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## Invention Article

# Automated high-resolution sampling and multi-mode *operando* spectroscopy of (bio-)chemical reactions for kinetic analysis, reaction characterization, and quality control



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## ABSTRACT

This invention describes an apparatus that enables the automated removal of small samples from fluids such as those encountered in (bio-)chemical reactors. These samples can then be used for, e.g., kinetic analysis and quality control applications. The system was explicitly designed to be compatible with harsh and aggressive reaction conditions and can be used up to 250°C and 345 bar. The system was incorporated into a high-pressure capable *operando* reaction analysis platform that enabled simultaneous sampling of the reaction mixture and *operando* monitoring of the reaction using multiple channels of spectroscopy, thereby offering accessible and convenient data-rich experimentation. We have started a company to further develop the technology and bring it to market. We are actively looking for early adopters, collaborators, joint-venturing, and investors.

## Specifications table

Subject code	1500-General chemical engineering
Specific subject area	Fluid sampling, sampling, kinetics, reaction characterization, operando spectroscopy, automation
Industry code	G-Physics
Details of inventors	Robbert van Putten (CyberHydra B.V. and TU Delft, <a href="mailto:r.vanputten@cyberhydra.nl">r.vanputten@cyberhydra.nl</a> ); Evgeny A. Uslamin (CyberHydra B.V. and TU Delft, <a href="mailto:e.uslamin@cyberhydra.nl">e.uslamin@cyberhydra.nl</a> ); Evgeny A. Pidko (TU Delft, <a href="mailto:e.a.pidko@tudelft.nl">e.a.pidko@tudelft.nl</a> )
Dates of invention	Conception: July 2019 Disclosure: 19 August 2021 ( <a href="https://patentscope.wipo.int/search/en/detail.jsf?docId=PCTNL2021050091">https://patentscope.wipo.int/search/en/detail.jsf?docId=PCTNL2021050091</a> ).
Patent details (only if patented)	Patent owner: Delft University of Technology/CyberHydra B.V. Patent attorney or agent: EDP Patent Attorneys (Wageningen, the Netherlands) Link to patent: <a href="https://patentscope.wipo.int/search/en/detail.jsf?docId=PCTNL2021050091">https://patentscope.wipo.int/search/en/detail.jsf?docId=PCTNL2021050091</a>
Intended use	We intend to commercialise the invention
Funding / sponsor acknowledgments	Funding: This work was partially supported by TU Delft, the European Research Commission (ERC) [Grant# 725686, 2017-2022], and the Dutch Research Council (NWO) [Grant# 741.018.402, 2019-2021]
Related research article	N/A
Related other sources: (datasets, software, diagrams, plans, etc.)	N/A

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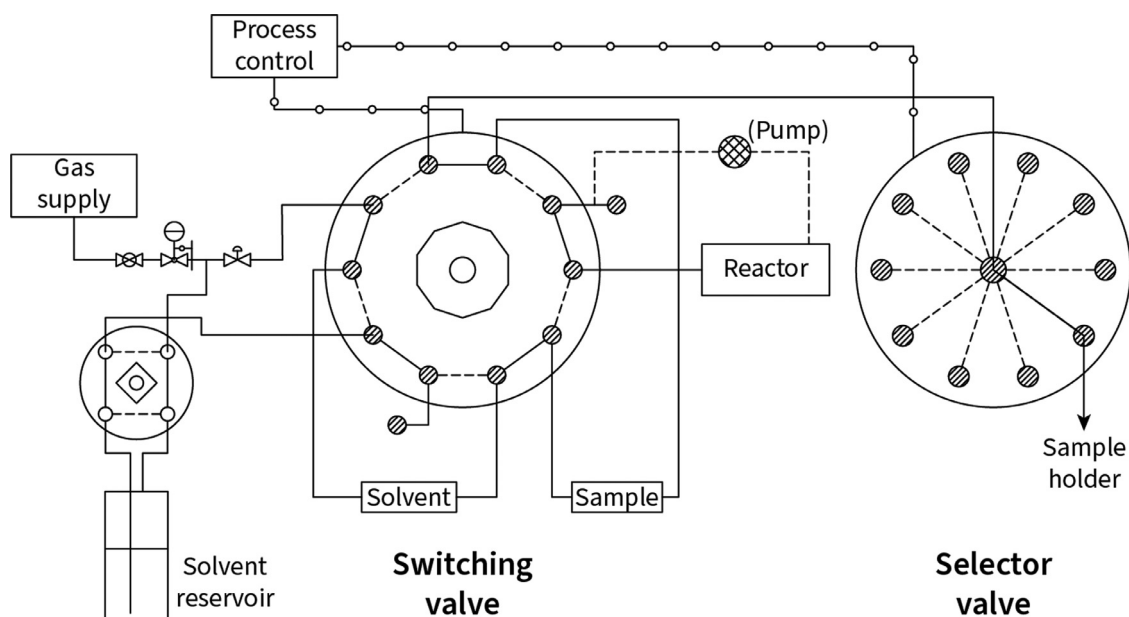


Fig. 1. Schematic overview of the sampling system (adapted from patent application).

## 1. Value of the invention

- The system provides convenient and fully automated sampling from reaction fluids for, e.g., high-resolution kinetic analysis of (bio-)chemical reactions under practically all possible reaction conditions;
- The system is particularly useful for applications that require periodic sample withdrawal from (bio-)chemical reaction fluids. It also provides access to easy data-rich experimentation. The system is thus relevant for industrial and academic (bio-)chemists, researchers, and engineers that regularly perform kinetic analyses, are upscaling (bio-)chemical reactions, or need sampling for quality control;
- Our invention might be incorporated into advanced reaction development platforms designed to produce rich, valuable, and insightful data on, e.g., reaction rates, selectivity, and impurity profiles;

## 2. Invention description

The system was developed around the functionality of two automated multi-position valves and a custom solvent refill system (Figs. 1 and 2). This assembled system can be used for stand-alone sampling for, e.g., kinetic reaction analysis, or as part of a more capable reaction analysis platform, and allows sampling from both pressurized or atmospheric vessels. (Currently up to 345 bar; sampling from atmospheric reactors may require the use of a circulation pump.) Samples of the desired volume are automatically withdrawn from the fluid mixture and are diluted and/or quenched with a solvent portion. The samples are then routed to a sample holder that contains standardized glass (chromatography) vials. This procedure saves a tedious and error-prone sample preparation step and provides the desired analysis-ready samples without input from the operator.

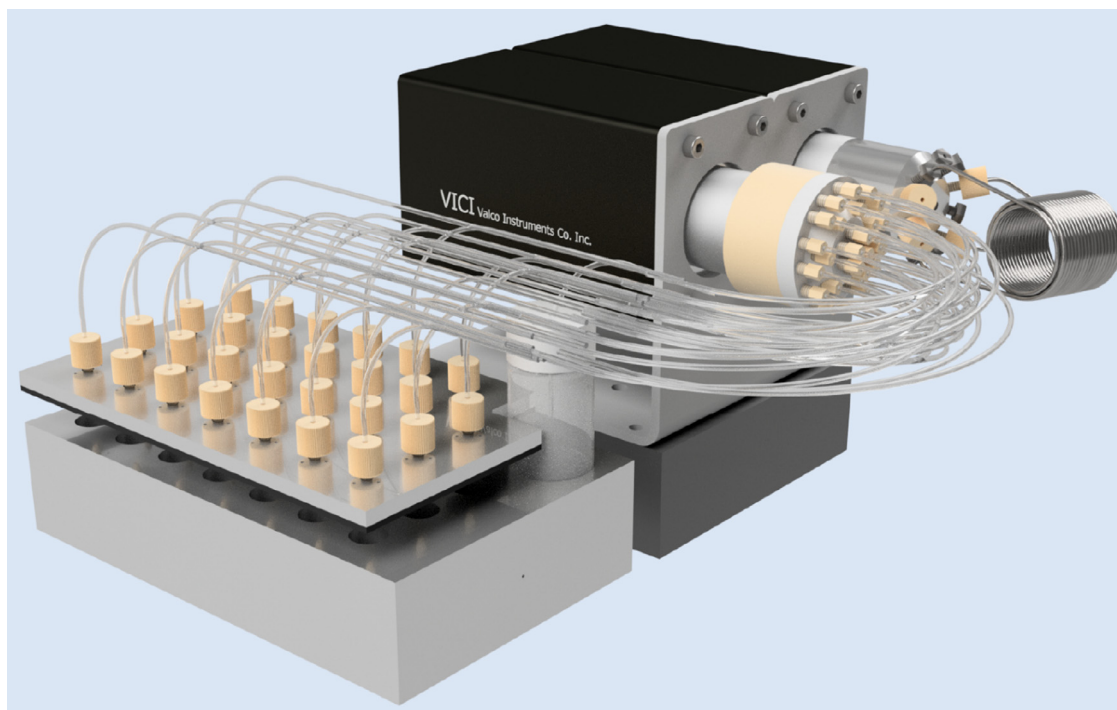
The system is designed to have two discrete operational modes. The first operational mode is used to acquire the sample, while the second operational mode is required to dispense and dilute the sample to the desired storage location. In the first operational mode (Fig. 1, dashed lines in switching valve), the reactor is fluidically coupled to the switching valve through a sample loop. At the same time a pressurized solvent reservoir is connected to the switching valve through a solvent loop. The solvent reservoir is pressurized by an external gas supply (>1 bar) and contains the dilutant and/or quench solution.

In the second operational mode (Fig. 1, solid lines) the switching valve is configured to provide fluidic contact between, successively, the gas supply, the solvent loop, the sample loop, and the sample container. This empties the sample loop, rinses it with the dilutant (or quenching solution), and tails it with gas. After the sample is dispensed, the system is reset and prepared for the next sample.

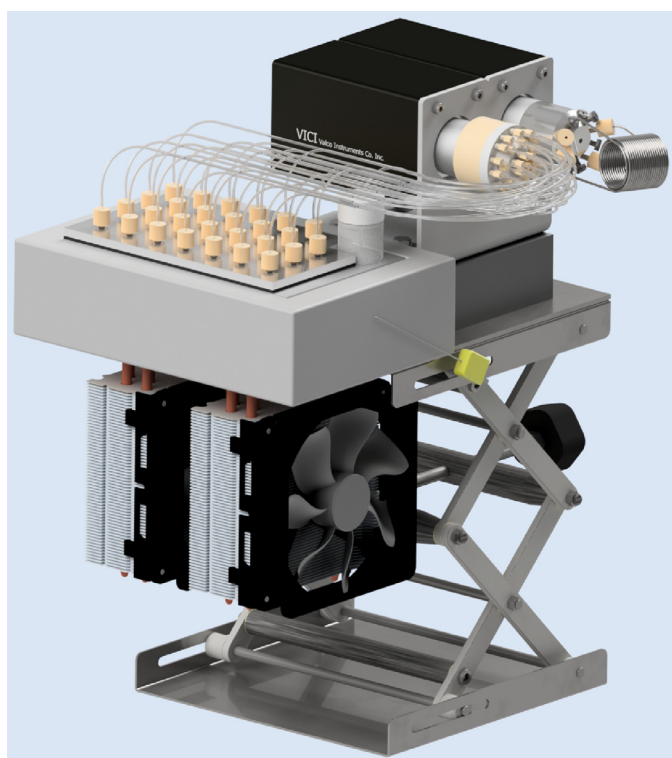
The system prototype was largely constructed with commercially available components. Other parts were manufactured by our in-house workshop. Wetted parts inside the system were made of chemically resistant materials that include stainless steel and a number of perfluorinated polymers. Both the sampling volume and dilutant volume can be modified by the user within minutes and samples are directly dispensed into standardized (chromatography) vials. This is important because it eliminates a tedious, repetitive, and error-prone sample preparation step.

The success of the initial device led us to develop a next-generation (MKII) system. This iteration further expanded the operational window and allowed for its direct integration with *operando* spectroscopy tools. The improved version also integrated a heating system for the valve assembly and its transfer lines, as well as a solid-state cooling system for the sample tray (Fig. 3). The heating system was incorporated in order to prevent heat-loss of the fluid mixture while it was circulated to-and-from the sampling system (the heating system is not shown in Fig. 3). This allows the system to operate with reaction mixtures that contain highly viscous compounds or materials that have high melting points. Heat is applied with a resistive heat tracing that is wrapped around the to-be heated components. The temperature of these lines is monitored with a type K thermocouple and is maintained at the desired setpoint with a PID-controller located inside an electrical box.

A cooling system was fitted to the sample tray to enable storage of (semi-)volatile materials. Such cooling is important to ensure that (quenched) samples stay representative over prolonged amounts of time and that volatile components do not evaporate. An important application of this system is unattended long-term sampling (e.g., overnight). The sample holder was CNC-machined from a solid block of aluminium and was equipped with a thermoelectric cooling system (Figs. 3 and 4). The aluminium sample tray is placed on a copper heat spreader that had machined-out slots for two 60W Peltier modules. Heat is removed from the Peltier elements with a set of off-the-shelf CPU coolers that are bolted to the copper plate and are connected with a thermally conductive compound. The cooling assembly is enclosed in a block of thermally insu-



**Fig. 2.** Technical rendering of (part of) the prototype system. The reactor is connected to the switching valve (right). After the sample is removed, it is routed through the selector valve (left) to the (Al) sample tray that contains standardized glass vials.



**Fig. 3.** Technical rendering of (part of) the MKII prototype system. The fluid mixture is connected to the switching valve (right). After the sample is removed, it is routed through the selector valve (left) to the (aluminium) sample tray that contains standardized glass vials. This system is outfitted with a thermoelectric sample tray cooling system.

lating expanded polyurethane foam (Fig. 3, polyurethane foam omitted from render for clarity). The current configuration achieves a maximum cooling temperature of approximately  $-10^{\circ}\text{C}$  (although cooling below the dew point is not recommended). The electrical hardware that is

required to operate and control the system is placed into a protective electrical box that is installed in the back of a fume hood or electrical cabinet.

The system is fully automated and is controlled with custom-made software written in LabVIEW 2019 (Fig. 5). The software displays a number of status indicators and allows the user to edit the sample queue. Before an experiment is started, the desired sampling times are edited in a text or spreadsheet editor. These times are then imported into LabVIEW and the sample queue is generated.

When the software is started, the user is asked to confirm that the system is ready by pressing the corresponding button. The PC then starts the communication protocol with the system and initializes the equipment. Valves are returned to their initial position and setpoints are changed for the temperature-control systems. The system is now ready for operation. Once both the system and the user are ready, the user initiates the sampling procedure/kinetic experiment by pressing the blinking 'start experiment' button. A countdown timer appears on screen to aid the user with the accurate/timely injection of reagents to start the experiment exactly at  $t = 0$ . This is important because the system supports high-frequency sampling that could otherwise become inaccurate.

A number of timers become operational once the experiment is started. From this moment the system is fully automated and does not require additional user-input. The internal clock references the current time to the programmed sample time and acts accordingly. An autosave file is generated/updated after each sample that contains the exact acquisition parameters, as well as the exact sample time compared to  $t = 0$ . The sample queue can be edited whilst an experiment is in progress. After completion of the last sample in the queue a pop-up window is shown and the user is requested to stop the experiment or to add additional samples using the main interface. Slower or faster than expected experiments can thus easily be accommodated with the system and experiments do not need to be reset. The user is finally requested to clean the system. This cleaning and rinsing is implemented in the software and can be performed automatically without user intervention.

The system could be incorporated into a high-pressure capable *operando* reaction analysis platform that integrated several modes of spectroscopy. This system facilitated simultaneous sampling of the re-

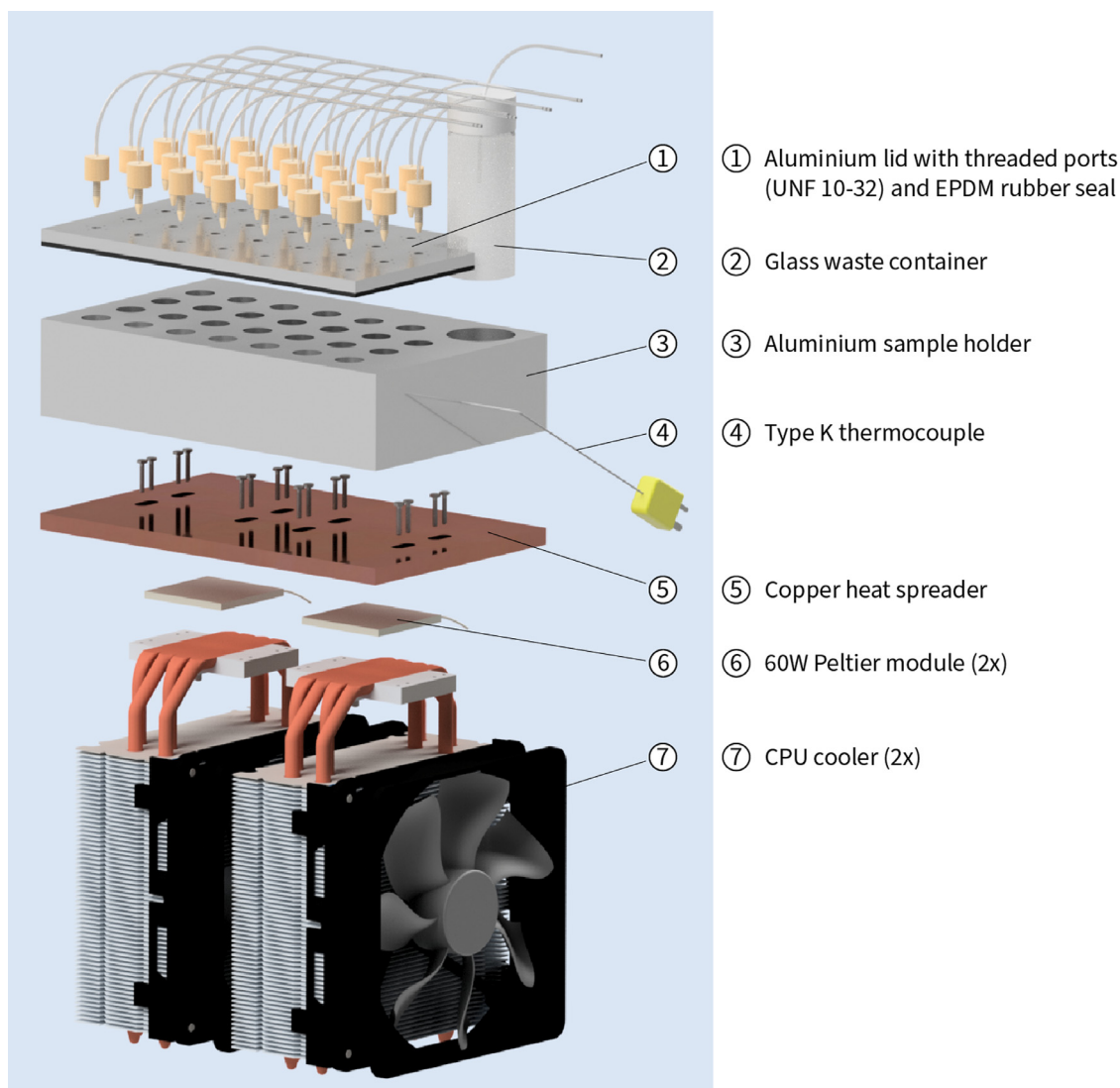


Fig. 4. Exploded-view technical rendering of (part of) the MKII sample cooling tray prototype. Polyurethane thermal insulation has been omitted for clarity.

action mixture and *operando* monitoring of the reaction using FTIR and UV-Vis spectroscopy in (high-pressure) flow cells. The fluid mixture was continuously circulated from the reaction vessel through the analysis system and was returned to the reactor after analysis. These reactions were performed in a commercial Parr autoclave with a magnetically-coupled gear pump. Final specifications of this system are summarized in **Table 1**. A very high sampling frequency could be obtained that depended on the specific use case. A higher frequency could be achieved if the reaction mixture was circulated through the system with a pump compared to when the sampling was only pressure-fed. Most specifications depend on the supplier's rating and can be improved if required.

### 3. Background

The development, detailed study, or scale-up of (novel) (bio-)chemical reactions almost always requires the availability of kinetic data. This information is then used to construct mathematical models that describe the process behaviour as a function of its conditions. These data are also useful for mechanistic works, where they can provide insight into, e.g., resting states, product selectivity, or catalyst deactivation phenomena.<sup>[1–3]</sup> However, despite its importance and potential for new insights, kinetic experimentation is not always straightforward or universally applied as a routine measurement. (As was described by Blackmond: “*Experimental kinetic studies are often regarded by organic*

**Table 1**

System specifications (state Summer 2021, subject to change).

Property	Specification
Sampling frequency	≤5 samples min <sup>-1</sup>
Temperature range (reaction mixture) <sup>a)</sup>	Sub-zero – 250°C
Pressure range (reaction mixture) <sup>a)</sup>	Vacuum – 345 bar
Sample/solvent loop volume <sup>b,c)</sup>	10 μl – 10 ml
Dead volume <sup>d)</sup>	≤50 μl
Heating system temperature range	Ambient – 250°C
Cooling system temperature range <sup>e)</sup>	-10°C - Ambient

<sup>a</sup> Estimated or based on supplier specification.

<sup>b</sup> Ideally  $V_{\text{Solvent}} \gg V_{\text{Sample}}$ .

<sup>c</sup> Increased volume may negatively impact the minimum sampling interval under certain conditions.

<sup>d</sup> Reactor to sampling system. Should ideally not exceed sample volume.

<sup>e</sup> Preferably  $T_{\text{set}} > T_{\text{Dew}}$  in condensing atmosphere.

*chemists as being too tedious, tough, and time-consuming to become standard practise for the initial report of a new reaction.*”)

A number of academic groups and companies have tried to reduce this perceived barrier and have developed tools that greatly simplify kinetic experimentation. Blackmond and co-workers have developed a convenient graphical system (named reaction progress kinetic analysis) that helps non-experts distinguish and rationalise complex kinetic be-

The screenshot shows the LabVIEW interface for an automated sampling system. It includes a top navigation bar with the TUDelft logo and user information. The main area is divided into several functional regions:
 

- Start-stop buttons:** A vertical stack of buttons labeled 'START EXP.', 'SAMPLE NOW', and 'SHUTDOWN'.
- Status indicators:** A section with five colored circles (green, red, green, red, red) and corresponding labels: 'Experiment in progress', 'Queue done', 'Waiting for next sample', 'Sampling', and 'Cleaning'. It also shows 'Next sample: 4 in 00:00:07' and 'Current Phase: Waiting for next sample'.
- Settings tab (3):** A panel with tabs for 'Heater', 'Cooler', 'File I/O', 'COM', 'Sampling', and 'Cleaning'. It contains text boxes for 'Sample table input path' (C:\Test\input\SamplingScheme.csv), 'Autosave file name' (ISE\_Autoclave\_Autosampler), and 'Sample table autosave path' (C:\Test\Autosave).
- Sample planner and queue (4):** A table with columns 'Sample ID# [-]', 'Interval [min]', 'Interval [s]', and 'Done? [Y/N]'. It lists 12 samples with increasing intervals and a 'Done?' status.
- Sample queue editor (5):** A section for managing the queue, including 'Insert new sample into queue\*' and 'Edit sample in queue\*' with input fields for intervals and IDs, and 'Remove sample from queue\*' with a 'REMOVE' button.
- Real-time clocks:** Three digital displays showing '13:09:50' (Experiment start), '13:11:44' (Experiment Clock), and '00:01:53' (Experiment duration).

① Start-stop buttons ② Experiment status indicators ③ Settings tab with additional options ④ Sample planner and queue ⑤ Sample queue editor

Fig. 5. Screenshot of the system software (v2.1, LabVIEW 2019).

haviours. Others have worked on practical aspects and have disclosed the (automated) measurement of kinetics in flow (sometimes combined with Design of Experiments, clever temperature and flow-rate ramps, and statistical methods) [4–6], with *in situ* or *operando* spectroscopy, gas uptake measurements or calorimetry [1–3,7], or with automated sampling systems [8–10]. The latter are important because they closely mimic regular kinetic experiments that are familiar to experimental (bio-)chemists. These systems effectively automate the tedious task of sampling while remaining conceptually similar. However, despite these significant advances, neither of these few commercially available stand-alone sampling systems could meet the needs of our specific research in (high-pressure) homogeneous catalysis. Most of these systems were prohibitively expensive and their operational window was relatively narrow (e.g., the sampling volume that could be withdrawn or the maximum allowable pressure from which could be sampled).

#### 4. Application potential

Data-rich (bio-)chemical experimentation is rapidly gaining prominence in industry and academia, and we therefore expect the market to grow significantly in the coming years.

#### Ethics statement

No specific ethics statement.

#### Declaration of Competing Interest

Authors have received funding from the Dutch Research Council (NWO) to perform a feasibility study and develop a business plan to bring the herein described technology to market (NWO Take-off Phase 1 grant, grant# 18842, 2020-2021). RvP and EAU are co-founders of the start-up company (CyberHydra B.V. and are bringing the technology to market.

#### CRedit authorship contribution statement

**Robbert van Putten:** Conceptualization, Methodology, Software, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Evgeny A. Us lamin:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Visualization, Funding acquisition. **Evgeny A. Pidko:** Conceptualization, Writing – review & editing, Funding acquisition.

#### Acknowledgments

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