SYSTEM AND METHOD FOR CONTINUOUS BIOPROCESSING SIMULATION

BACKGROUND

Relevant Field

[001] The present disclosure relates to bioprocessing. More particularly, the present disclosure relates to a system, method and apparatus for continuous bioprocessing simulations.

Description of Related Art

[002] In the engineering and simulation domains, there is a growing demand for efficient and standardized methods to integrate various simulation components or models into larger systems. These components, known as Functional Mock-up Units (FMUs), may play a role in simulating and analyzing complex systems.

[003] Currently, two widely used approaches for integrating FMUs into simulation environments are co-simulation and model exchange. In the co-simulation approach, each FMU implements its own simulation algorithm and exchanges information with other FMUs during simulation. Conversely, the model exchange approach involves an FMU providing a model description for a simulation algorithm to execute the simulation.

[004] The complexity of bioprocesses, encompassing sequential and parallel biological reactions occurring at various time steps, poses a modeling challenge, especially when modeling continuous bioprocessing systems. Developing separate models for each action and parametrizing them based on the biological system being modeled is a labor-intensive process. Additionally, creating new models entails undergoing the arduous software validation process, which carries legal implications. Thus, there is a need to generate fully-validated continuous bioprocessing simulations that account for the biologically-constrained processes.

[005] Existing literature has described the use of Functional Mock-Up (FMU) in other industries, albeit not yet applied to bioprocessing simulations. Typically, FMUs are used in a basic composed manner within a co-simulation framework at a metamodel level.

[006] There is a need for improved bioprocess modeling tools that can simulate the many coupled domains and timescales involved in bioprocesses. Enabling bioprocess models to be rapidly composed from pre-validated components could significantly improve productivity. The ability to quickly create and simulate bioprocess models with different parameters and conditions could reduce physical experiments needed during development. This could lead to substantial time and

cost savings compared to traditional bioprocess modeling approaches requiring full validation of each new model. Therefore, the present application addresses the need for a method to orchestrate parametrized simulations in the field of bioprocessing. Bioprocesses involve complex species, reactions, and kinetics, making modeling in this domain important for its future development.

SUMMARY

[007] The present disclosure relates to a system and method for continuous bioprocessing simulation utilizing parameterized and pre-validated model components. The system selects validated equations from a catalogue to construct modular unit operation models, which are then instantiated into configured instances. These instances are interconnected into an integrated flowsheet simulation, which is co-simulated to capture the transient behavior of components with different time constants. The parametrized, modular modeling approach enables rapid and robust simulation of continuous biopharmaceutical production processes by assembling simulations from pre-qualified building blocks. This facilitates efficient digital prototyping and analysis of integrated continuous bioprocess systems.

[008] The method for parametrized simulation in bioprocessing involves selecting multiple pre-validated equations from a catalogue to generate a model. A first instance of the model is instantiated by loading parameters including a first time-step parameter into the first instance. A second instance is also instantiated by loading a second time-step parameter into that instance. A continuous process simulation environment is then formed containing the first and second instances. The instances are co-simulated, with the first instance simulated according to the first time-step parameter and the second instance simulated according to the second time-step parameter. One or more outputs are determined from the continuous process simulation. In this manner, the method leverages pre-validated models configured into instances with distinct time constants to enable co-simulation of an integrated continuous bioprocess flowsheet.

[009] The method utilizes models that each correspond to a type of bioprocess component or unit operation. In some embodiments, the models may represent equipment types such as feeds, pumps, bioreactors, tubes, surge vessels, chromatography columns, filters, or other common elements found in continuous biopharmaceutical production workflows. Each model encapsulates the physical relationships and governing equations needed to simulate the behavior of its particular component type. This allows constructing process flowsheet simulations by combining different

standardized, pre-validated models from the catalogue to represent the various equipment types found in integrated continuous bioprocess systems.

[0010] The types of bioprocess components that may be modeled include, but are not limited to, feeds, pumps, bioreactors, tubes, surge vessels, chromatography columns, and more. The system contains a catalogue with validated model components covering common equipment types found in continuous biopharmaceutical production processes in order to enable rapid simulation model development by selecting and combining predefined, standardized sub-models rather than building custom models from scratch for each equipment variant. This configurability and flexibility in mixing and matching validated model building blocks from the catalogue facilitates efficient exploration and analysis of different continuous bioprocess flowsheet options and configurations.

[0011] The modular models that represent types of bioprocess components may be comprised of a plurality of interconnected sub-models. For example, a model of a continuous chromatography column could contain coupled sub-models for phenomena occurring at different points along the column length, with each sub-model described by its own set of mathematical relationships. These individual sub-models are integrated together into an overall model for the complete column component. Thus, the parameterized modeling approach enables breaking down complex bioprocess equipment into constituent modules described by first-principles. The composite model formed from the interconnected sub-models then provides a high-fidelity simulation of the entire component.

[0012] The method may instantiate multiple instances of the same model. In some embodiments, the second instance, which is interconnected into the continuous process simulation environment along with the first instance of the model, is also an instance of the same model template. By configuring the model template with distinct parameters, unique instances can be generated from a common model foundation to represent different equipment configurations or operating conditions of similar unit operations within the flowsheet simulation. The flexibility to instantiate multiple copies of a model tailored with specialized parameters facilitates efficiently prototyping integrated processes involving parallel units.

[0013] In some embodiments, the second instance that is interconnected within the continuous process simulation environment may be an instance of a second model, different from the original model used to generate the first instance. Thus, the simulation environment can link together model instances originating from distinct model templates selected from the catalogue. This enables simulating complex process workflows containing diverse equipment types, with each

component instance configured from the most suitable model template for that particular unit operation type. The flexibility to instantiate and couple instances from various model templates facilitates accurately representing the diversity of equipment found in real-world continuous biopharmaceutical production processes within the integrated simulation environment.

[0014] The method utilizes different time step parameters loaded into each model instance during instantiation. This enables configuring individual instances with appropriate time discretizations based on the dynamic characteristics of the process equipment being simulated. For example, a continuous bioreactor instance may be executed with 10 millisecond timesteps in order to resolve transient reactions, while a chromatography column instance operates on 10 minute timesteps reflective of its slower separation dynamics. Thus, the co-simulation orchestrates instances having different time constants running at varying timescales, synchronizing exchange of mass, energy, and data at coupling points. Capturing bioprocess components with both fast and slow responses within an integrated simulation environment provides a high degree of modeling flexibility and time resolution accuracy.

[0015] The method can leverage a co-simulation approach to integrate model instances potentially having vastly different timescales and timesteps. Specifically, each model instance contains metadata defining its own distinct simulation timestep as well as integration algorithm parameters. The co-simulator is configured to advance each model instance according to its individual timestep specification while coordinating synchronized data exchange between model instances at coupling points. This allows the system to simulate a complete bioprocess flowsheet containing unit operations with timesteps that may differ by at least an order of magnitude or more. The coordinated execution accounts for and reconciles the different dynamic characteristics of each equipment model.

[0016] In some embodiments, the method constructs process unit operation models by selecting only pre-validated equations from the catalogue. Since all model components originate from the qualified catalogue, all governing equations encapsulated in each model are pre-validated over relevant operating ranges. As a result, all models created by the system contain mathematical relationships and parameters verified against experimental data or first principles derivations. Building models solely from pre-validated catalogue elements ensures inherent reliability and accuracy of the simulation dynamics, critical for both compliance and operational needs. Utilizing equations that have undergone rigorous qualification testing accelerates model development while also guaranteeing robust behavior not prone to unexpected artifacts found in unverified models.

Overall, forming unit operation models only from pre-validated constituent relationships enables both rapid construction and robust simulations of continuous biopharmaceutical processes.

[0017] The method may optionally involves utilizing digital twin models that mirror associated physical continuous bioprocessing equipment. In some embodiments, the model generated from the pre-validated equations represents a digital twin of an actual continuous bioprocess device. This digital twin model can be periodically updated during simulations to match the current state of the physical system based on real-time or historical operational data. Updating the simulation state of the digital twin enables high-fidelity simulations for advanced applications like monitoring, control, and optimization that leverage real-world equipment data.

[0018] The method may utilize digital twin models that serve as virtual representations of physical continuous bioprocessing equipment. These digital twin models are periodically updated during simulations to match the current state of the physical devices based on real-time or historical operational data. This enables creating high-fidelity simulations for monitoring, control, and optimization applications by integrating live data from real-world bioprocessing systems into the digital twin models. Updating the simulation state of the digital twin models to align with the actual state of their corresponding physical devices provides an accurate digital profile that can be used for various analyses.

[0019] The method may utilize digital twin models that are periodically updated during simulations to match the current state of physical bioprocessing devices. In some embodiments, the digital twin models are updated based on real-time data from sensors or information systems associated with the actual continuous bioprocessing equipment. Synchronizing the simulation state to the physical equipment state in this manner enables high-fidelity digital twin representations for advanced monitoring, control, and optimization applications.

[0020] In some embodiments, the models utilized may represent digital twins of actual physical continuous bioprocessing equipment. The simulation state of these digital twin models can be periodically updated to match the current state of the physical devices based on historical operational data collected from the physical equipment over time. This enables creating high-fidelity simulations for monitoring, control, and optimization that leverage real-world data from the physical bioprocessing systems.

[0021] The method may couple model instances together in series via connectors representing bioprocess equipment like tubing. For example, the first model instance could represent a continuous bioreactor, while the second model instance represents a chromatography column.

These component simulations can be connected together by adding a tube model instance between the first and second instances. This tubes instance routes output streams from the first instance as input streams into the second instance. By daisy-chaining model instances in series, complete bioprocess flowsheets can be constructed digitally and simulated in an integrated manner. The co-simulation approach enables capturing the transient behavior across sequentially connected equipment having different dynamic characteristics. In this way, the parametrized modeling methodology can simulate both single unit operations as well as connected bioprocess systems.

[0022] The method may include coupling the first instance of the model and the second instance in parallel within the continuous process simulation environment. In some embodiments, this involves virtually linking the first instance and second instance such that they represent separate parallel branch flows that reconverge further downstream. Parallel coupling of model instances enables simulating complex bioprocess workflows containing parallel equipment trains, side streams, and multistage configurations within an integrated flowsheet model. Specifying parallel connectivity as well as material stream merges and splits between instances is handled automatically when forming the simulation environment. In this way, sophisticated continuous bioprocess topologies can be rapidly constructed and digitally prototyped by combining configurable model building blocks.

[0023] In embodiments, a system for parametrized simulation in the field of bioprocessing may comprise a component selector, an instantiator, a simulation environment former, and a co-simulator. The component selector is configured to select a plurality of pre-validated equations from a catalogue to generate a model. The instantiator is configured to instantiate a first instance of the model by loading parameters including a first time-step parameter into the first instance and to instantiate a second instance by loading a second time-step parameter into the second instance. The simulation environment former is configured to form a continuous process simulation environment having the first instance and the second instance. The co-simulator is configured to co-simulate the first instance in accordance with the first timestep parameter and the second instance in accordance with the second timestep parameter in order to determine at least one output of the continuous process simulation.

[0024] The system may includes a component selector configured to select pre-validated equations from a catalogue to generate models. In some embodiments, each model generated from the catalogue of equations may correspond to a type of bioprocess component or unit operation, such as a pump, tube, bioreactor, surge vessel, chromatography column, or other equipment found

in continuous biopharmaceutical production workflows. By selecting appropriate validated equations, the system can construct modular models representing different common types of bioprocess components. These models can then be instantiated into configured instances and interconnected to form an integrated continuous bioprocess simulation.

[0025] The system may include various types of bioprocess component models that can be selected from the catalogue and instantiated into flowsheet simulations. These component models may represent common equipment found in continuous biopharmaceutical production processes, including feed streams, pumps, bioreactors, tubes, surge vessels, chromatography columns, and more. By providing an extensive library of pre-validated models covering typical unit operations, the system aims to facilitate rapid construction of integrated process simulations by assembling modular building blocks representing all sections of a bioprocess flowsheet. Encapsulating the behaviors of individual components enables configuring and connecting the models to digitally prototype overall integrated systems and workflows.

[0026] In some embodiments, the second instance instantiated into the continuous bioprocess simulation environment is an additional instance of the same model template used to generate the first instance. Rather than connecting different model types together, multiple instances of the same equipment model can be included in the flowsheet simulation. This allows evaluating the system-wide impacts of parallel unit operations or recycle stream configurations by simulating duplicate equipment modules with shared parameters inherited from the parent model. Enabling instances of the same model template to be coupled as needed supports flexible arrangement of similar bioprocess components within the integrated digital prototype environment.

[0027] The system may allow interconnecting different model types into the integrated flowsheet simulation. Specifically, the second instance instantiated into the simulation environment may be generated from a second model distinct from the first model used to produce the first instance. Enabling instances derived from different base models to be coupled allows combining complementary equipment simulations to capture complex process workflows. This modeling flexibility further enhances representation of real-world systems where components often originate from multiple vendors with unique designs. Ultimately, supporting instances of disparate model types facilitates accurate and robust continuous bioprocess simulations.

[0028] The system enables configuring different model instances with unique timestep parameters. Specifically, the first timestep parameter loaded into the first model instance may be different than the second timestep parameter loaded into the second model instance. Defining

diverse timesteps allows co-simulation of integrated systems with components operating on disparate timescales. For instance, a continuous reactor model may warrant microsecond resolution to capture reaction kinetics while a large-scale chromatography model may only require updates every few minutes. Independent tuning of timestep parameters facilitates multi-timescale co-simulation. In some embodiments, the timestep parameters may differ by orders of magnitude across model instances. The flexible parametrization supports integrating both fast and slow components into a coupled flowsheet simulation. The system facilitates co-simulation of model instances that may have vastly different transient characteristics and timescales. The co-simulation approach coordinates data exchange between instances using timesteps differing by at least an order of magnitude or more. Capturing and integrating vastly different time constants under a range of timescales enables high fidelity simulations of complete bioprocess workflows containing sequential and parallel unit operations with both fast and slow kinetics.

[0029] The system may use pre-validated model components from the catalogue to construct simulation models, ensuring model reliability and accuracy. In particular, the models generated by the component selector are formed entirely from pre-validated equations that have been extensively tested and qualified. This model qualification process involves comparing simulation predictions to both first-principles theoretical results and experimental data from real systems to validate model fidelity over relevant operating ranges prior to use. As a result, the assembled models provide a rigorously validated, high-confidence simulation platform enabling robust digital prototyping of continuous biopharmaceutical processes. The exclusive reliance on pre-validated equations as building blocks maintains confidence in simulation integrity for critical applications.

[0030] The system may utilize digital twin models that mirror physical continuous bioprocessing devices. In some embodiments, the model generated from the component catalogue can represent a digital twin of an actual bioprocess equipment system or unit operation. The digital twin model may be periodically updated during simulations to match the current state of the physical system based on real-time or historical operational data. This enables simulations for monitoring, control, and optimization applications by integrating live data from real-world bioprocess plants. Updating the simulation state of the digital twin model to align with the physical twin system leverages real-world conditions and disturbances to enhance representation fidelity.

[0031] The system may further comprise an updater component configured to periodically update the digital twin model to match the current simulation state with the actual operating state of the physical continuous bioprocessing device represented by the digital twin. In some embodiments,

the updater can synchronize the simulation in real-time or near-real-time by incorporating latest sensor measurements and operational data from the physical twin system, thereby enabling high-fidelity digital twin applications for monitoring, control, and optimization. Alternatively or additionally, the updater can leverage historical process data to re-align the digital twin to observed physical conditions for refinement and validation purposes. By dynamically synchronizing with physical equipment, the parametrized modeling approach can produce accurate digital twins for continuous bioprocesses.

[0032] The system may further include an updater component configured to periodically synchronize the simulation state of digital twin models with the actual state of their corresponding physical continuous bioprocess devices. The updater can leverage real-time data collected from sensors, analyzers, and control systems associated with the physical equipment to update the matching virtual model. This enables the digital twin simulations to accurately mirror the current operating conditions, variability, disturbances, and other transient behavior occurring in the real production environment. By continually aligning the digital and physical worlds, the parametrized modeling approach can effectively leverage live production data to enhance monitoring, control, and optimization applications.

[0033] The system may include an updater configured to periodically update the simulation state of a digital twin model to match the current state of a physical continuous bioprocess device. In particular, the updater can leverage historical operational data collected from sensors, control systems, and manufacturing execution systems associated with the physical device in order to recalibrate and synchronize the digital twin simulation. This enables the parameterized modeling approach to closely represent the true, current behavior of real-world continuous bioprocessing equipment for monitoring, control, and optimization applications that require high-fidelity simulations.

[0034] The system may utilize digital twin models that are periodically updated to match the current state of physical continuous bioprocess devices based on historical operational data from those devices. In particular, the model instantiated in the system can represent a digital twin of an actual continuous bioreactor, chromatography column, or other bioprocess equipment. Historical data including previous temperatures, pressures, flow rates, and compositions from physical device sensors can be fed into the digital twin model to initialize and update its simulation state to mirror the physical equipment state.

[0035] The system can interconnect the parameterized model instances into an integrated flowsheet simulation environment. In some embodiments, the system may couple the model instances together in series via connectors that simulate transfer piping or tubing. This allows the output stream data from one model instance, such as a continuous bioreactor, to be routed as input stream data to the next downstream unit operation model, such as a chromatography column. Chaining model instances together into a complete process train enables simulating an end-to-end continuous biopharmaceutical production workflow.

[0036] The system may interconnect model instances in various configurations within the flowsheet simulation environment. For example, in some embodiments, the first and second model instances are connected together in parallel. Coupling model instances in parallel enables simulating parallel branches and equipment redundancy within an integrated continuous bioprocess. This provides flexibility in exploring flowsheet options and evaluating the impact of parallel configurations on factors such as equipment utilization, system reliability, and ease of maintenance during bioprocess simulation. Thus, the parametrized modeling system facilitates simulating model instances linked not only in series but also complex parallel arrangements.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] These and other aspects will become more apparent from the following detailed description of the various embodiments of the present disclosure with reference to the drawings wherein:

[0038] Fig. 1 shows a system for simulating a continuous bioprocess system in accordance with an embodiment of the current disclosure;

[0039] Fig. 2 shows an example model that is an incubation chamber in accordance with an embodiment of the present disclosure;

[0040] Fig. 3 shows an example model that is a vessel in accordance with an embodiment of the present disclosure;

[0041] Fig. 4 shows an example of how two model instances can be interconnected within a continuous bioprocess simulation environment in accordance with an embodiment of the present disclosure;

[0042] Fig. 5 shows an example configuration file that can be used to define and parameterize model instances in the continuous bioprocess simulation system in accordance with an embodiment of the present disclosure; and

[0043] Fig. 6 shows a graphical user interface as to how the simulation environment can appears when being simulated in accordance with an embodiment of the present disclosure.

[0044] **DETAILED DESCRIPTION**

[0045] Fig. 1 shows a system for simulating a continuous bioprocess system in accordance with an embodiment of the current disclosure. The system 100 provides a framework for parametrized simulation of continuous bioprocessing systems. The system 100 includes various components that enable selecting pre-validated model components, configuring model instances with specific parameters, forming a complete bioprocess flowsheet simulation environment from the model instances, and co-simulating the model instances within the simulation environment.

[0046] In particular, the system 100 utilizes a catalogue 102 which contains a library of validated model equations 104a-104c that can be used to represent a type of bioprocess component or unit operation. The catalogue 102 acts as a repository of pre-validated and standardized model components that can be readily selected and assembled into new bioprocess models. This allows rapid model development by combining and configuring predefined sub-models, rather than developing new models from scratch. The types of bioprocess components that may be modeled include, but is not limited to, the components shown below in Table 1:

Air compressors
Automated transfer systems
Bioreactors
Buffer Preparation System
Cell Disruption Units
Cell harvesting Systems
Centrifuges
Chillers
Chromatography columns
Clarifiers
Clean-in-Place Systems
Connectors
Container loading systems
Blenders

Control systems
Conveyors
Data collection systems
Depth Filters
Diversion panels
Feed systems
Filling machines
Filters
Final product storage areas
Flow control valves
Flow meters
Flowverters
Fluid Conduits
Freeze-Thaw units
Heat Exchangers
Heating Tanks
Holding tanks
Inline conditioning systems (e.g. pH adjustment, diluters, mixers)
Lyophilizers
Microfiltration units
Multi-variable transmitters
Packaging equipment
Pressure sensors
Product holding areas
Pumps
Robotic handling systems
Sampling System
Sensors
Steam generators
Sterilization units

Storage tanks
Surge vessels
Swing panels
Temperature sensors
Transfer Panel
Tubes/pipes
Valves
Vent filters
Waste Neutralization System

Table 1

[0047] The system 100 further includes a component selector 106 which enables selecting one or more of the validated model equations 104 from the catalogue 102 in order to generate a model 108. The model 108 represents a digital model of a particular bioprocess component that can be simulated, such as a bioreactor, chromatography column, pump, etc. The component selector 106 allows flexibility in choosing which specific model types are needed for a given bioprocess flowsheet simulation.

[0048] Additionally, the system 100 includes an instantiator 112 which takes a model 108 and loads specific parameters 110 into the model to generate a model instance 114. This instantiation process configures the model 108 with particular operating parameters, material properties, and other simulation settings to tailor it to represent a specific component instance. Multiple instances 114 can be instantiated from a single model 108 by loading different parameters 110.

[0049] Instantiated model instances 114 can then be utilized by a simulation environment former 120 to construct a complete bioprocess flowsheet simulation 116. The simulation environment 116 links together the model instances 114 to represent an integrated continuous bioprocessing system. The simulation environment former 120 provides means to connect the instances in different configurations (e.g. in series, parallel, etc.) along with specifying how material, energy, and information flows between the unit operation instances.

[0050] Finally, a co-simulator 118 executes the simulation by advancing each model instance 114 according to its own defined timescale while coordinating data exchange between instances. This allows the system 100 to simulate different unit operations with vastly different time constants and timesteps within an integrated bioprocess flowsheet. The co-simulator 118 runs the simulation to determine output variables of interest for analysis.

[0051] In summary, the system 100 enables rapid construction and simulation of continuous bioprocessing systems by configuring and integrating models built up from standardized, pre-validated components. The flexibility of composing flowsheets from well-characterized unit operation models facilitates efficient design space exploration and process optimization.

[0052] The system 100 may have various alternative architectures and component compositions. In some embodiments, the system 100 may be implemented as a centralized, cloud-based platform where the catalogue 102, models 108, instances 114, and simulation environment 116 reside on servers accessible by multiple users via thin clients. This enables convenient access and collaboration.

[0053] In other embodiments, the system 100 may utilize a decentralized architecture where the component selector 106, instantiator 112, and co-simulator 118 are installed locally for each user while the catalogue 102 resides in the cloud. This allows offline simulations. Hybrid architectures are also possible.

[0054] The system 100 utilizes a processor 122 to execute the software components and algorithms required to perform parametrized simulation of continuous bioprocess systems. The processor 122 may be a central processing unit (CPU), graphics processing unit (GPU), field-programmable gate array (FPGA), application-specific integrated circuit (ASIC), or any other computing device capable of executing instructions stored in the memory 124.

[0055] The memory 124 provides storage for the software instructions, simulation models, model instances, simulation environment configurations, operating parameters, and any other data necessary for the parametrized bioprocess simulations. The memory 124 may include random access memory (RAM), read-only memory (ROM), flash memory, hard drives, optical storage, or any other volatile or non-volatile memory capable of storing data accessible by the processor 122. The memory 124 works in conjunction with the processor 122 to load and execute the software components of the system 100.

[0056] In particular, the memory 124 may store the catalogue 102 containing the library of validated model equations 104, which can be selected by the component selector 106 to generate models 108. The memory 124 also provides storage for instantiated model instances 114 generated by the instantiator 112 loading specific parameters 110 into a model 108. Additionally, the memory 124 stores the complete simulation environment 116 formed by the simulation environment former 120 interconnecting model instances 114.

[0057] During simulation runtime, the memory 124 provides working memory for the co-simulator 118 to simulate the individual model instances 114 and exchange coupling data between instances. Simulation results and outputs are stored in the memory 124 for analysis. In some embodiments, the memory 124 may store historical or real-time data from physical bioprocess devices, which can be used to periodically update digital twin models to match the physical device state.

[0058] The network connection 126 allows the system 100 to communicate with external systems, services, instruments, and data sources. This enables capabilities such as remotely accessing the catalogue 102, integrating real-time sensor data from physical bioprocess equipment into simulations, and exporting simulation results to analytics dashboards or other systems.

[0059] The network connection 126 may utilize standard communication protocols such as TCP/IP, MQTT, OPC, etc. Different network topologies can be used, such as local connections within a facility, connections over a private intranet, or connections over the public Internet. This flexible connectivity allows the parametrized bioprocess simulations to incorporate live production data when creating digital twins of physical processes.

[0060] Thus, the processor 122, memory 124, and network connection 126 provide computing resources that enable the system 100 to leverage pre-validated model components to rapidly construct, configure, simulate, and analyze continuous bioprocess systems. The hardware architecture facilitates flexible software implementation and integration capabilities.

[0061] The catalogue 102 acts as a centralized repository containing a library of validated model components that can be utilized to rapidly construct simulations of continuous bioprocess systems. The catalogue 102 stores a collection of model equations 104a-104c, each representing the mathematical relationships describing the behavior of a particular type or part of bioprocess equipment or unit operation.

[0062] In preferred embodiments, the catalogue 102 is implemented as a standardized, globally accessible database that can be remotely accessed by multiple users and systems. Storing the catalogue 102 on a central server or cloud infrastructure allows the library of validated models to be maintained, updated, and distributed efficiently. The catalogue 102 may be accessed via common network protocols such as TCP/IP, REST APIs, etc. allowing connectivity over both private intranets and the public Internet.

[0063] The catalogue 102 contains a broad range of model equations 104 covering common components found in continuous bioprocess workflows. Examples include models of bioreactors,

chromatography columns, pumps, valves, sensors, tubes, control systems, and other equipment. Additionally, more complex elements such as complete separation sequences or cell culture trains may be included as pre-validated modules.

[0064] Each model equation 104 encapsulates the governing mass, energy, and momentum balances along with relevant reaction kinetics, transport phenomena, and thermodynamic properties required to fully characterize the behavior of a bioprocess component. The models 104 may also be validated using real equipment data and refined to ensure accuracy over relevant operating ranges. Validation may involve techniques such as comparison to first-principles models, calibration using historical process data, confirmation of steady-state conditions, and robustness testing using simulated disturbances or noise factors.

[0065] By leveraging the catalogue 102, users can rapidly develop bioprocess models by selecting appropriate pre-validated components and combining them, rather than deriving custom models from scratch. This composability allows efficient exploration of flowsheet options and configurations by mixing and matching modular building blocks that have been pre-qualified. Importing components from the catalogue 102 ensures model fidelity and compliance for regulated applications.

[0066] In some embodiments, the catalogue 102 may feature version control capabilities to manage model evolution over time. As improved model refinements become available, they can be released as new versions while retaining access to older versions for legacy continuity. The catalogue 102 may also support model metadata such as engineering units, modeling assumptions, and operational limitations to assist users in proper model selection and configuration.

[0067] Overall, the catalogue 102 and its library of validated model equations 104 enhances productivity in continuous bioprocess modeling by providing a centralized hub of pre-qualified, ready-to-use components. Rapid assembly of pre-validated building blocks enables faster design iterations along with ensuring model reliability critical for both regulatory and business outcomes. The catalogue 102 is a foundational element enabling the flexible yet robust parametrized modeling approach implemented by the system 100.

[0068] The catalogue 102 contains a library of validated equation components 104 that each describe the mathematical model representing a type or part of continuous bioprocessing equipment or unit operation. The validated equation components 104 encapsulate the mass, energy, and momentum balances along with reaction kinetics, transport phenomena, and other relationships required to fully characterize the dynamic behavior of a bioprocess component.

[0069] In preferred embodiments, the catalogue 102 contains a diverse range of validated equation components 104 covering various common bioprocessing equipment types and configurations. Examples of equation components include, but are not limited to, models of batch and continuous bioreactors, chromatography columns, depth filters, centrifuges, pumps, valves, connectors, sensors, feed systems, surge tanks, control systems, and more. The catalogue 102 seeks to provide extensive coverage of unit operations found in typical biopharmaceutical and biofuel production workflows.

[0070] The catalog 102 may contain a comprehensive library of pre-processing functions and data transformations that can be applied to the inputs and outputs of the validated equation components 104. These pre-processing items enable flexible data handling and enhanced integration of the equation components 104 when assembled into integrated process flowsheet simulations.

[0071] The catalog 102 includes an extensive set of mathematical functions for transforming and conditioning input data streams before they are fed into an equation component 104. Examples of pre-processing functions include interpolation, extrapolation, smoothing, filtering, normalization, outlier removal, error correction, unit conversion, reformatting, aggregation, discretization, linearization, and multivariate regression.The input pre-processing functions in the catalog 102 allow the raw data from upstream models or physical process sensors to be manipulated into the appropriate formats, values ranges, timestamps, etc. expected by the inputs of a particular equation component 104. This provides flexibility when connecting components 104 to handle real-world data imperfections.

[0072] In addition to input data pre-processing, the catalog 102 also contains preprocessing functions that can be applied to the outputs of equation components 104 before they are passed to downstream models. Examples of output pre-processing functions include data reconciliation, uncertainty quantification, moving averages, response modeling, dimensionality reduction, variable selection, clustering, classification, dynamic time warping, and other analytical transformations.

[0073] Output pre-processing enables post-processing the raw simulation results from an equation component 104 to derive higher level performance metrics, extract key attributes, improve result quality, align timestamps or dimensions, or prepare the data for downstream components. This enhances the modularity and interoperability of combining components 104 into complex flowsheets.

[0074] The catalog 102 may also contain predefined data processing sub-models for tasks like soft-sensor development, dynamic control loop simulation, and real-time optimization. These

data-centric components leverage underlying pre-processing functions to encapsulate commonly needed analytics operations when connecting hardware sensors, control systems, and models in a digital automation environment.

[0075] In addition to mathematical functions, the catalog 102 includes domain-specific capabilities needed for continuous bioprocessing workflows, such as handling incomplete or erroneous measurements from biosensors, reconciling redundant sensor arrays, correcting sample time delays, and mitigating process disturbances or variability. This allows the validated components 104 to integrate more seamlessly with real-world systems.

[0076] The catalog 102 also contains libraries of typical equipment performance metrics, product quality target ranges, regulatory constraints, operating envelopes, and other validation criteria needed for configuration, testing, and qualification of the equation component models 104 pre- and post-simulation. This assists in component re-use and compliance.

[0077]

[0078] Each validated equation component 104 is parameterized to enable configuring the model to specific equipment geometries, materials, and operating conditions. For instance, a bioreactor model component may allow specifying parameters such as vessel volume, impeller type, sparge rate, temperature setpoints, and control logic. This enables tailoring a general model template to match a particular physical bioreactor by setting appropriate parameter values.

[0079] The catalogue 102 may be implemented using various database technologies ranging from simple CSV files to robust relational databases. For example, the catalog 102 may be implemented as an SQL database, a NoSQL database, MongoDB, etc. Multiple catalogues 102 hosted by different providers could be aggregated into a federated catalogue architecture united by common APIs. The catalogue 102 may also employ blockchain-based data models for enhanced security and traceability.

[0080] In one embodiment, the catalogue 102 is implemented locally as an internal database within the system 100. The locally implemented catalogue 102 stores model components that have been derived and validated by the system owner organization. This allows an organization to maintain tight control over model IP while still benefiting from the parametrized modeling approach.

[0081] In an alternative embodiment, the catalogue 102 may be implemented in a decentralized fashion as a distributed ledger or blockchain. In this approach, different organizations can contribute validated model components to the catalogue 102 and receive attribution for their

contributions. Smart contracts can be used to control access and licensing of model IP. A decentralized catalogue enables collective development of model content while still tracking ownership.

[0082] In some embodiments, the catalogue 102 may be instantiated in the cloud and provided as a model marketplace or repository-as-a-service. Various biopharma and engineering organizations can publish validated models to the cloud-hosted catalogue 102. End user organizations can subscribe to the catalogue 102 and download models on-demand for a fee. This app store model allows monetization of model IP in an open ecosystem. Cloud hosting also enables easy maintenance, updates, and distribution of the catalogue 102.

[0083] Regardless of implementation, the catalogue 102 may feature robust version control capabilities to manage model evolution, branching, and deprecation over time. As improved model refinements are developed, they can be versioned for release while maintaining legacy access. Power users can also develop custom variants of models for specialized applications. The versioning system maintains pedigree and traceability of model IP.

[0084] The catalogue 102 may also offer different tiers or classes of model components tailored to use case needs. Simple, reduced-order models can meet requirements for real-time applications like model predictive control. Highly complex multifidelity models may be provided for detailed design studies. Different abstraction levels enable balancing model depth versus computational load.

[0085] Thus, the catalogue 102 can be instantiated via a number of embodiments - centralized or decentralized, local or cloud-hosted, closed or open - to provide validated, configurable model building blocks. Version control and tiering further enhance flexibility to serve diverse modeling requirements while managing model lifecycles and IP.

[0086] The validated equation components 104 encapsulate relevant mass, momentum, and energy conservation laws combined with phase equilibria, reaction kinetics, mass transfer rates, flow patterns, and other physical relationships needed to describe bioprocess equipment behavior. The complexity and fidelity of the model equations depends on the type of unit operation. For example, a pump model may use simple algebraic equations while a chromatographic separation model could involve partial differential equations.

[0087] Each equation component 104 is extensively validated using real experimental data to ensure prediction accuracy over relevant operating ranges. Validation may utilize techniques such as comparison to first-principles models, calibration to historical process data, confirmation of

steady-state conditions, and robustness testing using simulated perturbations. This qualification process ensures the catalogue model components 104 provide reliable, high-fidelity behavior prior to use in bioprocess simulations.

[0088] The component selector 106 enables flexible selection of validated model equations 104 from the catalogue 102 to generate simulation models 108 representing different types of bioprocess components. The component selector 106 provides a user interface and search/filtering tools to identify and choose appropriate model equations 104 for a given simulation model 108.

[0089] In some embodiments, the component selector 106 may feature a graphical drag-and-drop interface allowing users to browse through categories of model equations 104 covering various equipment types, such as bioreactors, columns, pumps, sensors, etc. Users can drag the desired model equations 104 into a workflow area to assemble a custom model 108 representing a type of bioprocess component. Metadata may be displayed such as model inputs/outputs, applicable parameters, and usage guidelines to assist in selecting suitable model equations.

[0090] Additionally, the component selector 106 may allow searching or filtering the catalogue 102 contents based on model characteristics and metadata. For example, users could query for model equations 104 applicable to continuous stirred tank reactors within a certain volume range. Search results help identify the most suitable model equation candidates from the catalogue for a given component type and specification.

[0091] The component selector 106 may also support comparing alternative model equations 104 side-by-side to understand key differences. Users can review model documentation, assumptions, complexity, and prior validation data to determine the most appropriate model for a particular simulation. Some models may provide higher fidelity at the expense of greater computational requirements.

[0092] Once the user finalizes the selection of model equations, the component selector 106 automatically integrates the different sub-models into a combined model 108 representing the overall bioprocess component. The component selector 106 handles linking model inputs and outputs as well as merging the underlying mathematical representations into a single model 108. This simplifies model assembly for the user.

[0093] The models 108 generated by the component selector 106 serve as digital templates representing categories of bioprocess equipment. These models can then be instantiated into configured instances by loading specific parameters to match desired specs. The flexibility of the selector 106 enables rapid construction of models from validated, pre-qualified sub-components.

This enhances productivity for continuous bioprocess simulations by leveraging the catalogue 102 building blocks.

[0094] To transform the model template 108 into a specific equipment instance, the instantiator 112 loads parameters 110 into the model 108. The parameters 110 include physical dimensions, materials of construction, operating setpoints, control logic, and all other configuration details required to define a particular bioprocess component. Loading the parameters 110 creates a configured model instance 114 matching the target equipment specifications.

[0095] Additionally, in some embodiments, the model #1 108 may represent a digital twin of a physical bioprocessing system. In this case, the model #1 108 may be periodically updated during simulations to match the current state of the physical system based on real-time or historical operational data. This enables high-fidelity simulations for monitoring, control, and optimization applications leveraging real-world equipment data.

[0096] The model #1 108 provides a foundation for parametrized, modular construction of bioprocess simulations using validated sub-models from the catalogue 102. Configuring the model template 108 with specific parameters 110 enables flexible yet high-fidelity representations of both real and hypothetical bioprocessing equipment. The model #1 108 is a core building block enabling rapid digital prototyping and simulation of continuous biopharmaceutical production systems.

[0097] Consider additional representations that the model # 1 108 can represent as follows:

[0098] Continuous Stirred-Tank Bioreactor: The model #1 108 can represent a continuous stirred-tank bioreactor (CSTR) for cell culture or microbial fermentation. The model equations would capture transient mass balances, reaction kinetics, mixing dynamics, and transport phenomena occurring within the CSTR vessel. Alternative embodiments may consider different impeller designs, sparge configurations, and vessel geometries.

[0099] Chromatography Column: The model #1 108 can represent a chromatography column for purification and separation of bioprocess streams. The model may simulate transient mass balances, adsorption equilibria, and pressure gradients within the packed column. Different embodiments could consider alternative packing materials, column lengths, and column diameters.

[00100] Inline Conditioning Unit: The model #1 108 can represent an inline conditioning unit such as a mixer, dilution system, or pH adjustment system. The model would capture transient mass and momentum balances as streams combine and flow through the unit. Alternative embodiments may adjust mixing energy, relative flow ratios of incoming streams, and conditioning reagent addition points.

[00101] Tubular Heat Exchanger: The model #1 108 can represent a tubular heat exchanger for cooling, heating, or maintaining process streams. The model would simulate transient energy balances and heat transfer dynamics between process and utility streams through the heat exchanger walls. Alternative embodiments can consider tube diameter, length, wall thickness, and materials of construction.

[00102] Holding Vessel: The model #1 108 can represent a holding vessel for temporary storage and surge capacity. The model would capture transient mass and energy balances within the vessel. Alternative embodiments can modify vessel volume, inlet/outlet configurations, and control logic.

[00103] Pump: The model #1 108 can represent a pump for moving fluid streams between bioprocess components. The model would simulate fluid transport based on pump curve characteristics and system backpressure. Alternative embodiments can consider different pump types (e.g. peristaltic, centrifugal), drive control mechanisms, and range of flow capacities.

[00104] Sensor: The model #1 108 can represent a sensor for monitoring properties of bioprocess streams. The model would mimic noise, drift, sampling lag, and other sensor artifacts. Alternative embodiments can modify measurement accuracy, precision, reliability, and other performance specifications of the simulated sensor.

[00105] Fig. 2 illustrates an example model 108 of an incubation chamber 200 for simulating aggregation kinetics in a continuous bioprocessing system. The incubation chamber 200 represents a modular, configurable model instance that can be interconnected with other model instances to form an integrated process flowsheet simulation.

[00106] The incubation chamber 200 model enables simulating the transient behavior of product aggregation within a vessel in a continuous bioprocess workflow. It can capture the impact of operating parameters like residence time distribution and shear on aggregation rate and species distribution. This allows evaluating approaches to mitigate aggregation which can enhance product purity and recovery.

[00107] As shown, the incubation chamber 200 model has defined input ports 202 and output ports 204. The input ports 202 allow connecting upstream model instances that provide inlet material streams to the chamber 200. The output ports 204 allow connecting downstream models that receive exiting material streams.

[00108] The incubation chamber 200 has an input 202 representing the mass flow rate of product entering the chamber. This product stream may contain a distribution of monomers, low-

order aggregates, and high-order aggregates. The relative fraction of each species can be specified or linked to the output of an upstream model.

[00109] Additionally, the input 202 include streams defining the mass flow rates of entering aggregates, precipitate, and liquid. The aggregates stream allows simulating pre-existing aggregates entering the chamber. The precipitate stream allows simulating insoluble particles that can induce aggregation. The liquid stream defines the carrier fluid mass flow rate.

[00110] The input 202 also include a stream defining the pH level of the entering fluid mixture. The pH can impact protein solubility and thus aggregation kinetics.

[00111] The incubation chamber model 200 contains parameterized equations to simulate the transient mass balance and reactions occurring within the chamber volume. This includes modeling the kinetics of aggregation and precipitate formation based on the mixed inlet species concentrations and operating conditions.

[00112] The model 200 may be used to calculate the aggregation rate and evolving species distributions. The kinetics are influenced by parameters 206 including the residence time and shear rate resulting from the chamber geometry and inlet flow rates. The model equations encapsulate detailed physics such as laminar flow profiles and protein-protein collision rates tied to shear and residence time.

[00113] The output 204 of the incubation chamber model 200 provide exit streams with transient compositions reflecting the mass balance and reactions occurring within the chamber 200. The outlet flow rates of product monomers, aggregates, precipitates, and liquid carrier are calculated by the model equations. The model outputs 204 can connect to downstream units in a process flowsheet model.

[00114] The species concentrations reported in the incubation chamber output streams 204 depend on the inlet conditions 202 along with internal parameters 206 over time. By simulating the incubation model 200 configured with different residence times, shear rates, and inlet compositions, users can assess the sensitivity of aggregation kinetics and product quality to operating choices.

[00115] Fig. 3 shows an example model 300 that is a vessel for simulating a continuous bioprocessing system. The vessel 300 represents a parameterized, configurable model instance that can be interconnected with other model instances to form an integrated process flowsheet simulation.

[00116] The vessel 300 model enables simulating the transient behavior and mass balances within a vessel during continuous bioprocessing workflows. It can capture the impact of operating

parameters like inlet flow rates, mixing speed, temperature setpoints, and control logic on species concentrations and reaction kinetics occurring within the vessel 300 over time. This allows evaluating different vessel 300 configurations and operating strategies to optimize yield, productivity, and product quality.

[00117] As illustrated, the vessel 300 model has defined inputs 302 and outputs 304. The inputs 302 allow connecting upstream model instances that provide inlet material streams to the vessel 300. The outputs 304 enable connecting downstream models that receive exiting material streams from the vessel 300.

[00118] The input 302 include current vessel volume, circulation pump flowrate, vessel concentration, pH, product mass flowrate, aggregate mass flowrate, and a liquid flowrate. These allow simulating transient flows of reactants, products, and carrier liquids into the vessel 300 from upstream equipment.

[00119] The parameters 306 include an initial vessel volume that can be specified based on the actual size and geometry of the physical vessel being modeled.

[00120] The output 304 include pH, product mass flow rate, aggregate mass flow rate, precipitate mass flow rate, circulation pump flowrate, updated vessel volume, and updated vessel concentration. These provide exit composition data to downstream models based on the inlet conditions 302 and reactions occurring within the vessel 300.

[00121] The vessel 300 model contains mathematical equations representing mass balances, reaction kinetics, mixing dynamics, and other relationships needed to simulate species transformation, heating, cooling, and fluid transport phenomena occurring continuously within the equipment.

[00122] The transient vessel concentration and temperature profiles are influenced by parameters 306 including vessel geometry, inlet flow rates, and mixing intensity. The model equations encapsulate detailed physics such as flow patterns, diffusion rates, and energy balances tied to the specific configuration defined by parameters 306.

[00123] By simulating the vessel 300 model instance configured with different sizes, materials, flow rates, setpoints, and control schemes, users can assess the impact of design choices and operating conditions on product quality attributes like aggregation and degradation. The flexible vessel 300 model supports rapid in silico experiments to optimize continuous bioprocess workflows.

[00124] Referring again to Fig. 1: the parameters 110 may include one or more of the following types:

[00125] – Residence time

[00126] – Aggregation formation factor

[00127] – initial vessel volume

[00128] - Vessel geometry (height, diameter, volume, etc.)

[00129] - Agitator properties (impeller type, power, speed range, etc.)

[00130] - Inlet/outlet sizes, numbers, and positions

[00131] - Construction materials for walls, impellers, spargers, etc.

[00132] - Temperature and pressure limits

[00133] - Pressure relief valve settings

[00134] - Insulation type and thickness

[00135] - Maximum flow rates for inlet streams

[00136] - Control system tuning parameters and logic

[00137] - Instrument specifications (accuracy, precision, etc.)

[00138] - Any other physical or operational characteristics of the bioprocess equipment

[00139]

[00140] The specific parameters 110 loaded into the Model #1 108 can widely vary to match different types of bioprocess components and configurations. The parameter values transform the generalized model template 108 into a particular instance 114 by defining the precise equipment specifications, dimensions, materials, and operating envelope.

[00141] In some embodiments, the parameters 110 may be loaded from a database of equipment specifications and operational data. For existing physical bioprocess systems, parameters can be imported from technical datasheets and sensor measurements to match the real equipment. For new designs, parameters can be set based on desired operating criteria and process requirements.

[00142] The flexible parametrization provided by the parameters 110 enables rapidly constructing a wide range of bioprocess configurations using a common model template 108. By changing the parameter values 110, a single bioreactor model can be instantiated into 5,000 L or 20,000 L reactors made of stainless steel or specialty alloys. This configurability saves development time compared to building custom models for each equipment variant.

[00143] Overall, the parameters 110 are a mechanism in the system 100 for quickly generating high-fidelity, customized equipment models from generalized, pre-validated model templates 108. The parameters 110 bridge the gap between standard model equations and the unique specifications of real continuous bioprocessing systems.

[00144] The instantiator 112 is a component of the system 100 that generates configured model instances 114 by loading specific parameters 110 into a model 108. The instantiator 112 tailors generic model templates 108 into particularized simulations matching desired bioprocess equipment specifications and operating conditions.

[00145] The instantiator 112 takes as inputs a model 108 along with associated parameters 110. The model 108 provides the generalized mathematical framework defining the mass, energy, and momentum balances; reaction kinetics; thermodynamics; and other relationships required to simulate the behavior of a type of bioprocess component. However, the model 108 on its own does not contain the specific configuration details.

[00146] The parameters 110 provide the necessary equipment-specific information to transform the model template 108 into a customized instance 114. The parameters 110 may include physical factors like vessel geometry, materials of construction, inlet/outlet sizes, flow capacity limits, insulation properties, and dimensions for a given bioreactor. The parameters 110 may also include operational factors like temperature and pressure setpoints, control logic tuning, sensor accuracy specifications, and impeller speeds for a particular system.

[00147] The instantiator 112 systematically loads the parameter values 110 into the appropriate places within the model template 108. This configures the model into a specific instance 114 representing the target bioprocess equipment based on the provided parameters. For example, inserting the parameter values for vessel volume, impeller type, and temperature control settings into a bioreactor model template 108 produces a model instance 114 tailored to simulate that particular system.

[00148] In some implementations, the instantiator 112 may provide a graphical user interface allowing users to map parameters 110 to locations within a model template 108. The interface may also support loading parameter values from CSV files, databases, or other sources. Sophisticated implementations of the instantiator 112 may utilize intelligent algorithms to recommend optimal parameter-to-model mappings.

[00149] The flexible parametrization provided by the instantiator 112 enables efficient reuse of model templates 108 to construct simulations for a wide range of bioprocess equipment types and configurations. By varying the parameter values 110, a single model template 108 can be instantiated into many distinct model instances 114 representing unique physical systems. This configurability simplifies and speeds up bioprocess modeling.

[00150] The model instances 114 generated by the instantiator 112 contain the full mathematical specification needed to simulate the behavior of specific bioprocess components under given operating conditions. The model instances act as modular, configurable building blocks that can be interconnected to form detailed bioprocess flowsheet simulations 116. The instantiator 112 is a key enabler of rapid, robust digital prototyping of continuous biopharmaceutical production processes.

[00151] The instance #1 114 represents a configured, parameterized model instance of a specific bioprocess component generated by the instantiator 112. The instance #1 114 contains a full mathematical specification defining the mass, energy, and momentum balances; reaction kinetics; thermodynamics; transport phenomena; and other relationships required to simulate the behavior of the bioprocess component under various operating conditions.

[00152] The instance #1 114 is created by the instantiator 112 loading a specific set of parameters 110 into a model template 108 selected from the catalogue 102. The model template 108 provides the generalized equations for simulating a type of bioprocess equipment, such as a continuous stirred-tank bioreactor. However, the model template 108 on its own does not contain the particular physical dimensions, materials properties, operating parameters, and other configuration details.

[00153] The instantiator 112 takes the model template 108 along with a set of parameters 110 that specify the precise equipment specifications and operating conditions for the target bioprocess component. The parameters 110 may include factors such as vessel geometry, inlet/outlet sizes, impeller design, temperature and pressure limits, flow capacitics, control logic, and instrumentation specifications.

[00154] The instantiator 112 inserts the parameter values 110 into the appropriate locations within the model template 108, generating a configured instance 114 matching the desired equipment configuration defined by the parameters. In this way, the instance #1 114 is customized to simulate the behavior of a specific bioreactor system based on its unique physical attributes and operating envelope specified in the parameters 110.

[00155] The instance #1 114 contains all the necessary mathematical relationships, initialized with specific parameter values 110, to simulate the mass balances, reactions, energy transfers, fluid flows, and other transient behavior of the particular bioprocess equipment under dynamic operating conditions. Multiple instances like instance #1 114, each configured with different parameters 110, can be rapidly generated from model templates 108 to simulate various bioprocess components.

[00156] The customized model instances 114 can be interconnected by the simulation environment former 120 to construct integrated bioprocess flowsheet simulations 116. The instance #1 114 represents a flexible, parameterized building block that can be combined with other instances to enable rapid digital prototyping of continuous bioprocess systems. The instance #1 114 encapsulates a high-fidelity simulation tailored to a particular equipment configuration defined by its parameters 110.

[00157] The simulation environment 116 represents an integrated continuous bioprocess flowsheet simulation formed by interconnecting multiple model instances 114. The simulation environment 116 provides a platform for simulating the transient behavior of a complete bioprocess workflow with different connected unit operations.

[00158] The simulation environment 116 is constructed by the simulation environment former 120 which takes as inputs multiple model instances 114. The model instances 114 are configured simulations of specific bioprocess components, such as bioreactors, chromatography columns, pumps, surge tanks, and sensors. The instances 114 are generated by the instantiator 112 loading parameters 110 into model templates 108 selected from the catalogue 102.

[00159] The simulation environment former 120 interfaces allow users to link together model instances 114 into any desired bioprocess flowsheet configuration. For example, the simulation environment former 120 may provide a graphical canvas where instances 114 can be dragged, dropped, and connected to form a process flow diagram. Complex arrangements can be constructed combining instances in series, parallel, and recycle stream configurations.

[00160] The simulation environment former 120 may automatically handle routing connections for material, energy, and information flows between instances 114. Material stream connections define the paths for processing feed stocks through various downstream unit operations. Energy stream connections capture heating, cooling, and other heat integration between instances. Information connections enable cascaded process monitoring and control between components.

[00161] In addition to connecting instances 114, the simulation environment former 120 allows specifying operating conditions for the overall continuous bioprocess flowsheet. This includes feed stream properties, production rate targets, equipment capacities, environmental conditions, and other parameters defining the complete bioprocess operation. Initial conditions throughout the process flowsheet may also be set.

[00162] Once constructed and configured, the simulation environment 116 containing interconnected model instances 114 can be executed by the co-simulator 118. The co-simulator 118

advances each instance 114 according to its individual time step while coordinating data exchange between instances at synchronization points. This allows simulating transient behavior of a continuous process flowsheet with unit operations having vastly different time constants.

[00163] The fully interconnected simulation environment 116 provides a digital prototype of an entire continuous bioprocessing workflow. The environment 116 enables analyzing production scenarios, evaluating design options, verifying control logic, performing optimization studies, and assessing responses to disturbances across an integrated system. The simulation environment 116 drives rapid and robust digital prototyping of continuous biopharmaceutical manufacturing processes.

[00164] The co-simulator 118 is a software component that executes the simulation of the interconnected model instances 114 within the simulation environment 116. The co-simulator 118 numerically integrates the mathematical models encapsulated in each instance 114 to simulate the transient behavior of the bioprocess system over time.

[00165] The co-simulator 118 leverages a co-simulation approach to integrate model instances 114 potentially having different timescales and timesteps. Each model instance 114 contains metadata defining its simulation timestep as well as integration algorithm parameters. The co-simulator 118 progresses each instance 114 according to its individual timestep while coordinating synchronized data exchange between instances at coupling points.

[00166] This coordinated execution allows simulating a complete bioprocess flowsheet containing unit operations with vastly different dynamic characteristics. For example, a continuous reactor instance may require a 10 millisecond timestep to resolve reactions, while a large chromatography column may operate on a 10 minute timestep. The co-simulator 118 allows simulating such systems together in a coupled manner.

[00167] In a typical workflow, the simulation environment former 120 constructs the simulation 116 by linking together model instances 114 representing units like reactors, columns, filters, pumps, and so on. The simulation environment 116 configures how material, energy, and information flows are routed between instances.

[00168] Once configured, the co-simulator 118 initializes the state of each instance 114 and commences execution. At each timestep, the co-simulator 118 numerically integrates the model equations for an instance 114 to calculate new state variable values. The co-simulator exchanges data between instances at the defined coupling points to simulate interactions.

[00169] This process repeats until the simulation duration is reached. The co-simulator 118 orchestrates synchronized data flows between unit operations to capture the integrated transient behavior of a complex bioprocess flowsheet. The co-simulator outputs simulation trajectories for analysis and visualization.

[00170] The co-simulator 118 may leverage established numerical integration techniques like Euler's method or Runge-Kutta as well as advanced parallel computing techniques to enhance simulation performance. Sensitivity analysis capabilities may also be included. The co-simulator 118 may be based on industry standards like the Functional Mockup Interface for integrated, robust co-simulation.

[00171] The simulation environment former 120 is a software component that constructs a complete simulation environment 116 by interconnecting multiple model instances 114. The simulation environment former 120 provides a flexible graphical user interface that allows users to link together model instances 114 representing various bioprocess components into an integrated continuous bioprocess flowsheet configuration.

[00172] The simulation environment former 120 displays a canvas where model instances 114 can be added from a palette and visually arranged into a process flow diagram. The instances 114 may represent equipment such as bioreactors, chromatography columns, depth filters, centrifuges, pumps, sensors, feed systems, and any other unit operations found in a bioprocess. The instances 114 are configured simulations generated by the instantiator 112 loading specific parameters 110 into model templates 108 selected from the catalogue 102.

[00173] Once instances 114 are placed in the flowsheet, the simulation environment former 120 enables connecting them together to define material, energy, and information flows. Material connections specify the routing of feed, intermediate, and product streams between unit operations. Energy connections represent heating, cooling, and heat integration between equipment. Information connections enable cascaded process monitoring, control, and data exchange between components.

[00174] The simulation environment former 120 provides convenient tools to link instances 114 both in series and parallel. Complex recycle stream configurations can also be constructed. The interface automatically handles the underlying data connections required to simulate integrated flows between unit operations. Additional tools allow inserting other elements like valves, pumps, and sensors at connection points.

[00175] Besides connecting instances 114, the simulation environment former 120 may provide controls to specify overall process parameters. This includes feed stream properties, production rate targets, equipment capacities, environmental conditions, and other settings defining the complete continuous bioprocess workflow. Initial state values throughout the flowsheet may also be set.

[00176] In other embodiments, the simulation environment former 120 may provide a text-based interface for defining model instance connections. The connections between instances can be specified in a configuration file that maps output variables from one instance to input variables on another instance. The configuration file acts as a parameter defining the topology of the flowsheet simulation when instantiated.

[00177] Additionally, the simulation environment former 120 may enable configuring global parameters that apply across the integrated flowsheet. Examples include production rate targets, feed stream properties, equipment capacities, environmental conditions, and control logic settings. Initial values for all state variables in the flowsheet may also be set. This allows simulating both batch startup and steady-state conditions.

[00178] The simulation environment former 120 could also provide tools to insert additional elements like pumps, valves, and sensors at connection points between model instances. These additional components enable simulating advanced control loops, automated valve sequencing, and online instrumentation within the flowsheet.

[00179] In some embodiments, the simulation environment former 120 may automatically balance and check material, energy, and data flows to ensure feasible connections between model instances prior to simulation. Mass and energy balances can be enforced, preventing invalid process configurations.

[00180] Some implementations of the simulation environment former 120 may utilize advanced algorithms to recommend optimal flowsheet configurations and topologies based on production objectives, equipment constraints, and raw material properties. The algorithms could iteratively construct and simulate different flowsheet options to determine ideal arrangements maximizing bioprocess performance metrics.

[00181] The simulation environment former 120 may also provide optimization tools to determine optimal operating parameters and conditions for the overall continuous bioprocess. The optimizer could adjust factors like feed rates, cycling times, column loading levels, and equipment

sizing to enhance productivity, yields, and economics. The optimizer relies on rapid flowsheet simulations to iteratively converge on optimized configurations.

[00182] To facilitate collaborative development, the simulation environment former 120 may enable multi-user environments where multiple process engineers can simultaneously construct and configure sections of an integrated flowsheet. Version control capabilities can track changes from each user. Data management tools could synchronize flowsheet simulations across distributed private or cloud-based environments.

[00183] Once constructed and configured, the simulation environment 116 encompassing the interconnected model instances 114 can be executed by the co-simulator 118. The co-simulator 118 advances each instance 114 according to its individual timestep while coordinating data exchange between instances at coupling points. This enables high-fidelity dynamic simulation of the integrated continuous bioprocess system.

[00184] Refer to Fig. 4 for an example as how two models 402 and 404 can be connected together. The model 502 includes inputs, parameters, and outputs. The outputs of model 4032 can be the inputs for the model 404. The outputs of the model 404 are then the simulation of both models 402, 404. Thus, Fig. 4 shows an example of how two model instances 402 and 404 can be interconnected within a continuous bioprocess simulation environment. The first model instance 402 represents a configurable, parameterized simulation of a first type of bioprocess component, such as a continuous stirred-tank bioreactor. The second model instance 404 likewise represents a configurable, parameterized simulation of a second type of bioprocess component, such as a chromatography column.

[00185] The first model instance 402 has a defined set of input ports 406 and output ports 408. The input ports 406 allow connecting upstream model instances that provide input material streams, energy streams, and information streams to the first model instance 402. The output ports 408 allow connecting downstream model instances that receive output material streams, energy streams, and information streams from the first model instance 402.

[00186] Similarly, the second model instance 404 has a defined set of input ports 410 and output ports 412. The input ports 410 allow connecting upstream model instances, such as the first model instance 402, that provide input streams to the second model instance 404. The output ports 412 allow connecting downstream model instances that receive output streams from the second model instance 404.

[00187] The first model instance 402 and second model instance 404 each contain mathematical relationships representing mass balances, energy balances, reaction kinetics, thermodynamics, fluid dynamics, and other equations required to simulate the behavior of their respective bioprocess component types. The model instances are configured by loading specific parameters to tailor them to particular equipment configurations and operating conditions, as described previously for Fig. 1.

[00188] As shown in Fig. 4, the output ports 408 of the first model instance 402 are connected to the input ports 410 of the second model instance 404. This coupling enables simulating the integrated behavior of the two bioprocess components by routing output streams from the first instance 402 as inputs to the second instance 404.

[00189] The connection 414 between the first instance output ports 408 and the second instance input ports 410 represents a physical pipe or conduit in the bioprocess flowsheet. This connection 414 allows simulating the flow of material, energy, and information between the two model instances during co-simulation. In addition to physical connections, virtual data connections may be made between instances to implement process control loops, data collection, and other logical interactions.

[00190] In this example, the first model instance 402 may operate on a faster timescale than the second model instance 404. For instance, the first instance 402 may execute using one second timesteps while the second instance 404 uses one-minute timesteps. The co-simulator automatically handles coordinating the data exchange at connection 406 between the different timescales. This allows simulating bioprocess components with vastly different dynamics in a coupled flowsheet.

[00191] The model instances 402 and 404, constructed by configuring templates from a catalogue with specific parameters, enable rapid digital prototyping of continuous production workflows. Connecting model instances into integrated environments as shown in Fig. 4 provides a flexible simulation platform for design, monitoring, control, and optimization of continuous bioprocess systems.

[00192] Referring again to Fig. 1, in summary, the intuitive graphical interface and streamlined tools provided by the simulation environment former 120 enable rapid construction and configuration of integrated continuous bioprocess flowsheet simulations 116 from modular, pre-configured model instances 114. The simulation environment former 120 is a key component facilitating flexible digital prototyping and analysis of continuous biopharmaceutical manufacturing processes.

[00193] Fig. 5 shows an example configuration file that can be used to define and parameterize model instances in the continuous bioprocess simulation system. The configuration file contains sections that allow specifying metadata about a model instance, defining its variables and connections to other instances, and setting parameter values.

[00194] In particular, the configuration file in Fig. 5 has a "components" section that lists the model instances included in the simulation. For each model instance, the configuration file provides a "filename" field that points to the source file containing the actual model equations and implementation for that instance.

[00195] The "name" field assigns a unique identifier to the model instance. The "variables" field enumerates the input and output variables exposed by the model instance that are available for connecting to other instances. For example, the model instance "model1" in Fig. 5 exposes "input 1", "input 2", and "output 1" variables.

[00196] The "connections" section defines how variables on different model instances are connected together to form the integrated bioprocess flowsheet simulation. Each connection specifies the source model instance and variable as well as the destination model instance and variable to link. For instance, Fig. 5 shows a connection linking "output 1" on model instance "model1" to "input 2" on model instance "model2".

[00197] In this manner, the configuration file couples model instances together by mapping their exposed variables. The file acts as a parameter that defines the topology and connectivity of the bioprocess simulation when instantiated by the system. The configuration can encode complex flowsheets with multiple feed-forward and feed-back connections between unit operations.

[00198] In addition to topology, the configuration file may also contain sections that define global parameters for the simulation, such as feed stream properties, production rates, equipment capacities, control logic, and initial conditions throughout the process flowsheet. Specific parameters for individual model instances can also be set, such as residence time distribution for a vessel or column packing properties.

[00199] The flexible configuration file structure and parameters shown in Fig. 5 enable encoding both the connectivity and properties of a continuous bioprocess simulation in a digital format that can be rapidly constructed, validated, and executed using the parametrized modeling approach described in this disclosure. The configuration file acts as a mechanism to fully specify a particular flowsheet design based on parameters instead of custom code.

[00200] Fig. 6 shows an example graphical user interface (GUI) for the simulation environment when being executed and simulated in accordance with an embodiment of the present disclosure. The GUI provides a visual representation of the continuous bioprocess flowsheet defined by the interconnected model instances. The GUI allows users to monitor the simulation execution in real-time as well as adjust operating parameters and conditions.

[00201] As illustrated, the GUI shows icons representing different bioprocess components that have been instantiated from model templates selected from the catalogue. These components include items such as tanks, pumps, valves, and bioreactors. Lines between the icons represent both physical and data connections between the component instances.

[00202] The GUI depicts how material streams flow between components, enabling users to trace the path of feedstocks as they are processed through various downstream unit operations. Stream colors may indicate composition, allowing visualization of how impurities are removed across purification steps. Stream widths can represent mass flow rates.

[00203] Key operating parameters such as temperature, pressure, flow rate, and composition are displayed for each component instance. Users can click on icons to view additional runtime variables and trends for that particular instance. Control dashboards allow manipulating setpoints and conditions dynamically during the simulation.

[00204] The GUI may animate flows, reactions, and other transient behavior occurring within each instance according to the underlying model equations. This provides an intuitive dynamic view into how feedstocks are being processed over time at each step of the continuous bioprocess.

[00205] The simulation runspeed may also be adjusted in the GUI, allowing users to accelerate or slow down the execution to better analyze transient phenomena. Playback controls support pausing, rewinding, and replaying segments of the simulation for closer inspection. The simulation can be stopped, modified, and resumed at any point.

[00206] In summary, the interactive GUI shown in Fig. 6 enables users to visualize, monitor, and control the integrated continuous bioprocess flowsheet simulation in real-time. The GUI facilitates rapid debugging, optimization, and training scenarios leveraging the parametrized modeling approach described in this disclosure.

[00207] Various alternatives and modifications can be devised by those skilled in the art without departing from the disclosure. Accordingly, the present disclosure is intended to embrace all such alternatives, modifications and variances. Additionally, while several embodiments of the present disclosure have been shown in the drawings and/or discussed herein, it is not intended that

the disclosure be limited thereto, as it is intended that the disclosure be as broad in scope as the art will allow and that the specification be read likewise. Therefore, the above description should not be construed as limiting, but merely as exemplifications of particular embodiments. And, those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto. Other elements, steps, methods and techniques that are insubstantially different from those described above and/or in the appended claims are also intended to be within the scope of the disclosure.

[00208] The embodiments shown in the drawings are presented only to demonstrate certain examples of the disclosure. And, the drawings described are only illustrative and are non-limiting. In the drawings, for illustrative purposes, the size of some of the elements may be exaggerated and not drawn to a particular scale. Additionally, elements shown within the drawings that have the same numbers may be identical elements or may be similar elements, depending on the context.

[00209] Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun, e.g., "a," "an," or "the," this includes a plural of that noun unless something otherwise is specifically stated. Hence, the term "comprising" should not be interpreted as being restricted to the items listed thereafter; it does not exclude other elements or steps, and so the scope of the expression "a device comprising items A and B" should not be limited to devices consisting only of components A and B. This expression signifies that, with respect to the present disclosure, the only relevant components of the device are A and B.

[00210] Furthermore, the terms "first," "second," "third," and the like, whether used in the description or in the claims, are provided for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances (unless clearly disclosed otherwise) and that the embodiments of the disclosure described herein are capable of operation in other sequences and/or arrangements than are described or illustrated herein.

What is claimed is:

1. A method of parametrized simulation in the field of bioprocessing, comprising:

selecting a plurality of pre-validated equations from a catalogue to generate a model;

instantiating a first instance of the model by loading parameters including a first time-step parameter into the first instance;

instantiating a second instance by loading a second time-step parameter into the second instance;

forming a continuous process simulation environment having the first instance and the second instance;

co-simulating the first instance in accordance the first timestep parameter and the second instance in according with the second timestep parameter,

determining at least one output of the continuous process simulation.

2. The method according to claim 1, wherein each model corresponds to a type of bioprocess component.

3. The method according to claim 2, wherein the type of bioprocess component is formed from a plurality of models including the model.

4. The method according to claim 1, wherein the first timestep parameter and the second timestep parameter are different by at least one order of magnitude.

5. The method according to claim 1, wherein the model is formed from only pre-validated equations.

6. The method according to claim 1, wherein the model is a digital twin.

7. The method according to claim 6, wherein the model is periodically updated to a simulation state corresponding to an actual state of a physical continuous bioprocessing device.

8. The method according to claim 1, wherein the first and second instances are coupled in series via a tube.

9. The method according to claim 1, wherein the first and second instances are coupled in parallel.

10. A system for parametrized simulation in the field of bioprocess, comprising:

a component selector configured to select a plurality of pre-validated equations from a catalogue to generate a model;

an instantiator configured to instantiate a first instance of the model by loading parameters including a first time-step parameter into the first instance and a second instance by loading a second time-step parameter into the second instance;

a simulation environment former configured to form a continuous process simulation environment having the first instance and the second instance; and

a co-simulator configured to co-simulate the first instance in accordance the first timestep parameter and the second instance in according with the second timestep parameter, the co-simulator configured to determine at least one output of the continuous process simulation.

11. The system according to claim 10, wherein each model corresponds to a type of bioprocess component.

12. The system according to claim 10, wherein the first timestep parameter and the second timestep parameter are different.

13. The system according to claim 10, wherein the model is formed from only pre-validated equations.

14. The system according to claim 10, wherein the model is a digital twin.

15. The system according to claim 14, further comprising an updater configured to periodically update the model to a simulation state corresponding to an actual state of a physical continuous bioprocessing device.