

TITLE OF THE INVENTION:

PAT Interface

BACKGROUND OF THE INVENTION

[0001] The disclosed invention relates to a method and a system to provide an Interface for connectivity of Process Analytical Technology (PAT) instruments.

[0002] The invention belongs to the technical fields of measuring instruments for
5 bioprocessing systems.

[0003] The pharmaceutical industry's quality approach is focused on improving and increasing productivity in the manufacture of biochemical compounds. This requires the use of complex bioprocesses with real-time monitoring integrated within the production line. In-line analysis can enable process automation, thus
10 the process optimization by saving a significant amount of time and materials. Currently, there is a wide range of instruments and offline analytical technologies on the market capable of monitoring essential variables in a cell culture (biomass, radius, nutrient quantity, metabolic indicators ...), as well as critical parameters of a bioprocess, but few of them are converted into in situ sensors.

[0004] The conversion of analytical tools into in situ sensors is a current
15 exploratory trend, aiming at improving the frequency of their measurements, to be close to be real-time and also their quality too, as no sampling is required by definition. Moreover, with these advanced sensors, called Process Analytical Technologies (PAT), the conditions of continuous or discontinuous cell cultures
20 may be adjusted and controlled in real time thanks to physical measurements converted through models to quantitative and qualitative information. This adaptation to inline sensors will have a lot of benefits: reduced samplings, contamination, costs, and leading to less system downtime.

[0005] Another exploration tendency is to associate several sensors and PATs
25 together to develop advanced process fusion models. These process sensors

and analytical tools require specific connectivity with systems and host for advanced models.

[0006] These approaches comprise of several problems:

[0007] A first problem is the difficulty to connect a PAT to a system from a communication protocol standpoint. While some PATs have a bus communication like OPC UA, customer systems do not have necessarily a ready-to-use bus communication available. In that case, PATs cannot be connected and then used for feedback control and process optimization. A second aspect is that a system in development would be more suitable to anticipate and integrate this specific communication protocol but each PAT has its own communication protocol so the integration work would work only for one instrument. Anticipating a future-proof communication for various instruments is then too heavy to integrate in the system software or even impossible if instruments do not exist yet.

[0008] Another problem is that optimizing the process run and the MABs production and quality cannot rely only on one parameter at a time. The current control methods are based on process parameters like pressure, temperature and also some physico-chemical parameters of biosolutions like pH and conductivity. However, there is nearly no control available based on quality attributes to ensure the cell health and high MABs productivity or quality, although several biological parameters like viable cell density (VCD) and radius, nutrient concentration, protein titer and aggregates are measured by PATs. This second problem to be solved is the use of these parameters for process control. It actually requires some advanced data processing models to extract some quality parameters to give to a system some easy control commands. These models do not exist today and therefore have no host in the current bioprocessing manufacturing units.

[0009] To comply with and enhance such state of the art it would therefore be desirable to find a new approach to connect a PAT to another system, like a customer's system, where the usage of process control parameters is possible.

BRIEF SUMMARY OF THE INVENTION

[0010] This task can be solved by an Interface System for connecting hardware based data sources with a System for producing biochemical compounds comprising the following components of an User Interface to configure the Interface System; an Input Interface for receiving data from the hardware based data sources including at least one standard hardware connector; at least one software based model configured to process the received data from the hardware based data sources to calculate biochemical process parameters for the system; an Output Interface to provide the processed digital data provided by the at least one software based model to the System for producing biochemical compounds, including at least one standard hardware connector; and at least one computer to host the User Interface, the model and control the input and output interfaces. The key components of the interface system are the following: the User Interface: This component allows users to configure the interface system according to their requirements. The Input Interface: It receives data from the hardware-based sensors using standard hardware connectors. Software-based Model(s): These models process the received data from the sensors to calculate biochemical process parameters for the system. Processing in this context can mean anything: From merely receiving and forwarding the data to converting it to a new format to outright deleting it, if necessary. The Output Interface: It provides the processed data, either in a digital or analog form, generated by the software-based models to the system responsible for producing biochemical compounds, using standard hardware connectors. A Computer: The computer hosts the User Interface, the models, and controls the input and output interfaces. The advantages of this interface system include Compatibility: The use of standard hardware connectors enables seamless integration of various types of biochemical sensors with the bioreactor system; Real-time Monitoring: The system processes the raw data from the sensors to calculate biochemical process parameters, allowing for real-time monitoring of the bioprocesses; Data-driven Optimization: By incorporating machine learning models, the system can

optimize the bioprocess parameters based on the processed data, leading to improved efficiency and quality in biochemical compound production; Flexibility: The user interface allows for easy configuration and customization of the interface system based on individual requirements and specific bioprocesses;

5 Centralized Control: The computer hosts the components of the interface system, providing centralized control for efficient management and coordination of data flow between hardware sensors and the bioreactor system. In summary, the invented Interface System enables seamless connectivity between biochemical sensors and the bioreactor system, facilitating real-time monitoring, data

10 processing, and optimization of bioprocesses for improved productivity and quality control.

[0011] Advantageous and therefore preferred further developments of this invention emerge from the associated sub claims and from the description and the associated drawings.

15 **[0012]** One of those preferred further developments of the disclosed System Interface comprise that the User Interface comprises a touchscreen which provides a Graphical User Interface to configure the Input-, Output-interfaces and/or the at least one software based model. This feature provides several advantages: User-Friendly Configuration: The touchscreen with a GUI enhances

20 user experience by providing a visually intuitive interface for configuring the Input Interface, Output Interface, and software-based models. Users can easily interact with the system by selecting options, entering values, and making adjustments through touch gestures. Simplified Navigation: The touchscreen GUI allows users to navigate through different configuration settings more conveniently. They can

25 access and modify settings directly on the screen, eliminating the need for external input devices or complex menus. Enhanced Visualization: The GUI on the touchscreen enables the display of relevant information, status indicators, and parameter settings in a visually appealing manner. This makes it easier for users to understand and interpret the configuration options, improving the overall

30 usability of the interface system. Efficient Configuration Updates: With the touchscreen interface, users can quickly update and modify the configuration

settings of the Input and Output Interfaces, as well as the software-based models. It reduces the time and effort required for making changes to the system's setup, allowing for more agile and responsive operation. Potential for Customization: The touchscreen GUI can be customized to meet specific user preferences or accommodate different user roles, making the interface system adaptable to individual requirements and enhancing usability for different user groups. In summary, the addition of a touchscreen GUI to the User Interface further enhances the user experience, simplifies configuration processes, offers better visualization of system parameters, enables efficient updates, and provides potential for customization in the interface system

[0013] Another one of those preferred further developments of the disclosed System Interface comprise that the at least software based model is a machine learning model or a physical model, wherein physical model includes empirical models, phenomenological models and/or equation based-models. The inclusion of both machine learning models and physical models, e.g empirical models, phenomenological models and/or equation based-models, in the interface system allows for versatile data processing, improved accuracy, robustness, complementary insights, and potential optimization of bioprocess parameters. This feature enhances the capabilities of the system, enabling effective monitoring and control of the surveyed bioprocesses in a way that suits various data characteristics and requirements of the bioprocesses.

[0014] Another one of those preferred further developments of the disclosed System Interface comprise that the Output Interface provides an analog output via a Digital-to-Analog-Converter to convert the processed digital data provided by the at least one software based model to respective analog data. The addition of an Output Interface that provides analog output using a DAC in the interface system offers advantages such as interface compatibility, signal accuracy, direct compatibility with analog devices, simplicity of operation, and versatility for integration with analog-driven systems. This Digital-analog-processing can be done for instance by scaling the data to a range of values, e.g. to 4-20 mA set to correspond to 0-10 g/L, or 0-15 g/L.

[0015] Another one of those preferred further developments of the disclosed System Interface comprise that the at least one hardware connector of the Input- and Output-Interface include RJ-45 and/or M12 and/or Sub-D9 Connectors. Incorporating RJ-45 and/or M12 and/or Sub-D9 connectors in the Input- and Output-Interfaces of the interface system offers advantages such as standardization, versatility, robustness, ease of installation, and scalability. The use of these connectors ensures compatibility, reliable connections, and simplifies the integration process with a wide range of hardware-based data sources commonly used in bioprocesses. Corresponding communication protocols used with those connectors may include, but are not limited to, RS232, RS485, Ethernet IP (TCP/IP, UDP/IP), USB and OPC UA.

[0016] Another one of those preferred further developments of the disclosed System Interface comprise that the System for producing biochemical compounds produces monoclonal antibodies, antibody-drug conjugates, vaccines, and/or adeno-associated virus as biochemical compounds. The invented System Interface is not limited to this application though.

[0017] A further component of the claimed invention is a method for connecting data sources comprising of hardware and software components with a System for producing biochemical compounds via the mentioned Interface System, comprising the following steps of Connecting at least one digital sensor via a standard hardware connector of the Input Interface to the Interface System; Connecting the Interface System to the System for producing biochemical compounds via the Output Interface; Selecting different process parameters, at least one software based model from respective lists delivered by a User Interface, and a signal output type; Calculating and/or converting the different process parameters via a software, in particular the at least one software based model; Sending the calculated and/ or converted process parameters to the System for producing biochemical compounds via the Output Interface; and Controlling the System for producing biochemical compounds to produce at least one biochemical compound by performing a high level automation recipe with the sent process parameters. The method outlines a process that leverages the

Interface System to connect hardware-based data sources with a bio-production system. The method enables real-time monitoring and control, customization and flexibility, integration of advanced models, and high-level automation, ultimately enhancing the efficiency and accuracy of the production of biochemical

5 compounds. The System will therefore calculate new parameters, but can also just convert and route some parameters to the output without any specific model, except a scaling of the range if the output is an analog connection.

[0018] Another one of those preferred further developments of the disclosed method comprise that the high level automation recipe is using the process
10 parameters of viable cell density (VCD), a specific growth rate, glucose concentration, lactate concentration protein titer, glycosylation, specific glucose consumption rate, specific lactate production rate and/or metabolic yield, which are calculated by the at least one model from spectroscopic data provided by the at least one digital sensor. Metabolic yields in this context are indicators of
15 carbon partitioning, like use of glucose to produce either more cells, lactate or antibodies. The inclusion of process parameters based on spectroscopic data from digital sensors enhances the method's capabilities for comprehensive monitoring, real-time analysis, accuracy, efficiency, process optimization, and data-driven decision-making in the bio-production process. These features
20 contribute to improved control, quality, and yield of the produced biochemical compounds. Using a Dielectric spectroscopy sensor and/or a Raman spectroscopy sensor as at least one digital sensor are thereby the most common types of sensors.

[0019] A further component of the claimed invention is a System for producing
25 biochemical compounds, comprising of at least one hardware based data source, a System for producing biochemical compounds and an interface as disclosed before, which is furthermore configured to perform the previously disclosed method. This system provides advantages such as seamless integration, real-time monitoring and control, data-driven optimization, enhanced efficiency and
30 yield, automation and standardization, as well as process optimization and quality

control. These advantages collectively contribute to improved productivity, consistency, and quality in the production of biochemical compounds.

[0020] Another one of those preferred further developments of the disclosed system comprise that the hardware based data sources include standard digital
5 sensors, like a permittivity probe or a Raman spectroscope, and/or advanced digital sensors, like Process Analytical Technologies, for monitoring essential variables in a cell culture. A permittivity probe allows for real-time monitoring of cell density in the bioreactor. This provides valuable information on the growth and proliferation of cells, allowing for timely adjustments and optimization of the
10 culture conditions. A Raman spectroscope enables the detailed chemical analysis of biochemical compounds, metabolic byproducts, and even intracellular components. It provides insights into molecular compositions and structural information, aiding in process monitoring, quality control, and the identification of optimal production conditions. PAT sensors offer the capability to monitor multiple
15 parameters simultaneously, such as cell density, nutrient levels, metabolite concentrations, and other critical variables in real-time. This comprehensive monitoring provides a holistic view of the production process, allowing for rapid interventions and adjustments. In summary, the advantages of the specific types of sensors - permittivity probe, Raman spectroscope, and advanced digital
20 sensors like PAT - include real-time cell density monitoring, detailed chemical analysis, non-invasive and label-free measurements, multi-parametric monitoring, improved process understanding, optimization, and the facilitation of Quality by Design (QbD) approaches.

[0021] Another one of those preferred further developments of the disclosed
25 system comprise that the System to produce biochemical compounds is a bioreactor, wherein the bioreactor is either of benchtop, process development or manufacturing sizes, while the produced biochemical compounds are monoclonal antibodies, vaccines, cell gene therapy and cell therapy products, while the cell culture modes of working are either batch, fed batch or perfusion.

[0022] It is understood that all features of those preferred further developments can be combined together, if not stated otherwise explicitly or obviously being impossible due to the nature of the respective features.

5 BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[0023] Figure 1: a PAT Interface prototype

[0024] Figure 2: an overview about the Layers connected through the PAT Interface

[0025] Figure 3: a schematic overview of the PAT Interface, with its benefits

10 **[0026]** Figure 4: a schematic representation of the data processing from two PATs to the outputs sent to a bioreactor for process control and automation

DETAILED DESCRIPTION OF THE INVENTION

[0027] The invention will be explained in more detail by presenting a preferred
15 exemplary embodiment. Figure 1 shows a respective prototype for such an invented PAT Interface. This embodiment detailed here is the design of a plug and play interface to connect multiple PATs with different communication modes to bioreactors. This interface also enables raw data measured by the sensors to be processed through models to obtain quality parameters to be monitored for
20 bioprocesses and included in system recipes. The problems described before are solved one by one.

[0028] In this proof of concept, the main goal of this PAT Interface is to ensure the possibility to connect PAT sensors (ProCellics, Capacitance probe (Incyte) from Hamilton) to a system as iFlex. In the current state as described before, this
25 is not feasible due to various reasons:

[0029] -the communication protocol is not handled by the system (OPCUA),

[0030] -the number of outputs variables for various models is greater than the number of inputs on the system (Can go up to 75 outputs),

[0031] -the model cannot be computed by the integrated computer of the system, as models usually requires hard and complex computations and integrated advanced mathematical tools.

[0032] For the stated first problem, the PAT Interface can act upon these issues
5 and solves them completely, without interfering neither with the PAT sensors, the customer installation, nor the system, by being a simple intermediate between the system and the PAT sensors. Indeed, the Interface is mounted with standard connectors for each of these "High level" communication protocols (M12,
Ethernet RJ45), and can integrate these communications "software-wise" through
10 a careful choice of components and adequate software programming. This way, the PAT Interface can integrate various communication protocols, as long as the connector are suited to the hardware, and the software is adapted to various new language protocols.

[0033] Regarding the first problems second aspect, by definition a system will
15 handle only standard protocols and won't be able to connect to any system using non-standard protocol, or any new protocol developed after the system launch without a customer change notification about software and hardware updates. A reliable and future-proof data communication to systems can be based upon the analog standard protocol as 4-20 mA as they all have externals IOs. Thanks to
20 high resolution DAC (Digital to Analog Converter) and with the standard connector, the measurement value coming from the PAT Sensor can be transformed through scaling to an analog output and be connected right to the system.

[0034] First, the user needs to plug in the PAT Interface and ensure connectivity
25 to the PAT sensor. Once done, the user can select the different required variables amongst the full list of variables delivered by the PAT instrument, select the model, select a specific signal smoothing filter, the range of input & output signals (for instance, if the "glucose" variable can be set between 0 to 20 g/l in this use case, but other use cases could be 0-12 g/L; 0-10 g/L ... } and the signal
30 output type. The user has full control over the variable and processes he can induce on these. The user can then connect the PAT Interface to the system on

the predefine "External IOs", that can be found on most of the systems on the market. The user is now able to connect a sensor to a system that was unavailable at first and gather external data to its system through the connectivity of the PAT Interface. Figure 2 shows how the specific layers of Input and Output are connected through the PAT Interface. Thanks to a specific Model builder, the user can also derive parameters from the specific inputs of the invention and have access to advanced variables derived from the initial variables, mainly concentration of nutrients or cells from the different PAT sensors. These derived parameters can be sent to the system and used in high level automation through recipes. For instance, a user can define a "Glucose consumption rate" variable based on the evolution of Glucose, send the information as an analog signal to the system, which can actuate a pump to deliver glucose to the iFlex system as a fixed rate equivalent to the Glucose consumption through a personalized recipe. Figure 3 shows thereto a schematic overview of the PAT Interface, with its respective benefits.

[0035] Regarding the second problem the PAT interface provides several models which are embedded to monitor in situ and in real time cell physiology such as VCD, radius, nutrient consumption and bioproduct production.

[0036] A first model processes data from a permittivity probe and provides the VCD and the mean cell radius after smoothing the data. From this VCD values, the model gives at each measurement point a derived parameter indicative of the cell growth.

[0037] The second model uses as inputs two metabolite concentrations monitored with a Raman sensor: glucose and lactate. These concentrations are then smoothed to extract derivatives values and a metabolic yield indicating how cells consume nutrients in the bioreactor.

[0038] By combining these two sources of information, it is possible to monitor growth and cell metabolism in real time. The interface proposed in this invention enables these critical parameters to be transferred to the bioreactor control software with an analog connection. Figure 4 shows a schematic representation

of such data processing from two PATs to the outputs sent to a bioreactor for process control and automation. Control recipes can thus be configured in the system with simple data entries coming from the PATs interface, as described as follows for a typical and preferred mode of operation:

- 5 **[0039]** The main mode of operation is to control the pumps adding glucose to the bioreactor as a function of cell metabolism in a typical fed-batch case. Adding too much glucose when the cells don't need it to grow could reduce growth or even crash the culture. So, using the two spectroscopic sensors mentioned
10 beforehand both connected to the PAT interface, it is possible to create control recipes to automate glucose addition according to real cellular metabolic needs.

[0040] One possible recipe is based on four parameters derived from both spectroscopic data processed in the interface: VCD, growth rate, glucose concentration and metabolic yield:

[0041] If:

- 15 **[0042]** - Glucose concentration is below 1 g/L, meaning that there is a glucose depletion

[0043] - Metabolic yield is above 0.7, meaning that there is a glucose limitation and lactate production, because a metabolic glucose misuse results in high a lactate production

- 20 **[0044]** - VCD is high above 7 million cells/ml, meaning that cells were growing to reach 7 million

[0045] - But growth rate is close to 0 h⁻¹, meaning that the cells are not growing anymore

[0046] Then:

- 25 **[0047]** - add enough glucose to reach 1 g/L knowing the pump flow rate for a certain amount of time

[0048] This approach, which is closer to reality and to cellular needs, reduces the amount of glucose added, the amount of lactate produced by cells, while increasing the yield and quality of the antibodies secreted.

CLAIMS

1. An Interface System for connecting hardware based data sources with a System for producing biochemical compounds comprising the following components:
- An User Interface to configure the Interface System;
 - An Input Interface for receiving data from the hardware based data sources including at least one standard hardware connector;
 - At least one software based model configured to process the received data from the hardware based data sources to calculate biochemical process parameters for the system;
 - An Output Interface to provide the processed digital data provided by the at least one software based model to the System for producing biochemical compounds, including at least one standard hardware connector; and
 - At least one computer to host the User Interface, the model and control the input and output interfaces.
2. An Interface System according to any of the preceding claims, wherein the User Interface comprises a screen, in particular a touchscreen or a normal screen plus other input-/output means, which provides a Graphical User Interface to configure the Input-, Output-interfaces and/or the at least one software based model.
3. An Interface System according to any of the preceding claims, wherein the at least one software based model is a machine learning model or a physical model, wherein physical model includes empirical models, phenomenological models and/or equation based-models.

4. An Interface System according to any of the preceding claims,
wherein
the Output Interface provides an analog output via a Digital-to-
Analog-Converter to convert the processed digital data provided by
5 the at least one software based model to respective analog data.
5. An Interface System according to any of the preceding claims,
wherein
the at least one hardware connector of the Input- and Output-
10 Interface include RJ-45 and/or M12 and/or Sub-D9 Connectors.
6. An Interface System according to any of the preceding claims,
wherein the System for producing biochemical compounds
comprises a bioreactor which is configured to produces monoclonal
15 antibodies, antibody-drug conjugates, vaccines, and/or adeno-
associated virus.as biochemical compounds.
7. A method for connecting data sources comprising of hardware and
software components with a System for producing biochemical
20 compounds via an Interface System according to the claims 1 to 6,
comprising the following steps:
- Connecting at least one digital sensor via a standard hardware
connector of the Input Interface to the Interface System.
 - Connecting the Interface System to the System for producing
25 biochemical compounds via the Output Interface.
 - Selecting different process parameters, at least one software
based model from respective lists delivered by a User Interface,
and a signal output type.
 - Calculating and/or converting the different process parameters
30 via a software, in particular the at least one software based
model;

- Sending the calculated and/ or converted process parameters to the System for producing biochemical compounds via the Output Interface
 - Controlling the System for producing biochemical compounds to produce at least one biochemical compound by performing a high level automation recipe with the sent process parameters.
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8. The method of claim 7, wherein
- 10 the high level automation recipe is using the process parameters of viable cell density (VCD), specific growth rate, glucose concentration, lactate concentration protein titer, glycosylation, specific glucose consumption rate, specific lactate production rate and/or metabolic yield, which are calculated by the at least one model from spectroscopic data provided by the at least one digital sensor.
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9. The method of claim 8, wherein
- a Dielectric spectroscope sensor and/or a Raman spectroscope sensor is used as at least one digital sensor.
- 20
10. A System for producing biochemical compounds, comprising of at least one hardware based data source, a System for producing biochemical compounds and an Interface System according to the claims 1 to 6.
- 25
11. The System according to claim 10, which is configured to perform the method of claims 7 to 9.
- 30
12. The System according to claim 11, wherein
- the hardware based data sources include standard digital sensors, like a permittivity probe or a Raman spectroscope, and/or advanced

digital sensors, like Process Analytical Technologies, for monitoring essential variables in a cell culture.

5 13. The System according to any of the preceding claims 10 to 12,
 wherein
 the System to produce biochemical compounds is a bioreactor.

10 14. The System according to claim 13, wherein
 the bioreactor is either of benchtop, process development or
 manufacturing sizes, while the produced biochemical compounds are
 monoclonal antibodies, vaccines, cell gene therapy and cell therapy
 products, while the cell culture modes of working are either batch, fed
 batch or perfusion.

15 15. The System according to claim 13 or 14, wherein
 the system comprises at least one pump adding glucose to the
 bioreactor to produce the monoclonal antibodies as a function of a
 cell metabolism in a typical fed-batch case.

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