacement volume of cell culture media in b) and/or c) is greater than the amount of spent cell culture media removed.

[0169] Example 135 is the method of any one of examples 130-132, wherein the replacement volume of cell culture media in b) and/or c) is less than the amount of spent cell culture media removed.

[0170] Example 136 is the method of any one of examples 130-135, wherein the replacement volume of cell culture media is fresh cell culture media.

[0171] Example 136.1 is the method of any one of examples 130-136, wherein the perfusion process comprises more than one perfusion stage.

[0172] Example 136.2 is the method of any one of examples 130-136.1, wherein the perfusion process comprises more than one perfusion stage, and the HF filter is used for more than one perfusion stage, an in-between perfusion and harvest process, and a harvest process.

[0173] Example 137 is the method of any one of examples 130-136.2, wherein the first flow rate is less than or equal to about 5 LPM, and a second flow rate is greater than about 5 LPM.

[0174] Example 138 is the method of any one of examples 130-137, wherein the HF filter is constructed of and/or comprises polypropylene, and/or polyethylene terephthalate.

[0175] Example 139 is the method of any one of examples 130-138, wherein the HF filter comprises isotropic pore structures, and/or comprises an average pore lumen diameter of about 0.65 µm to about 8 µm, or about 2 µm to about 5 µm.

[0176] Example 140 is the method of any one of examples 130-139, wherein the cells are shear sensitive cells.

[0177] Example 141 is the method of any one of examples 130-140, wherein the cells are animal cells.

[0178] Example 142 is the method of any one of examples 130-141, wherein the cells are mammalian cells.

[0179] Example 143 is the method of any one of examples 130-142, wherein the cells are CHO cells.

[0180] Example 144 is the method of any one of examples 130-142, wherein the cells are HEK293 cells.

[0181] Example 145 is the method of any one of examples 130-144, wherein the biologic comprises an antibody, peptide, and/or virus.

[0182] Example 146 is a method of producing biologics from cells, comprising use of a bioreactor system or multi-purpose filter assembly according to any one of examples 1-129.

[0183] Example 147 is a use of a multi-purpose filter assembly of any one of examples 74-129 in a bioreactor system.

[0184] Example 148 is the use of example 147, wherein the bioreactor system comprises the features of any of examples 1 to 73.

[0185] Example 149 is a use of a bioreactor system of any one of examples 1 to 74 for the culturing of cells.

[0186] Example 150 is the use of example 149, wherein the cells produce biologics and the use further comprises harvesting cell culture fluid through the HF filter to obtain the biologics.

[0187] Example 151 is the system, assembly, method, or use of any one of examples 1-150, wherein the system, assembly, method, or use results in one or more of improved productivity, improved performance, improved efficiency, reduced contamination rates, reduced capital investment, reduced physical footprint, reduced consumables attrition, or reduced operation costs for a facility comprising a biologics production process.

BRIEF DESCRIPTION OF THE DRAWINGS

[0188] The present disclosure is described in conjunction with the appended figures: