Simulation and Control of a Fed-Batch Recombinant Fermentation, 2003, *Biochem Eng J.*, 15, 165-175. Unfortunately, due to the time-varying characteristics of the fed-batch fermentation and limited amount of training data, the models typically do not have high accuracy.

[0005] As stated above, models such as Monod kinetics may result in a large number of unknown parameters. However, the discrete feed stream in fed-batch processes may cause insensitivity of the target variables to the feed strategy. Furthermore, the complex multilevel reactions in the process, quick adaptability of cells in the process (*see* Sinclair et al., Fermentation Kinetics and Modelling, 1987, *Open University Press, Milton Keynes*, 44, xi-113), and random variability that occurs during a batch operation may also decrease the accuracy of these simplified models. *See* Jose et al., Developmental Studies of an Adaptive On-Line Softsensor for Biological Wastewater Treatments, 1999, *Can. J. Chem. Eng.*, 77, 707-717.

BRIEF SUMMARY

[0006] Bioprocesses can often be characterized by their nonlinearity, variability, and complexity that arise due to metabolic network pathways inside the cells. Once there is an acceptable understanding of the process, sophisticated advanced control strategies can be employed to increase the reliability and efficiency of the process. Model predictive control (MPC) uses a real-time process model to make predictions, by optimizing an objective (cost) function at each time interval while preserving custom constraints. By predicting upcoming disturbances and guaranteeing prediction stability, MPC results in prescriptive control actions. In the MPC framework, the prediction of the process under consideration computes control actions based on future outcomes as it relates to the model objectives and constraints, and the future behavior of the dynamic model is based on the prediction model. Hence, the prediction model plays a crucial role in MPC.

[0007] Systems and methods described herein generally provide a hybrid approach to prediction in an MPC system by using both first-principles and data-driven modeling. For example, the systems and methods may use data-driven models (e.g., a linear regressor and/or neural network) trained on historical data from real-world cell culture processes to predict future values of certain metabolite concentrations and/or other cell culture attributes (e.g., viable cell density (VCD), osmolality, etc.), while also using a first principle (e.g., mass balance) model to predict future values of glucose concentration, with the latter predictions being based on feed rate as well as data-driven model predictions (e.g., VCD predictions). Use of the first principle model mitigates shortcomings of data-driven models when predicting glucose concentration (e.g., poor sensitivity of the model to the feed), while use of the data-driven model mitigates the inability of first principle models (for example, current mass balance models) to accurately and consistently model relationships between glucose and other metabolites.

[0008] As a whole, the hybrid model can more accurately and consistently predict future cell culture attributes for the predictive stage of a MPC over a desired prediction horizon. An optimization stage of the MPC can then calculate control values (e.g., glucose feed rate values) over a control horizon by solving an optimization problem for an objective function subject to certain constraints (e.g., minimum and maximum feed rates). At any given time interval, the first control value determined by the MPC (i.e., the value for the earliest time interval of the control horizon) is used to control a physical input to the cell culture process (e.g., a glucose feed rate provided by a glucose pump), and the prediction and optimization stages repeat/update for each time interval (e.g., each day, or each hour, etc.).

[0008a] In one aspect, the present disclosure refers to a method of controlling a cell culture process using hybrid predictive modeling in a model predictive controller, the method comprising, for a plurality of time intervals during the cell culture process: obtaining current values of cell culture attributes associated with a cell culture; generating, by processing hardware, a control value for a physical input to the cell culture process, wherein generating the control value includes predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future

values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and determining the control value by optimizing an objective function subject to the predicted future values of the cell culture attributes; and controlling, by the processing hardware and using the control value, the physical input to the cell culture process.

[0008b] In another aspect, the present disclosure refers to one or more non-transitory, computer-readable media storing instructions that, when executed by processing hardware of a computing system and for a plurality of time intervals during a cell culture process, cause the computing system to: obtain current values of cell culture attributes associated with a cell culture; generate a control value for a physical input to the cell culture process, wherein generating the control value includes predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and determining the control value by optimizing an objective function subject to the predicted future values of the cell culture attributes; and control the physical input to the cell culture process using the control value.

[0008c] In yet another aspect, the present disclosure refers to a system comprising: a bioreactor configured to hold a cell culture during a cell culture process; an electronically-controllable input device configured to provide physical input to the cell culture process; one or more analytical instruments configured to measure one or more cell culture attributes associated with the cell culture; and a computing system configured to, for one or more time intervals during the cell culture process, obtain, based on measurements by the one more analytical instruments, current values of cell culture attributes associated with the cell culture, generate a control value for the physical input to the cell culture process, wherein generating the control value includes predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and determining the control value by optimizing an function equation subject to the predicted future values of the cell culture attributes, and control the physical input to the cell culture process using the control value, by sending a control signal to the electronically-controllable input device.

[0009] The techniques disclosed herein may obviate the need for manual adjusting of control set-points. Moreover, by mitigating shortcomings of both data-driven and first-principles models, these techniques may provide improved prediction accuracy relative to other modeling techniques, thereby allowing for control actions that lead to better performance of the cell culture process (e.g., superior product quality attributes).

BRIEF DESCRIPTION OF THE DRAWINGS

WHAT IS CLAIMED:

1. A method of controlling a cell culture process using hybrid predictive modeling in a model predictive controller, the method comprising, for a plurality of time intervals during the cell culture process:

obtaining current values of cell culture attributes associated with a cell culture;

generating, by processing hardware, a control value for a physical input to the cell culture process, wherein generating the control value includes

predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and

determining the control value by optimizing an objective function subject to the predicted future values of the cell culture attributes; and

controlling, by the processing hardware and using the control value, the physical input to the cell culture process.

2. The method of claim 1, wherein:

the physical input to the cell culture process is a glucose feed rate;

the second one or more attributes include a glucose concentration of the cell culture; and

controlling the physical input to the cell culture process includes controlling the glucose feed rate by sending a control signal to a glucose pump.

3. The method of claim 2, wherein the first one or more attributes include viable cell density, total cell density, viability, osmolality, lactate concentration, glutamine concentration, glutamate concentration, ammonium concentration, sodium concentration, and/or potassium concentration.

4. The method of any one of claims 1-3, wherein using the one or more first principle models to predict the future values of the second one or more attributes includes applying a predicted future value of a first attribute of the first one or more attributes as an input to at least one of the one or more first principle models.

5. The method of claim 4, wherein the first attribute is viable cell density.

6. The method of any one of claims 1-5, wherein the one or more data-driven models include a linear regression model, a probabilistic regression model, or a feed-forward neural network.

7. The method of claim 6, wherein the probabilistic regression model is a Gaussian process regression model.

8. The method of any one of claims 1-7, wherein predicting the future values of the cell culture attributes is based on (i) the current values of the cell culture attributes and (ii) one or more earlier values of the cell culture attributes.

9. The method of any one of claims 1-8, wherein using the one or more first principle models to predict the future values of the second one or more attributes includes applying one or more previous control values as inputs to the one or more first principle models.

10. The method of any one of claims 1-9, wherein the current values of the cell culture attributes are obtained based on measurements from one or more analytical instruments.

11. One or more non-transitory, computer-readable media storing instructions that, when executed by processing hardware of a computing system and for a plurality of time intervals during a cell culture process, cause the computing system to:

obtain current values of cell culture attributes associated with a cell culture;

generate a control value for a physical input to the cell culture process, wherein generating the control value includes

predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and

determining the control value by optimizing an objective function subject to the predicted future values of the cell culture attributes; and

control the physical input to the cell culture process using the control value.

12. The one or more non-transitory, computer-readable media of claim 11, wherein:

the physical input to the cell culture process is a glucose feed rate;

the second one or more attributes include a glucose concentration of the cell culture; and

controlling the physical input to the cell culture process includes controlling the glucose feed rate by sending a control signal to a glucose pump.

13. The one or more non-transitory, computer-readable media of claim 11 or 12, wherein the first one or more attributes include viable cell density, total cell density, viability, osmolality, lactate concentration, glutamine concentration, glutamate concentration, ammonium concentration, sodium concentration, and/or potassium concentration.

14. The one or more non-transitory, computer-readable media of any one of claims 11-13, wherein using the one or more first principle models to predict the future values of the second one or more attributes includes applying a predicted future value of a first attribute of the first one or more attributes as an input to at least one of the one or more first principle models.

15. The one or more non-transitory, computer-readable media of claim 14, wherein the first attribute is viable cell density.

16. The one or more non-transitory, computer-readable media of any one of claims 11-15, wherein the one or more data-driven models include a linear regression model,

a probabilistic regression model, or a feed-forward neural network.

17. The one or more non-transitory, computer-readable media of claim 16, wherein the probabilistic regression model is a Gaussian process regression model.

18. The one or more non-transitory, computer-readable media of any one of claims 11-17, wherein predicting the future values of the cell culture attributes is based on (i) the current values of the cell culture attributes and (ii) one or more earlier values of the cell culture attributes.

19. The one or more non-transitory, computer-readable media of any one of claims 11-18, wherein using the one or more first principle models to predict the future values of the first attribute includes applying one or more previous control values as inputs to the one or more first principle models.

20. A system comprising:

a bioreactor configured to hold a cell culture during a cell culture process;

an electronically-controllable input device configured to provide physical input to the cell culture process;

one or more analytical instruments configured to measure one or more cell culture attributes associated with the cell culture; and

a computing system configured to, for one or more time intervals during the cell culture process,

obtain, based on measurements by the one more analytical instruments, current values of cell culture attributes associated with the cell culture,

generate a control value for the physical input to the cell culture process, wherein generating the control value includes

predicting, based on the current values, future values of the cell culture attributes, at least by (i) using one or more data-driven models to predict future values of a first one or more attributes of the cell culture attributes, and (ii) using one or more first principle models to predict future values of a second one or more attributes of the cell culture attributes, and

determining the control value by optimizing an function equation subject to the predicted future values of the cell culture attributes, and

control the physical input to the cell culture process using the control value, by sending a control signal to the electronically-controllable input device.

21. The system of claim 20, wherein:

the electronically-controllable input device includes a glucose pump;

the physical input to the cell culture process is a glucose feed rate; and

the second one or more attributes include a glucose concentration of the cell culture.