up and flow of material. Additionally, the described system displays superior fault tolerance compared to multi-column serial units, in that if a single unit is unable to function, only the single column is impacted and can be easily isolated and extracted, without the entire run being lost and/or brought to a stop.

SUMMARY

[0008] In accordance with a first aspect, a continuous parallel chromatography system is described herein that includes a plurality of chromatography column skids having no flow path between or connecting the plurality of chromatography skids to one another, where each chromatography column skid is suitable for independent batch processing. Each chromatography column skid includes a chromatography column, an inlet selectively coupled to an upstream source, at least one pump, at least one filter, and an outlet sensor. The system further includes a control circuit configured to control the operation of the plurality of chromatography column skids through one or more full cycles of a chromatography process, where each full cycle includes a long step and a plurality of shorter steps, each of the plurality of shorter steps having a processing time shorter than or equal to a processing time of the long step. The control circuit is configured to receive a synchronization signal associated with a first one of the plurality of chromatography column skids that the long step is complete and, in response to reception of the synchronization signal, direct operation of a second one of the plurality of chromatography column skids to commence operation of the long step.

[0009] In some forms, the control circuit can be configured to direct operation of the plurality of shorter steps on the first one of the plurality of chromatography column skids to complete the full cycle of the chromatography process therefor after reception of the synchronization signal. In these forms, the control circuit can further be configured to receive a second synchronization signal associated with the second one of the plurality of chromatography column skids that the long step is complete and, in response to reception of the second synchronization signal, direct operation of the first one of the plurality of chromatography column skids to commence a second operation of the long step. In yet further forms, the control circuit can be configured to direct operation of the plurality of shorter steps on the second one of the plurality of chromatography column skids to complete the full cycle of the chromatography process therefor after reception of the second synchronization signal.

[0010] In any of the above forms, the long step can be an eluting step for the chromatography column, where the plurality of shorter steps can include two or more of: an equilibration step, a loading step, one or more washing steps, a regeneration step, or a flushing step and/or the long step can be a loading step for the chromatography column, where the plurality of shorter steps can include two or more of: an equilibration step, one or more washing steps, an elution step, a regeneration step, or a flushing step. In forms having the long step being a loading step, the first one of the plurality of chromatography column skids can be configured to receive a feed of feedstock from the upstream source and send the synchronization signal to the control circuit indicating that a load of the feedstock in the chromatography column of the first one of the plurality of chromatography columns is complete and, in response to reception of the synchronization signal, the control circuit is configured to switch the feed of the feedstock from the upstream source to the second one of the plurality of chromatography column skids to perform the loading step for the chromatography column thereof. In these forms, the control circuit can be configured to direct a feed of one or more processing feedstocks to the first one of the plurality of chromatography column skids to perform processing of the short steps on the loaded chromatography column thereof and, if desired, after completion of the processing of the short steps on the loaded chromatography column, the first one of the plurality of chromatography column skids can be configured to await a generation of a second synchronization signal associated with the second chromatography column skid that the loading step for the chromatography column thereof is complete. In any of these forms, the feedstock can be a protein, an antibody, a multispecific protein, a bispecific protein, or a bi-specific T cell engager and/or the upstream source of the feedstock can be one of: a stream or pool of harvested cell culture fluid, an elution stream or pool from a capture chromatography column, a viral inactivated pool from a capture chromatography column, or a neutralized viral inactivated pool from a capture chromatography column.

[0011] In any of the above forms, the chromatography columns of the plurality of chromatography skids can be capture chromatography columns. The capture chromatography columns can be one or more of: affinity chromatography columns, size exclusion chromatography columns, ion exchange chromatography columns, hydrophobic interaction chromatography columns, multi-modal chromatography columns, hydroxyapatite chromatography columns, or immobilized metal affinity chromatography columns. The capture chromatography columns can be affinity chromatography columns consisting of Protein A chromatography columns, Protein G chromatography columns, or Protein L chromatography columns. The capture chromatography columns can be ion exchange chromatography columns consisting of cation exchange chromatography columns or anion exchange chromatography columns.

[0012] In any of the above forms, the system can include at least one of a viral filtration device and/or an ultrafiltration device fluidly connected downstream of the plurality of chromatography column skids; the control circuit can be a plurality of controllers of each of the plurality of chromatography column skids in communication with one another or a central controller in communication with each of the plurality of chromatography column skids; the chromatography columns of the plurality of chromatography column skids can have a plurality of different sizes relative to one another; or one or more of the chromatography columns of the plurality of chromatography column skids can be single-use chromatography columns.

[0013] In any of the above forms, the system can include one or more collection tanks fluidly coupled downstream of the plurality of chromatography column skids and/or a downstream capture chromatography column. In some forms, the downstream chromatography column can be an ion exchange chromatography column, a hydrophobic interaction chromatography column, a multi-modal chromatography column, or a hydroxyapatite chromatography column. The downstream chromatography column can be a cation exchange or anion exchange column. In further forms, the downstream chromatography column can be a first downstream chromatography column and the system can include a second downstream chromatography column connected directly in series with the first downstream chromatography column, where the first and second downstream chromatography columns can be cation and/or anion exchange columns. In other forms, the downstream chromatography column can be a first downstream chromatography column and the system can further include a second downstream chromatography column, where the first and second downstream chromatography columns are disposed on first and second downstream chromatography column skids, respectively, and the first and second downstream chromatography column skids are each suitable for independent batch processing and an inlet, at least one pump, at least one filter, and an outlet sensor. In these forms, the control circuit can be configured to control operation of the first and second downstream chromatography column skids through one or more full cycles of a downstream chromatography process, each full cycle including a long elution step and a plurality of shorter steps, each of the plurality of shorter steps having a processing time shorter than or equal to a processing time of the long elution step, and to: receive a synchronization signal associated with the first downstream chromatography column skid that the long elution step is complete and, in response to reception of the synchronization signal, direct operation of the second chromatography column skid to commence operation of the long elution step.

[0014] A method for purification of a recombinant protein from one or more contaminants is described that includes subjecting the protein to an affinity chromatography unit operation, subjecting the elution pool from the affinity chromatography unit operation to low pH viral inactivation and neutralization, and subjecting the neutralized pool to one or more polishing chromatography unit operations. At least one of the affinity chromatography unit operation or at least one of the one or more polish chromatography unit operations are operated according to a parallel chromatography process configured to control the operation of a plurality of chromatography column skids through one or more full cycles of a chromatography process, where each full cycle includes a long step and a plurality of shorter steps and each of the plurality of shorter steps has a processing time shorter than or equal to a processing time of the long step. The parallel chromatography process includes the steps of: receiving a synchronization signal associated with a first one of the plurality of chromatography column skids that the long step is complete at a control circuit of a parallel chromatography system and in response to reception of the synchronization

signal, directing operation with the control circuit of a second one of the plurality of chromatography column skids to commence operation of the long step.

[0015] In some forms, the affinity chromatography unit operation is performed according to the parallel chromatography process and, in further forms, the long step can be loading a column of the chromatography column skids and the plurality of shorter steps can be two or more of: an equilibration step, one or more washing steps, an elution step, a regeneration step, or a flushing step. In other forms, at least one of the one or more polish chromatography unit operations can be performed according to the parallel chromatography process and, in further forms, the long step can be eluting a column of the chromatography column skids and the plurality of shorter steps can be two or more of: an equilibration step, a loading step, one or more washing steps, a regeneration step, and a flushing step. In yet further forms, both the affinity chromatography unit operation and at least one of the one or more polish chromatography unit operations can be performed according to the parallel chromatography process.

[0016] In some forms, the parallel chromatography process can include the step of directing operation of the plurality of shorter steps on the first one of the plurality of chromatography column skids with the control circuit to complete the full cycle of the chromatography process therefor after reception of the synchronization signal and, in further forms, the parallel chromatography process can include the steps of: receiving a second synchronization signal associated with the second one of the plurality of chromatography column skids at the control circuit that the long step is complete and, in response to reception of the second synchronization signal, directing operation of the first one of the plurality of chromatography column skids with the control circuit to commence a second operation of the long step.

[0017] In some forms, the method can include one or more of the following: at least one of the one or more polish chromatography unit operations can include first and second polish chromatography unit operations with a first capture chromatography column connected in series with a second capture chromatography column; the one or more polish chromatography unit operations can include separate first and second polish chromatography unit operations; the first polish chromatography unit operation precedes or follows the second polish chromatography unit operation; the virus inactivated elution pool can be neutralized using a neutralizing buffer system capable of minimizing volume expansion of a viral inactivated eluate pool while maintaining conductivity less than or equal to 10 ms/cm, wherein the buffer system includes a titrant that does not have buffer capacity in the target pH range and a buffering agent which buffers at a desired pH; the viral inactivation can be 30 minutes or more; the method can include subjecting the neutralized pool to a depth filtration operation; the method can include subjecting an elution of the one or more polish chromatography unit operations to one or more of: an ultrafiltration/diafiltration unit operation or a virus filtration unit operation; the affinity chromatography unit operation can be Protein A chromatography, Protein G chromatography, or Protein L chromatography; at least one of the one or more polish chromatography unit operations can be cation exchange chromatography, anion exchange chromatography, multi-modal chromatography, or hydrophobic interaction chromatography.

[0018] Any of the above forms can be a method for producing an isolated, purified, recombinant protein of interest. An isolated, purified, recombinant protein of interest of the above method is disclosed and a pharmaceutical composition including the isolated, purified, recombinant protein of interest of the above method is disclosed.

[0019] A system for neutralizing a viral inactivated pool to a target pH with minimal volume expansion is disclosed that includes a titrant that does not have buffer capacity in a target pH range and a buffering agent which buffers at the target pH, where the conductivity of the neutralized viral inactivation elution pool is maintained at less than or equal to 10 ms/cm.

[0020] In some forms, the system can include one or more of the following aspects: the titrant can have a pKa greater than 7 and the buffering agent can have a pKa in the range of 4.5 to 6.0; the titrant can be acetate and the buffering agent can be Tris

What is Claimed is:

1. A continuous parallel chromatography system, the system comprising:

a plurality of chromatography column skids having no flow path between or connecting the plurality of chromatography skids to one another, each chromatography column skid suitable for independent batch processing and comprising:

a chromatography column;

an inlet selectively coupled to an upstream source;

at least one pump;

at least one filter; and

an outlet sensor;

a control circuit configured to control the operation of the plurality of chromatography column skids through one or more full cycles of a chromatography process, each full cycle including a long step and a plurality of shorter steps, each of the plurality of shorter steps having a processing time shorter than or equal to a processing time of the long step, wherein the control circuit is configured to:

receive a synchronization signal associated with a first one of the plurality of chromatography column skids that the long step is complete; and

in response to reception of the synchronization signal, direct operation of a second one of the plurality of chromatography column skids to commence operation of the long step.

2. The system of claim 1, wherein the control circuit is further configured to direct operation of the plurality of shorter steps on the first one of the plurality of chromatography column skids to complete the full cycle of the chromatography process therefor after reception of the synchronization signal.

3. The system of claim 2, wherein the control circuit is further configured to:

receive a second synchronization signal associated with the second one of the plurality of chromatography column skids that the long step is complete;

in response to reception of the second synchronization signal, direct operation of the first one of the plurality of chromatography column skids to commence a second operation of the long step; and

direct operation of the plurality of shorter steps on the second one of the plurality of chromatography column skids to complete the full cycle of the chromatography process therefor after reception of the second synchronization signal.

4. The system of any one of the preceding claims, wherein the long step comprises an eluting step for the chromatography column; and the plurality of shorter steps comprise two or more of: an equilibrium step, a loading step, one or more washing steps, regeneration step, or a flushing step.

5. The system of any one of the preceding claims, wherein the long step comprises a loading step for the chromatography column; and the plurality of shorter steps comprise two or more of: an equilibrium step, one or more washing steps, an elution step, a regeneration step, or a flushing step.

6. The system of claim 5, wherein:

the first one of the plurality of chromatography column skids is configured to receive a feed of feedstock from the upstream source and send the synchronization signal to the control circuit indicating that a load of the feedstock in the chromatography column of the first one of the plurality of chromatography columns is complete; and

in response to reception of the synchronization signal, the control circuit is configured to switch the feed of the feedstock from the upstream source to the second one of the plurality of chromatography column skids to perform the loading step for the chromatography column thereof.

7. The system of claim 6, wherein the control circuit is further configured to direct a feed of one or more processing feedstocks to the first one of the plurality of chromatography column skids to perform processing of the short steps on the loaded chromatography column thereof.

8. The system of claim 7, wherein, after completion of the processing of the short steps on the loaded chromatography column, the first one of the plurality of chromatography column skids is configured to await a generation of a second synchronization signal associated with the second chromatography column skid that the loading step for the chromatography column thereof is complete.

9. The system of any one of claims 6 to 8, wherein the feedstock comprises a protein, an antibody, a multispecific protein, a bispecific protein, or a bi-specific T cell engager.

10. The system of any one of claims 6 to 8, wherein the upstream source of the feedstock comprises one of: a stream or pool of harvested cell culture fluid, an elution stream or pool from a capture chromatography column, a viral inactivated pool from a capture chromatography column, or a neutralized viral inactivated pool from a capture chromatography column.

11. The system of any one of the preceding claims, wherein the chromatography columns of the plurality of chromatography skids comprise capture chromatography columns comprising one or more of: affinity chromatography columns, size exclusion chromatography columns, ion exchange chromatography columns, hydrophobic interaction chromatography columns, multi-modal chromatography columns, hydroxyapatite chromatography columns, or immobilized metal affinity chromatography columns.

12. The system of claim 11, wherein the capture chromatography columns comprise affinity chromatography columns consisting of Protein A chromatography columns, Protein G chromatography columns, or Protein L chromatography columns; or ion exchange chromatography columns consisting of cation exchange chromatography columns or anion exchange chromatography columns.

13. The system of any one of the preceding claims, further comprising at least one of a viral filtration device and/or an ultrafiltration device fluidly connected downstream of the plurality of chromatography column skids.

14. The system of any one of the preceding claims, wherein the control circuit comprises:

a plurality of controllers of each of the plurality of chromatography column skids in communication with one another; or

a central controller in communication with each of the plurality of chromatography column skids.

15. The system of any one of the preceding claims, wherein the chromatography columns of the plurality of chromatography column skids have a plurality of different sizes relative to one another.

16. The system of any one of the preceding claims, wherein one or more of the chromatography columns of the plurality of chromatography column skids comprise single-use chromatography columns.

17. The system of any one of the preceding claims, further comprising:

one or more collection tanks fluidly coupled downstream of the plurality of chromatography column skids; and

a downstream capture chromatography column.

18. The system of claim 17, wherein the downstream chromatography column comprises an ion exchange chromatography column, a hydrophobic interaction chromatography column, a multi-modal chromatography column, or a hydroxyapatite chromatography column.

19. The system of claim 17 or 18, wherein the downstream chromatography column comprises a first downstream chromatography column; and further comprising a second downstream chromatography column connected directly in series with the first downstream chromatography column.

20. The system of any one of claims 17 to 19, wherein:

the downstream chromatography column comprises a first downstream chromatography column; and further comprising a second downstream chromatography column;

the first and second downstream chromatography columns are disposed on first and second downstream chromatography column skids, respectively, the first and second downstream chromatography column skids each suitable for independent batch processing and comprising:

an inlet;

at least one pump;

at least one filter; and

an outlet sensor;

the control circuit is configured to control operation of the first and second downstream chromatography column skids through one or more full cycles of a downstream chromatography process, each full cycle including a long elution step and a plurality of shorter steps, each of the plurality of shorter steps having a processing time shorter than or equal to a processing time of the long elution step, wherein the control circuit is configured to:

receive a synchronization signal associated with the first downstream chromatography column skid that the long elution step is complete; and

in response to reception of the synchronization signal, direct operation of the second chromatography column skid to commence operation of the long elution step.