applied sciences

MDPI

Article

Structured Data Storage for Data-Driven Process Optimisation in Bioprinting

Barbara Schmieg [1,2,†], Nico Brandt [3,†], Vera J. Schnepp [1], Luka Radosevic [1], Sarah Gretzinger [1,2], Michael Selzer [3,4] and Jürgen Hubbuch [1,2,*]

1 Institute of Functional Interfaces, Karlsruhe Institute of Technology (KIT), 76344 Eggenstein-Leopoldshafen, Germany; barbara.schmieg@partner.kit.edu (B.S.); vera.schnepp@student.kit.edu (V.J.S.); luka.radosevic@student.kit.edu (L.R.); sarah.gretzinger@partner.kit.edu (S.G.)
2 Institute of Engineering in Life Sciences—Section IV: Molecular Separation Engineering, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany
3 Institute for Applied Materials (IAM), Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany; nico.brandt@kit.edu (N.B.); michael.selzer@kit.edu (M.S.)
4 Institute for Digital Materials Science (IDM), Karlsruhe University of Applied Sciences, 76133 Karlsruhe, Germany
* Correspondence: juergen.hubbuch@kit.edu
† These authors contributed equally to this work.

Abstract: Bioprinting is a method to fabricate 3D models that mimic tissue. Future fields of application might be in pharmaceutical or medical context. As the number of applicants might vary between only one patient to manufacturing tissue for high-throughput drug screening, designing a process will necessitate a high degree of flexibility, robustness, as well as comprehensive monitoring. To enable quality by design process optimisation for future application, establishing systematic data storage routines suitable for automated analytical tools is highly desirable as a first step. This manuscript introduces a workflow for process design, documentation within an electronic lab notebook and monitoring to supervise the product quality over time or at different locations. Lab notes, analytical data and corresponding metadata are stored in a systematic hierarchy within the research data infrastructure Kadi4Mat, which allows for continuous, flexible data structuring and access management. To support the experimental and analytical workflow, additional features were implemented to enhance and build upon the functionality provided by Kadi4Mat, including browser-based file previews and a Python tool for the combined filtering and extraction of data. The structured research data management with Kadi4Mat enables retrospective data grouping and usage by process analytical technology tools connecting individual analysis software to machine-readable data exchange formats.

Keywords: bioprinting; data-driven process development; data filtering; digitisation; electronic lab notebook; open source; research data management; systematic data storage

Citation: Schmieg, B.; Brandt, N.; Schnepp, V.J.; Radosevic, L.; Gretzinger, S.; Selzer, M.; Hubbuch, J. Structured Data Storage for Data-Driven Process Optimisation in Bioprinting. *Appl. Sci.* **2022**, *12*, 7728. https://doi.org/10.3390/app12157728

Academic Editors: Patrycja Szymczyk-Ziółkowska and Jerzy Detyna

Received: 14 June 2022
Accepted: 28 July 2022
Published: 1 August 2022

1. Introduction

Bioprinting is a promising fabrication method for the on-demand production of tailor-made objects. The process generates three-dimensional structures from biocompatible material and embedded cells. This may potentially be applied in pharmaceutical research, where high-content cell-based screenings in 3D would mimic natural tissue better than traditional 2D cell cultures [1] or in medical environments for the production of patient-specific tissue replacements with complex geometries [2,3].

This individual assembly includes bioink material preparation, 3D printing and post-processing [4]. Small batches of bioink with ingredients and biological components

which are dependent on the specific application [5,6] as well as a decentralised, on demand production with locally available systems create a high number of interconnected variables [7,8].

The uniqueness of the process and the manufactured product represents a challenge for the entry to the market of bioprinting into clinics in comparison to other industries that use 3D printed parts. In disciplines such as mechanical engineering, the quality of 3D printed model geometries can be compared to parts that were manufactured by established procedures but are intended to have the same functionality. Here, standardisation efforts can adapt existing protocols and have already progressed [9,10]. In contrast, the bioprinted objects may be designed for the treatment of an individual patient. This may generate a new class of product in the field of personalised medicine [11]. The uniqueness of the bioprinted product may furthermore require "new regulatory processes for assessing the safety and effectiveness of therapy [11].

As a consequence, there is a need for an improved, data-driven process understanding in the field of bioprinting [8,12–18] to ensure the safety of the process from the early stages of development. Some (isolated) aspects linking specific manufacturing parameters to a 3D printing outcome have already been investigated. Examples are the relation between rheological behaviour of the bioink and strand thickness [19,20], the control of the bioink flow rate by sensors [21,22], and online image analysis to detect deviations from the design [23,24]. Other aspects concerning the transferability and safety of processes need to be addressed [11,25].

For the transfer to industry, a comprehensive, continuous and secure documentation of the manufacturing history of each product item will be crucial [25] to meet standards such as those already established in the pharmaceutical industry [26]. To allocate the manifold data of a bioprinting process including design, execution, analysis data and metadata of the respective process steps, full digitalisation of all work packages is favourable [17] even in early-stage university research [27]. This includes the systematic documentation of the experiments within an electronic lab notebook (ELN), providing the standard operating procedures (SOPs) in a structured or even interactive protocol [28] and machine-readable data transfer to automated analysis interfaces. Hanna and Pantanowitz [29] stressed in their report on histology analysis in the medical field that further meaningfulness can be reached by limiting the number of possible analysis outcomes by drop-down lists and categorisation. To access complex data sets, many commercial and non-commercial database system and software solutions are available [30]. Among projects for storage as open-access data repositories [31,32], national and international initiatives as well as non-governmental organisations establish systems to make information available long-term for further research and retrospective analysis. For example, the European Cloud Initiative [33,34] supports the development of secure cloud technologies. Collaboration and digitalisation in the field of materials science are encouraged by the Materials Genome Initiative [35]. The RCSB Protein Data Bank [36] shares biochemical information for science and education. The German National Research Data Infrastructure for Engineering Sciences (NFDI4Ing) offers concepts to stimulate the findable, accessible, interoperable and re-usable (FAIR) management of research data [37,38].

As a part of NFDI4Ing, Kadi4Mat (Karlsruhe Data Infrastructure for Materials Science) [39] is an open source software for managing research data that is developed at the Karlsruhe Institute of Technology. The software is best described as a virtual research environment that combines and builds upon features of ELNs and repositories, enabling a comprehensive documentation of scientific workflows. While materials science is the current focus of development, Kadi4Mat is mostly kept generic, not least due to the heterogeneity of materials science-related disciplines. For example, Kadi4Mat has already been successfully used for structured data management in experimental tribology [40,41]. As a result, the usage and adaption to specific fields such as bioprinting is not only possible but highly encouraged. This generic approach and combination of functionalities sets Kadi4Mat apart from other open source systems, which are either focused on specific disciplines

or workflows. Examples of discipline-specific systems are the NOMAD Repository [42], which focuses on materials science data of specific codes, or the Chemotion ELN [43], which targets experimental work in organic chemistry. To the best of the authors' knowledge, however, there are no tailor-made solutions for bioprinting. Generic systems such as eLabFTW [44] can in principle be used in bioprinting, but due to its focus on handwritten notes and unstructured data and metadata as a core part of its ELN functionality, it is less suitable for implementing standard operating procedures and machine-readable data transfer, as intended in this work.

In an effort to analyse the robustness and the transferability of the bioprinting process, the project SOP_BioPrint, which is funded by the German Federal Ministry of Education and Research, establishes and validates an infrastructure for standardisation and collaboration in extrusion-based bioprinting. This includes the development of standardised protocols and the systematic documentation of SOPs, lab journal entries and results across different sites for automated analysis and the validation of their practicability. This manuscript thus presents a concept for a data management structure for round robin tests including all steps of a bioprinting process from raw material characterisation to the analysis of the printed objects. To address the fact that data-driven research can mean not only sharing, but also protecting, sensitive research data, a double-blind round robin test with 15 participating laboratories was designed within the research data infrastructure Kadi4Mat [39] as a proof of concept for the developed infrastructure. Workflows, SOPs and construction data for bioprinting model geometries were pre-set in the system with the aim to increase the reproducibility between the locations. Bioprinting groups 3D printed a series of hydrogel structures and documented their experimental data in Kadi4Mat. Templates for the documentation of experimental data within Kadi4Mat standardised the scope, type and layout of stored information and offered settings for privacy. For the analysis of certain (anonymised) data, Python scripts to extract specific information were developed as machine-interoperable and flexible interfaces. This systematic procedure allows for automatic processing of the data by participating analysis groups. In this manuscript, the preparation and use of the infrastructure in terms of technical extent and digital workflow is presented.

2. Materials and Methods

2.1. Design of a Round Robin Test

When interdisciplinary teams from biology, materials science, engineering and data science at different locations work together, data must not only be stored in a structured way but also with explanatory remarks to provide an overview for collaborators and to allow referencing. The presented process monitoring concept aims to standardise process steps and monitor the reproducibility in bioprinting with locally available equipment. The process steps of the round robin test were executed based on standardised workflows and standardised templates for data collection provided digitally in Kadi4Mat. Pre-tests at the laboratory responsible for the respective sub-topic were executed to define the design space for operational parameters and SOPs. Detailed instructions guided the users through the process and encouraged the documentation of deviations. For each sub-topic, a responsible person could be contacted in case of questions. The resource descriptions within Kadi4Mat were applied to prominently communicate updates and amendments. Annotations could directly be integrated into the respective environment with a timestamp to alert the participants of changes in specific topics. A double-blind concept of the round robin test ensured that data of individual bioprinting labs were only visible for the respective project group and not for other participants. Data were transferred to data scientists as an anonymised data set.

The sub-topics of the whole process were grouped hierarchically in a workflow to be executed at different laboratories. Figure 1 visualises the concept of storing thematically defined data packages. Chronologically, the systematic documentation starts with the centralised design of SOPs including windows of operation for system requirements and

environment as well as the execution of the individual process steps. SOPs were designed using a step-by-step approach with a detailed explanation and visualisation of manual process steps to ensure comparable execution. For the documentation of the experimental data, tasks were clearly stated as "standardised actions" or "to be executed with regard to local conditions within a parameter window". As an example, this means that the design draft of the 3D printed geometry can easily be transferred between different locations, whereas the settings of the local bioprinting equipment might differ depending on ambient conditions, location and/or as a function of time. Similarly, batch monitoring of the bioink components could be executed directly at the supplier, while the biomaterial preparation for the individual experiment and the printing process were integrated within the daily working schedule of the bioprinting lab.

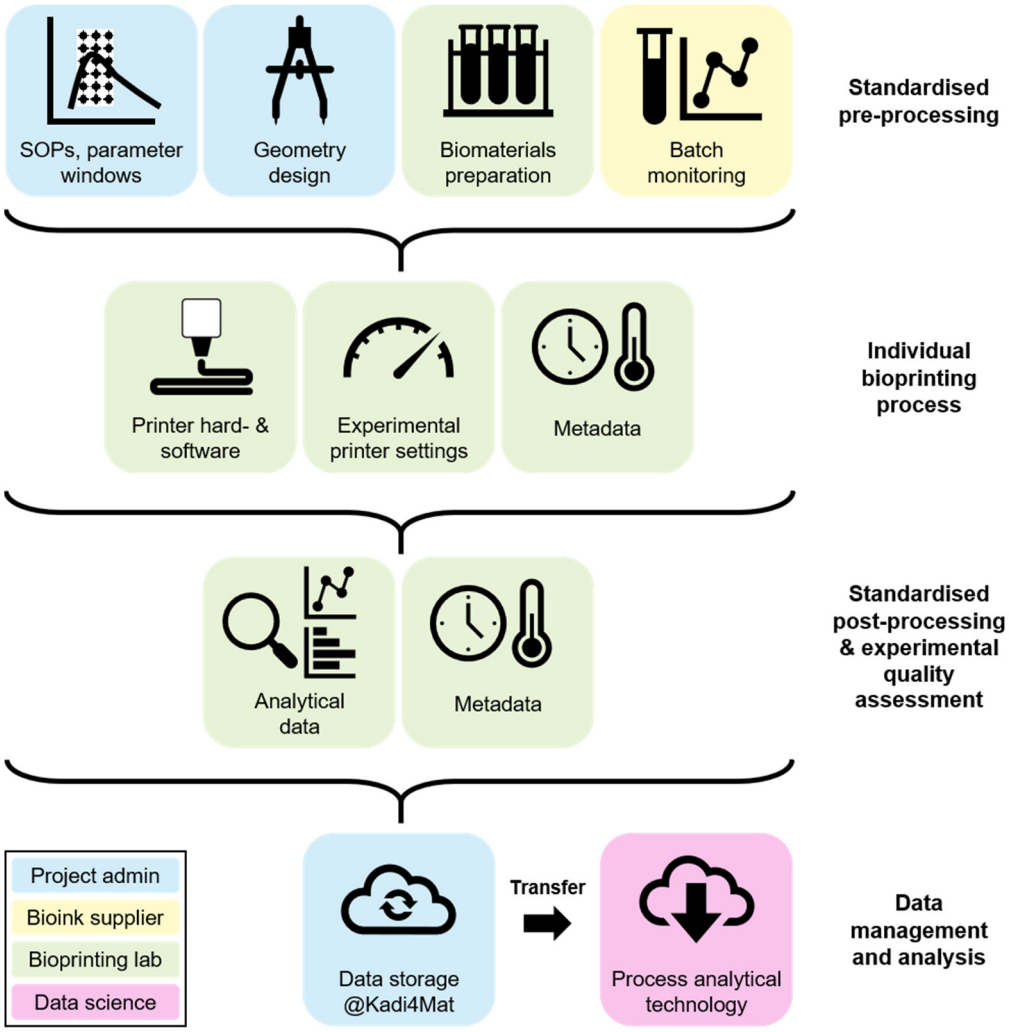

Figure 1. Schematic workflow of a bioprinting experiment and its connected data. The bioprinting process can be separated in pre-processing phase, the actual 3D printing procedure and post-processing [4], which includes the preparation for the application of the 3D printed object (in a biological experiment) and the analysis of the printing outcome. Data of a variety of file formats are collected describing the equipment, consumables and the execution of the process step, including metadata on the ambient conditions and deviations from the SOPs. The colour code illustrates that data are generated by all participants.

2.2. Design of Research Data Management

Kadi4Mat's platform-independent graphical user interface (GUI), usable via a regular web browser, is well suited for a decentralised project design or the direct documentation

of data from different locations. The system supports the researcher throughout the whole experimental process from displaying workflow information and SOPs throughout the documentation in an electronic notebook to the sharing of analytical results, including the reuse and annotation of data. A modular approach allows the continuous modification of workflows and documentation, with a high flexibility to include data formats that may improve process knowledge in a later stage. For the automated, machine-interoperable use of Kadi4Mat's functionality, a REST-like [45] HTTP application programming interface (API) is available, using JSON as an exchange format. The JSON file format is often used for such APIs because it integrates with most programming languages and is still easily readable by humans. Within a defined set of data, the structured storage will enable its analysis by automated tools using the API of Kadi4Mat.

3. Results

3.1. Implementation of Round Robin Test

Retrospective analysis currently is an important tool in the field of bioprinting as no standards exist yet. Thus, monitoring of the bioprinting process includes a broad spectrum of data from bioink raw material to the 3D printed object. A risk assessment for the respective process steps and manual handles was allocated based on literature research, as illustrated in Table 1. The monitored parameter sets were thematically allocated within Kadi4Mat to standardise the ELN documentation.

Table 1. Risk assessment for the process steps of the round robin test. Based on literature research, actions for standardisation and quality control within the scope of the experiments were established.

Process Parameter/ Consumable/ Device	Possible Findings	Impact of Deviation	Standardised Parameter within Scope of Experiments
Bioink raw material	Batch-to-batch variations, ageing, change of composition by purification or sterilisation steps [46–50]	Variations in viscosity, rheological behaviour and printing properties [14,20,51,52]; risk of process interruption because of nozzle clogging or increased bioink flow	Batch monitoring: analysis protocols for physicochemical characterisation, rheology, degree of (individual) functionalisation (adapted to individual bioink)
			Components are used as received at bioprinting lab
			SOP for storage
Bioink preparation	Commonly still a manual step [14]. May lead to inhomogeneities, air bubbles [53], etc.	Deviations in bioink flow within one experimental run or between runs [22,53]	SOPs for preparation steps, standardised consumables, documentation of deviations
			Images of cartridge for visual air bubble control
			Small batches (limit storage time of preparations within process)
Geometry transfer from design to local device	Adaption to local software and printer [25,54]; individual settings (user-controlled and algorithm-based)	Different printing outcome	Pre-defined design of basic geometries (line, circle, edges) that are possible with all hardware equipment
			Use of small object sizes for high number of technical replicates
			SOPs for parameter window of user-controlled settings
			Documentation of algorithm-based deviations by user
Printer hardware and software	Resolution of printers [55], position effects on printing platform, availability of settings/addons such as temperature control jackets, flow settings [16,21,56]	Different printing outcome [57,58]	Transfer by user according to process window of SOP
		Lack of process control for simple devices without addons	Documentation and characterisation of used addons and parameters
Experimental extrusion parameters device /software	Deviations in bioink flow [22], response time and acceleration of device at start/end of movement	Experimental geometry deviations: closed/open circles, line uniformity and thickness [23,59,60]	Operate within pre-defined process window, document parameters and collect comments of user

Table 1. *Cont.*

Process Parameter/ Consumable/ Device	Possible Findings	Impact of Deviation	Standardised Parameter within Scope of Experiments
Non-biological consumables for printing	Cartridge size is dependent on hardware. Possibility of dead-volume effects and acceleration	Surface tension effects on filament extrusion	Standardised material of single-use components as cartridges. Standardised transferable items (nozzles and wellplates)
			Document type of consumable used
Ambient conditions	Temperature, humidity, process duration [58,61,62]	Rheology deviations, bioink ageing, drying of recently printed scaffold part	Set parameter window, set max process time, document experimental values
Resulting geometry–imaging	Drying of samples [60], reflective surfaces, low contrast	Individual image quality	Standardized devices, pre-set imaging parameters, scale bar for image analysis
Biological functionality (highly dependent on individual application)	Deviations in biological functionality (cell viability [63], diffusion limitations [64]) compared to expected values or control group	Decreased reproducibility of assays	Analysis of results only with consideration of experimental conditions of the whole process
	Decreased biological functionality as a result of other process deviations		

The bioprinting process contains several interlocking steps. In order to create an unbiased data collection, operational parameters to be considered were identified according to the risk analysis. One example for direct transfer is the critical process parameter (cPP) "bioink temperature", which is directly connected to the viscosity of the bioink [8]. Ensuring high reproducibility in the rheological behaviour of the bioink can reduce deviations in several consecutive steps, such as the extrusion flow or the spreading of the printed objects on the substrate. Local adaptions concern the desired object geometry. The volumetric object and its design data can be strictly defined by coordinates or file formats describing the surface area, for example in an STL file. The individual execution will depend on local conditions such as software pre-processing, which will slice the desired geometry based on proprietary algorithms. In the case of local adaptations, SOPs describe the desired outcome within a parameter window as a critical quality attribute (cQA), and the participants of the round robin test were asked to set the local settings to achieve the highest congruence and describe deviations. For the round robin test, the cQA "desired hydrogel strand thickness" was used. The executing bioprinting lab was able to perform internal pre-tests, measure the experimental hydrogel strand thickness and adapt the used parameters with regard to the local conditions and the given parameter windows. As small hydrogel objects are prone to drying and thus shrinkage after 3D printing, maximum processing times between working steps were proposed in SOPs, and the experimental duration was monitored in the ELN.

3.2. Data Management in Kadi4Mat

The basic units to manage data within Kadi4Mat are the so-called records. Records combine an arbitrary amount and arbitrary formats of data with corresponding metadata and can represent any kind of digital or physical input and output, processing step or experimental device. The metadata are split into two parts: fixed metadata for common elements such as titles or descriptions of records, as well as generic metadata that can be specified as key-value pairs of different types in a JSON-like composition, allowing for a high amount of flexibility. To establish relationships between multiple records, directed links can be created, each linking two records together with an arbitrary link name. Within the round robin test, a series of experiments is executed and documented in records, which were systematically named and tagged, as well as record links. Multiple records can also be grouped into one or more, possibly nested, collections for improved organisation. In the scope of a round robin test, this was used to organise the records of one experimental series, all data of one lab or a set of SOPs for thematic access.

Templates can be created to simplify the repeated creation of records with uniform structure or records sharing common metadata, reducing manual work as well as human error. In addition to the actual metadata that is applied to new records, templates may also

contain instructions on how to use them. In this project, the templates were predefined by the project admin. Besides detailed usage instructions, the templates contained all common, fixed record metadata, such as descriptions with hyperlinks to connected items (for example SOPs), as well as generic metadata to query all applicant-specific parameters. By using basic validation instructions when creating the template, fixed selections of values can be specified for individual metadata entries, which are shown as dropdown lists to the applicant. The way in which the different record functions were used to collect all the process information is shown in Table 2. Figure 2 shows an exemplary screenshot of a template used for bioink preparation from Kadi4Mat (personal data has been removed).

Table 2. Collected parameters for the bioink preparation and bioprinting process within one experimental run. Analogous to the process steps shown, the analytical process steps (which might be image data to describe the geometry or kinetic data on cellular metabolism) are connected to the description of the used devices, methods and consumables as well as the acquired assay raw data. Each enumeration in the column "Allocated information, datasets and/or files" can contain groups of generic data.

Template	Type of Data	Allocated Information, Datasets and/or Files
Standardised bioink preparation	Fixed metadata	Changelog
		Description for user: Aim of template and instructions on how to apply it (includes embedded images)
		Link to: corresponding SOPs
	Generic metadata	Experiment identification number
		Name and batch identifier of bioink
		User identification (anonymised)
		Timestamps of preparation and storage duration
		Weighed portions of bioink components
		Checkpoints: Bioink preparation executed as specified in SOP?
		Deviations/comments (free text option for user)
	Attached files (to generated record)	Image on ready-to-use bioink cartridge before bioprinting for air bubble assessment
	Linked records (to generated record)	Raw material analysis Individual bioprinting process
Individual bioprinting process (within pre-defined window of operation)	Fixed metadata	Analogous to template "Standardised bioink preparation"
	Generic metadata	Experiment identification
		User identification (anonymised)
		Timestamp of start and end
		Temperature (ambient conditions, 3D printer cabinet, heating mantle, nozzle heater)
		Printer settings (flowrate, printhead speed, layer height, pre-/postflow, tear off settings at end of strands, etc.)
		Checkpoints: used consumables
		Deviations/comments
	Attached files (to generated record)	Bioprinting log files, images, comment files of experimental deviations
	Linked records (to generated record)	Used bioink preparation Used hardware and methods
Description of used hardware or method	Fixed metadata	Analogous to template "Standardised bioink preparation"
	Generic metadata	Identification of method/device (supplier, version)
		User identification (anonymised)
		Description of connected process steps and hardware addons (example bioprinter: manufacturer, model, configuration of device, type of air flow in printer cabinet, software, used calibration method, etc.)
	Attached files (to generated record)	Individual data files, image of hardware for visualisation
	Linked records (to generated record)	(links from individual bioprinting process are incoming)

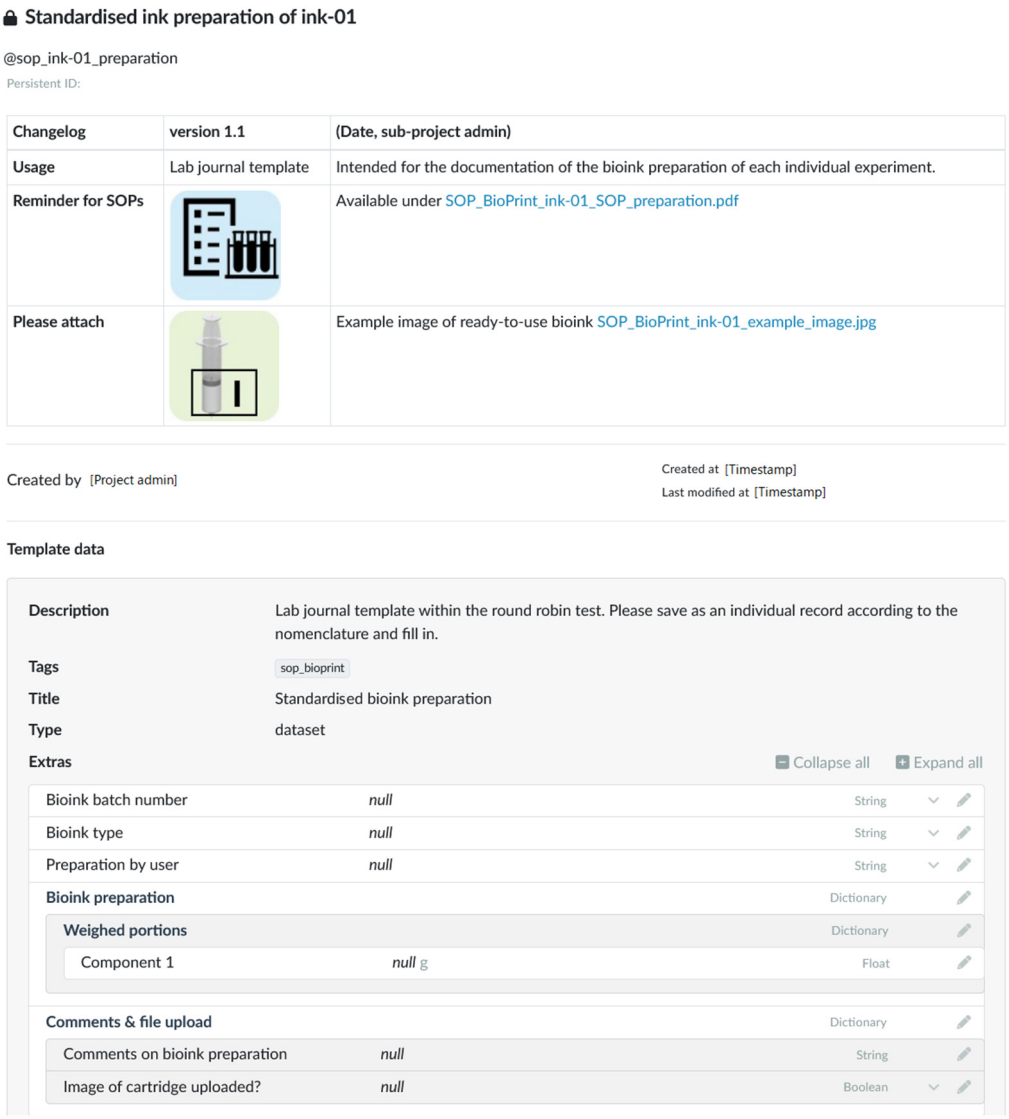

Figure 2. Screenshot of a record template in Kadi4Mat for the documentation of bioink preparation where personal data has been removed. The upper half of the template shows its title and instructions, while the actual template data can be seen in the lower half. The latter contains both fixed metadata types, such as the description and type of a record, as well as generic metadata entries, including their keys, types and additional validation instructions.

For the analysis of the data, filtering and grouping options within Kadi4Mat facilitate structured data handling and processing. Whereas automated filtering is useful for machine-assisted analysis, various visualisation options are provided for manual review of the metadata, data and their relationships. One such example is presented in Figure 3 (additional visualisation in Video S1 and Figure S1 in the Supporting Information), which shows a graphical representation of all incoming and outgoing links of a given record within the ELN. These interactive graphs can be generated automatically via the GUI of Kadi4Mat and were used to check on the progress of the documentation during the experimental phase. As the visualisation is based on links between the records, the user can display not only the hierarchical experimental structure but also the connected SOPs. To support the digital workflow in the laboratory such as the execution of process steps according to the SOP, a browser-based preview of corresponding file formats, such as Excel or PDF files, is possible. In order to view the result data, additional previews for STL and TIFF files were implemented. Some examples are shown in Figures S2–S4 in the Supporting Information.

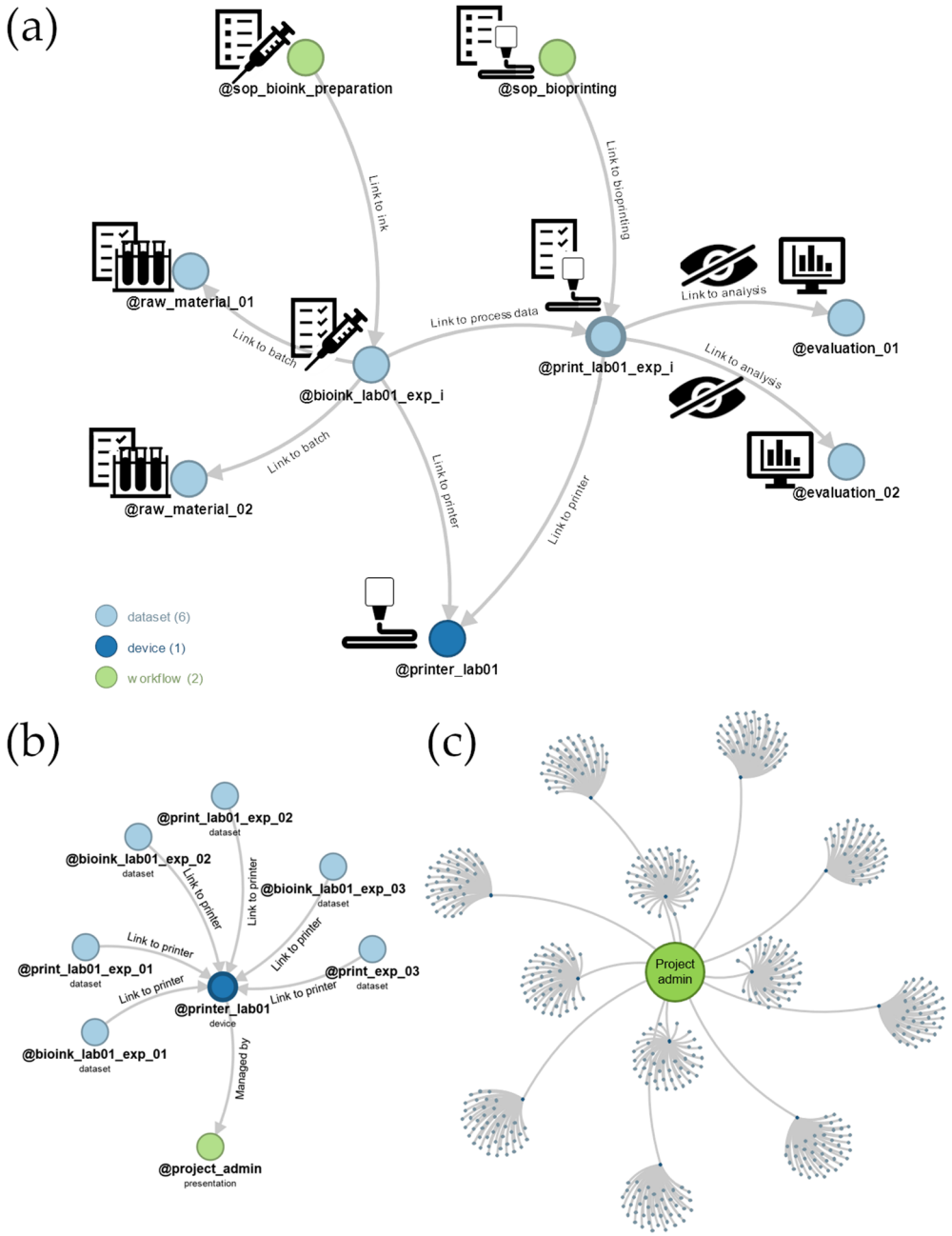

Figure 3. Visualisation of record links generated via Kadi4Mat, showing all outgoing and incoming links of the dataset record represented by the node in the centre (highlighted edges of node) up to a certain link depth. The linked records represent related datasets (light blue node), devices (dark blue) and workflows (green) in the form of SOPs. (**a**) An example dataset concerning bioprinting data of one run from pre- to post-processing and its linked records (link depth 3) of the process workflow: information contain the used devices (3D printer), the bioink batch and linked data as well as the used SOPs, each labelled with different icons. (**b**) All experiments executed with one printer within one lab are connected with a link depth of 1. (**c**) For the round robin test, only the project admin is able to access all hierarchically stored data from different labs (link depth 2 connecting project admin, printer and laboratory notebook entries of printing).

The round robin test was designed with independent analysis of the results, meaning the bioprinting labs and the analytical units were anonymised, resulting in a double-blind study. To manage access to the data within Kadi4Mat, the built-in permission management was used, which enables the assignment of roles to individual users or groups of users,

each granting various permissions. Within the frame of the round robin test, this was used to define a project management group and project teams for the individual bioprinting labs, material suppliers and analysis units. Access to the data was assigned to the members of the different groups, which not only allows data to be shared, but also limits the visibility and access rights for certain groups to protect sensitive data. For the double-blind transfer of the bioprinting data set to process analysis, an anonymised version of each relevant collection (optionally with limited transfer of metadata) was generated by the project admin.

To enable automated analysis in application-specific software, the (anonymised) data of the bioprinting had to be made available to the project partners responsible for independent analysis. For this, a separate tool was developed using the Python programming language, serving as a bridge between the experimenters needs and the HTTP API of Kadi4Mat. As displayed in Figure 4, data concerning the execution of the process were collected by the project admin and forwarded as a uniform, anonymised data collection. The tool was built on top of kadi-apy [65], a Python-based library that facilitates the use of Kadi4Mat's API by providing high-level interfaces and reducing the amount of boilerplate code. Via an additional GUI, using the tool makes it possible to extract all shared data necessary from a batch of records for the analysis with a single button press and some prior configuration. In addition to the actual data, all metadata in both machine-interoperable and user-readable formats are exported, using JSON and PDF files, respectively. While these steps are also possible via the web-based GUI of Kadi4Mat, the tool ensures that all required information can be exported in a flexible, targeted and automated manner. In principle, the underlying code also enables direct integration with existing analysis tools.

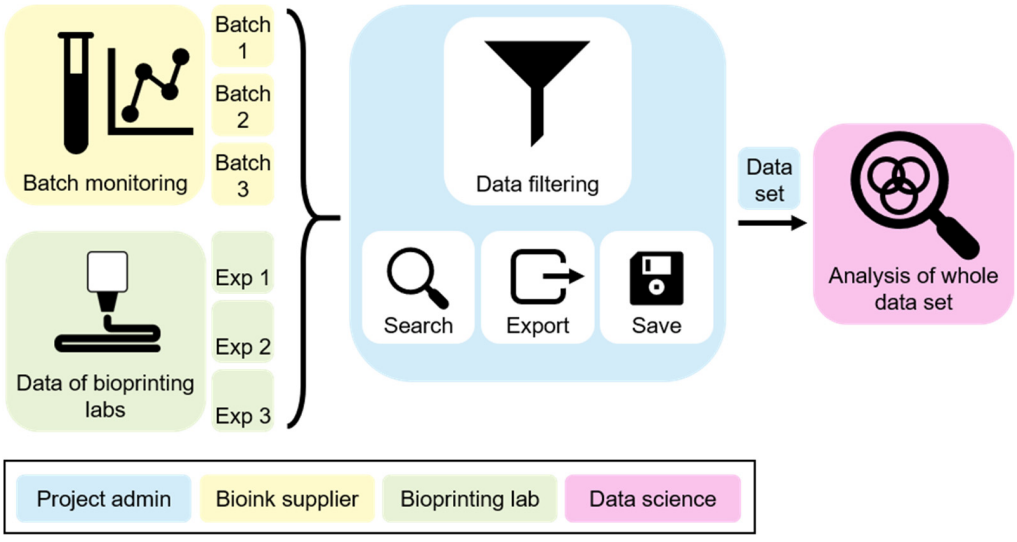

Figure 4. Visualisation of the workflow centred around the developed Python tool. An arbitrary number of records organised in a collection from bioink suppliers (raw material batch analysis data) and bioprinting labs (bioink preparation and bioprinting protocols) is edited with the Python script by the project admin with the aim of filtering out certain data. A new (anonymised) collection is created and transferred to analysis.

4. Discussion

Parameters influencing the outcome of bioprinting are diverse and highly interconnected. For the transfer of bioprinting towards industrial application, a systematic process monitoring that enables the connectivity to process analytical technology (PAT) approaches, online-process control tools or traceability systems is favourable. This manuscript presents a concept for data management using the research data infrastructure Kadi4Mat that provides templates to enable standardised workflows and structured data storage and exchange. In a round robin test, data were collected systematically covering all process

steps in a comprehensive way. Applying a Python tool that was programmed to filter certain data, a double-blind study design could be realised.

By using templates within Kadi4Mat, standardised parameters were inserted in predefined lists, while comments could also be added to allow for additional free-text information. In the case of workload, the use of templates increased the velocity of the user in comparison to traditional paper lab journals. As the data safety measures might be quite high in research labs, the unhindered access to Kadi4Mat needs to be guaranteed, which includes electronic devices (stationary PCs or mobile devices) that can be connected to the network within the lab.

The structured data storage and exchange functionality of Kadi4Mat assisted in managing the data in a consistent manner. For participants of the round robin tests, no programming skills were necessary, and the training to use the templates took a maximum of one hour. Especially, the possibility to copy digital entries was found by the users to save time compared to paper-based lab journals. Due to the different experiences and previous knowledge of the experimenters in dealing with such systems, using Kadi4Mat was natural for some users and for others more difficult. Even if not a phenomenon unique to Kadi4Mat, it is clear that functionality must be developed to account for these factors. This can include more guidance functionality and integrated help texts, as well as extending the current template functionality to allow for more customisation, while still limiting the value range of metadata entered by users of the templates. The identification of such requirements is only made possible by close cooperation between developers and users, as presented in this work.

5. Conclusions

Based on the structured data collection concept within Kadi4Mat, the bioprinting process steps can be documented in a comprehensive way from material preparation to post-processing. In a round robin test, researchers from different disciplines and locations contributed to examine the transferability of the bioprinting process. Meanwhile, sensitive information was protected by grouping and sub-grouping users according to their tasks and laboratories. For the transfer of data, the developed Python tool for the creation of filtered export files that are based on a machine-readable file format was used. While the focus in this work was on a specific use case, establishing standardised monitoring concepts and storing allocated data within flexible systems such as Kadi4Mat can pave the way to transfer the data to automated analytical tools. Continued use of structured data collection concepts helps to identify deviations of parameters of individual processes or enhance the process knowledge on larger datasets for the development of robust processes suitable for industrial and clinical applications. Although further work is needed to streamline the described workflows and evaluate the overall increase in efficiency or product consistency through the use of a research data management system such as Kadi4Mat, this work can serve as a blueprint for other applications in bioprinting and similar fields.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app12157728/s1, Figure S1: Record Link Visualisation Tool; Figure S2: Preview of XLSX tables; Figure S3: Preview of STL Files; Figure S4: Preview of TIFF Files; Video S1: Interactive Use of Link Visualisation Tool.

Author Contributions: Conceptualisation, B.S. and N.B.; Methodology, B.S.; Software, N.B., V.J.S. and L.R.; Project Administration, B.S., N.B. and S.G.; Writing—Original Draft Preparation, B.S. and N.B.; Writing—Review and Editing, B.S., N.B., V.J.S., L.R., S.G., M.S. and J.H.; Funding Acquisition, M.S. and J.H. All authors have read and agreed to the published version of the manuscript.

Funding: We would like to acknowledge the German Federal Ministry of Education and Research (BMBF) for its financial support within the project SOP_BioPrint, under the grant number 13XP5071B, and within the project FB2 TheoDat, under the grant number 03XP0435D. We acknowledge support by the KIT-Publication Fund of the Karlsruhe Institute of Technology.

Data Availability Statement: A snapshot of the source code of the version of Kadi4Mat used in this work (including the developed preview tools) is publicly available on Zenodo [66]. The source code of the Python helper scripts is available upon request from the corresponding author. Data of the round robin test are not available due to contractual restrictions of SOP_BioPrint.

Acknowledgments: We would like to thank Domenic Frank and Christof Ratz for their administrative support in maintaining the centralised Kadi4Mat instance used in this project. We would also like to thank the participants of the round robin tests "extrusion-based 3D printing" and "image analysis" within the project SOP_BioPrint for their valuable comments and thoughtful feedback during the execution of the round robin tests. Last but not least, we would like to thank Svenja Strauß for sharing her photo of the 3D-printed hydrogel circle in context of the preview tool.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Xu, F.; Celli, J.; Rizvi, I.; Moon, S.; Hasan, T.; Demirci, U. A three-dimensional in vitro ovarian cancer coculture model using a high-throughput cell patterning platform. *Biotechnol. J.* **2011**, *6*, 204–212. [CrossRef] [PubMed]
2. Vermeulen, N.; Haddow, G.; Seymour, T.; Faulkner-Jones, A.; Shu, W. 3D bioprint me: A socioethical view of bioprinting human organs and tissues. *J. Med. Ethics* **2017**, *43*, 618–624. [CrossRef] [PubMed]
3. Kilian, D.; Sembdner, P.; Bretschneider, H.; Ahlfeld, T.; Mika, L.; Lützner, J.; Holtzhausen, S.; Lode, A.; Stelzer, R.; Gelinsky, M. 3D printing of patient-specific implants for osteochondral defects: Workflow for an MRI-guided zonal design. *Bio-Des. Manuf.* **2021**, *4*, 818–832. [CrossRef]
4. Mironov, V.; Boland, T.; Trusk, T.; Forgacs, G.; Markwald, R.R. Organ printing: Computer-aided jet-based 3D tissue engineering. *Trends Biotechnol.* **2003**, *21*, 157–161. [CrossRef]
5. Gungor-Ozkerim, P.S.; Inci, I.; Zhang, Y.S.; Khademhosseini, A.; Dokmeci, M.R. Bioinks for 3D bioprinting: An overview. *Biomater. Sci.* **2018**, *6*, 915–946. [CrossRef]
6. Wenger, L.; Radtke, C.P.; Goepper, J.; Woerner, M.; Hubbuch, J. 3D-Printable and Enzymatically Active Composite Materials Based on Hydrogel-Filled High Internal Phase Emulsions. *Front. Bioeng. Biotechnol.* **2020**, *8*, 713. [CrossRef] [PubMed]
7. Malda, J.; Visser, J.; Melchels, F.P.; Jüngst, T.; Hennink, W.E.; Dhert, W.J.A.; Groll, J.; Hutmacher, D.W. 25th Anniversary Article: Engineering Hydrogels for Biofabrication. *Adv. Mater.* **2013**, *25*, 5011–5028. [CrossRef]
8. Mancha Sánchez, E.; Gómez-Blanco, J.C.; López Nieto, E.; Casado, J.G.; Macías-García, A.; Díaz Díez, M.A.; Carrasco-Amador, J.P.; Torrejón Martín, D.; Sánchez-Margallo, F.M.; Pagador, J.B. Hydrogels for Bioprinting: A Systematic Review of Hydrogels Synthesis, Bioprinting Parameters, and Bioprinted Structures Behavior. *Front. Bioeng. Biotechnol.* **2020**, *8*, 776. [CrossRef]
9. Pei, E.; Ressin, M.; Campbell, R.I.; Eynard, B.; Xiao, J. Investigating the impact of additive manufacturing data exchange standards for re-distributed manufacturing. *Prog. Addit. Manuf.* **2019**, *4*, 331–344. [CrossRef]
10. Kawalkar, R.; Dubey, H.K.; Lokhande, S.P. A review for advancements in standardization for additive manufacturing. *Mater. Today-Proc.* **2021**, *50*, 1983–1990. [CrossRef]
11. Li, P.; Faulkner, A.; Medcalf, N. 3D bioprinting in a 2D regulatory landscape: Gaps, uncertainties, and problems. *Law Innov. Technol.* **2020**, *12*, 1–29. [CrossRef]
12. Di Prima, M.; Coburn, J.; Hwang, D.; Kelly, J.; Khairuzzaman, A.; Ricles, L. Additively manufactured medical products—The FDA perspective. *3D Print. Med.* **2016**, *2*, 1. [CrossRef] [PubMed]
13. Jamroz, W.; Szafraniec, J.; Kurek, M.; Jachowicz, R. 3D Printing in Pharmaceutical and Medical Applications—Recent Achievements and Challenges. *Pharm. Res.* **2018**, *35*, 176. [CrossRef]
14. Gillispie, G.; Prim, P.; Copus, J.; Fisher, J.; Mikos, A.G.; Yoo, J.J.; Atala, A.; Lee, S.J. Assessment methodologies for extrusion-based bioink printability. *Biofabrication* **2020**, *12*, 22003. [CrossRef]
15. Shafiee, A.; Ghadiri, E.; Ramesh, H.; Kengla, C.; Kassis, J.; Calvert, P.; Williams, D.; Khademhosseini, A.; Narayan, R.; Forgacs, G.; et al. Physics of bioprinting. *Appl. Phys. Rev.* **2019**, *6*, 21315. [CrossRef]
16. Rimann, M.; Bono, E.; Annaheim, H.; Bleisch, M.; Graf-Hausner, U. Standardized 3D Bioprinting of Soft Tissue Models with Human Primary Cells. *JALA* **2016**, *21*, 496–509. [CrossRef] [PubMed]
17. Hunsberger, J.G.; Shupe, T.; Atala, A. An Industry-Driven Roadmap for Manufacturing in Regenerative Medicine. *Stem Cells Transl. Med.* **2018**, *7*, 564–568. [CrossRef] [PubMed]
18. An, J.; Chua, C.K.; Mironov, V. Application of Machine Learning in 3D Bioprinting: Focus on Development of Big Data and Digital Twin. *Int. J. Bioprint.* **2021**, *7*, 342. [CrossRef]
19. Poessl, A.; Hartzke, D.; Schmidts, T.M.; Runkel, F.E.; Schlupp, P. A targeted rheological bioink development guideline and its systematic correlation with printing behavior. *Biofabrication* **2021**, *13*, 35021. [CrossRef]
20. Rahimnejad, M.; Labonte-Dupuis, T.; Demarquette, N.R.; Lerouge, S. A rheological approach to assess the printability of thermosensitive chitosan-based biomaterial inks. *Biomed. Mater.* **2021**, *16*, 15003. [CrossRef]
21. Fisch, P.; Holub, M.; Zenobi-Wong, M. Improved accuracy and precision of bioprinting through progressive cavity pump-controlled extrusion. *Biofabrication* **2021**, *13*, 15012. [CrossRef]

22. Strauss, S.; Schroth, B.; Hubbuch, J. Evaluation of the Reproducibility and Robustness of Extrusion-based Bioprinting Processes applying a Flow Sensor. *Front. Bioeng. Biotechnol.* **2022**, *10*, 831350. [CrossRef]
23. Armstrong, A.A.; Alleyne, A.G.; Johnson, A.J.W. 1D and 2D error assessment and correction for extrusion-based bioprinting using process sensing and control strategies. *Biofabrication* **2020**, *12*, 45023. [CrossRef]
24. Deneault, J.R.; Chang, J.; Myung, J.; Hooper, D.; Armstrong, A.; Pitt, M.; Maruyama, B. Toward autonomous additive manufacturing: Bayesian optimization on a 3D printer. *MRS Bull.* **2021**, *46*, 566–575. [CrossRef]
25. Hourd, P.; Medcalf, N.; Segal, J.; Williams, D.J. A 3D bioprinting exemplar of the consequences of the regulatory requirements on customized processes. *Regen. Med.* **2015**, *10*, 863–883. [CrossRef] [PubMed]
26. Cao, H.; Mushnoori, S.; Higgins, B.; Kollipara, C.; Fermier, A.; Hausner, D.; Jha, S.; Singh, R.; Ierapetritou, M.; Ramachandran, R. A Systematic Framework for Data Management and Integration in a Continuous Pharmaceutical Manufacturing Processing Line. *Processes* **2018**, *6*, 53. [CrossRef]
27. Foster, E.D.; Whipple, E.C.; Rios, G.R. Implementing an institution-wide electronic lab notebook initiative. *J. Med. Libr. Assoc.* **2022**, *110*, 222–227. [CrossRef]
28. Porr, M.; Marquard, D.; Stanislawski, N.; Austerjost, J.; Russo, M.; Bungers, S.; Klimmt, C.; Scheper, T.; Beutel, S.; Lindner, P. smartLAB—Working Interactively in a Digitalized Laboratory Environment. *Chem. Ing. Tech.* **2019**, *91*, 285–293. [CrossRef]
29. Hanna, M.G.; Pantanowitz, L. The role of informatics in patient-centered care and personalized medicine. *Cancer Cytopathol.* **2017**, *125*, 494–501. [CrossRef]
30. Higgins, S.G.; Nogiwa-Valdez, A.A.; Stevens, M.M. Considerations for implementing electronic laboratory notebooks in an academic research environment. *Nat. Protoc.* **2022**, *17*, 179–189. [CrossRef]
31. re3data.org Project Consortium. Registry of Research Data Repositories. Available online: https://www.re3data.org/ (accessed on 14 June 2022).
32. European Organization for Nuclear Research. OpenAIRE. *Zenodo.* Available online: https://www.zenodo.org/ (accessed on 14 June 2022).
33. European Commission. Commission Welcomes Member States' Declaration on EU Cloud Federation [Press Release]. Available online: https://digital-strategy.ec.europa.eu/en/news/commission-welcomes-member-states-declaration-eu-cloud-federation (accessed on 14 June 2022).
34. European Commission. European Alliance for Industrial Data, Edge and Cloud. Available online: https://digital-strategy.ec.europa.eu/en/policies/cloud-alliance (accessed on 14 June 2022).
35. Jain, A.; Persson, K.A.; Ceder, G. Research Update: The materials genome initiative: Data sharing and the impact of collaborative ab initio databases. *APL Mater.* **2016**, *4*, 53102. [CrossRef]
36. Goodsell, D.S.; Zardecki, C.; Berman, H.M.; Burley, S.K. Insights from 20 years of the Molecule of the Month. *Biochem. Mol. Biol. Educ.* **2020**, *48*, 350–355. [CrossRef] [PubMed]
37. Schmitt, R.H.; Anthofer, V.; Auer, S.; Baskaya, S.; Bischof, C.; Bronger, T.; Claus, F.; Cordes, F.; Demandt, É.; Eifert, T.; et al. NFDI4Ing—The National Research Data Infrastructure for Engineering Sciences. Available online: https://zenodo.org/record/4015201 (accessed on 14 June 2022).
38. Scheffler, M.; Aeschlimann, M.; Albrecht, M.; Bereau, T.; Bungartz, H.-J.; Felser, C.; Greiner, M.; Groß, A.; Koch, C.T.; Kremer, K.; et al. FAIR data enabling new horizons for materials research. *Nature* **2022**, *604*, 635–642. [CrossRef]
39. Brandt, N.; Griem, L.; Herrmann, C.; Schoof, E.; Tosato, G.; Zhao, Y.; Zschumme, P.; Selzer, M. Kadi4Mat: A Research Data Infrastructure for Materials Science. *Data Sci. J.* **2021**, *20*, 8. [CrossRef]
40. Brandt, N.; Garabedian, N.T.; Schoof, E.; Schreiber, P.J.; Zschumme, P.; Greiner, C.; Selzer, M. Managing FAIR Tribological Data Using Kadi4Mat. *Data* **2022**, *7*, 15. [CrossRef]
41. Garabedian, N.T.; Schreiber, P.J.; Brandt, N.; Zschumme, P.; Blatter, I.L.; Dollmann, A.; Haug, C.; Kümmel, D.; Li, Y.; Meyer, F.; et al. Generating FAIR Research Data in Experimental Tribology. *Sci. Data* **2022**, *9*, 315. [CrossRef]
42. Draxl, C.; Scheffler, M. NOMAD: The FAIR concept for big data-driven materials science. *MRS Bull.* **2018**, *43*, 676–682. [CrossRef]
43. Tremouilhac, P.; Nguyen, A.; Huang, Y.-C.; Kotov, S.; Lütjohann, D.S.; Hübsch, F.; Jung, N.; Bräse, S. Chemotion ELN: An Open Source electronic lab notebook for chemists in academia. *J. Cheminform.* **2017**, *9*, 54. [CrossRef]
44. Carpi, N.; Minges, A.; Piel, M. eLabFTW: An open source laboratory notebook for research labs. *J. Open Source Softw.* **2017**, *2*, 146. [CrossRef]
45. Fielding, R.T. Architectural Styles and the Design of Network-Based Software Architectures. Ph.D. Dissertation, University of California, Irvine, CA, USA, 2000.
46. Bernhardt, A.; Wehrl, M.; Paul, B.; Hochmuth, T.; Schumacher, M.; Schuetz, K.; Gelinsky, M. Improved Sterilization of Sensitive Biomaterials with Supercritical Carbon Dioxide at Low Temperature. *PLoS ONE* **2015**, *10*, e0129205. [CrossRef]
47. Yu, H.; Cauchois, G.; Schmitt, J.-F.; Louvet, N.; Six, J.-L.; Chen, Y.; Rahouadj, R.; Huselstein, C. Is there a cause-and-effect relationship between physicochemical properties and cell behavior of alginate-based hydrogel obtained after sterilization? *J. Mech. Behav. Biomed. Mater.* **2017**, *68*, 134–143. [CrossRef] [PubMed]
48. Lorson, T.; Ruopp, M.; Nadernezhad, A.; Eiber, J.; Vogel, U.; Jungst, T.; Luehmann, T. Sterilization Methods and Their Influence on Physicochemical Properties and Bioprinting of Alginate as a Bioink Component. *ACS Omega* **2020**, *5*, 6481–6486. [CrossRef]
49. Rizwan, M.; Chan, S.W.; Comeau, P.A.; Willett, T.L.; Yim, E.K.F. Effect of sterilization treatment on mechanical properties, biodegradation, bioactivity and printability of GelMA hydrogels. *Biomed. Mater.* **2020**, *15*, 65017. [CrossRef] [PubMed]

50. Stoppel, W.L.; White, J.C.; Horava, S.D.; Henry, A.C.; Roberts, S.C.; Bhatia, S.R. Terminal sterilization of alginate hydrogels: Efficacy and impact on mechanical properties. *J. Biomed. Mater. Res. Appl. Biomater.* **2014**, *102*, 877–884. [CrossRef] [PubMed]
51. Schwab, A.; Levato, R.; D'Este, M.; Piluso, S.; Eglin, D.; Malda, J. Printability and Shape Fidelity of Bioinks in 3D Bioprinting. *Chem. Rev.* **2020**, *120*, 11028–11055. [CrossRef] [PubMed]
52. Diamantides, N.; Dugopolski, C.; Blahut, E.; Kennedy, S.; Bonassar, L.J. High density cell seeding affects the rheology and printability of collagen bioinks. *Biofabrication* **2019**, *11*, 45016. [CrossRef]
53. Zidan, A.; Alayoubi, A.; Asfari, S.; Coburn, J.; Ghammraoui, B.; Aqueel, S.; Cruz, C.N.; Ashraf, M. Development of mechanistic models to identify critical formulation and process variables of pastes for 3D printing of modified release tablets. *Int. J. Pharm.* **2019**, *555*, 109–123. [CrossRef]
54. Šljivic, M.; Pavlovic, A.; Kraišnik, M.; Ilić, J. Comparing the accuracy of 3D slicer software in printed enduse parts. *IOP Conf. Ser. Mater. Sci. Eng.* **2019**, *659*, 012082. [CrossRef]
55. Prendergast, M.E.; Burdick, J.A. Recent Advances in Enabling Technologies in 3D Printing for Precision Medicine. *Adv. Mater.* **2020**, *32*, e1902516. [CrossRef]
56. Schmieg, B.; Gretzinger, S.; Schuhmann, S.; Guthausen, G.; Hubbuch, J. Magnetic Resonance Imaging as a tool for quality control in extrusion-based bioprinting. *Biotechnol. J.* **2022**, *17*, e2100336. [CrossRef]
57. Chimene, D.; Kaunas, R.; Gaharwar, A.K. Hydrogel Bioink Reinforcement for Additive Manufacturing: A Focused Review of Emerging Strategies. *Adv. Mater.* **2020**, *32*, 1902026. [CrossRef]
58. Gomez-Blanco, C.J.; Mancha-Sanchez, E.; Marcos, A.C.; Matamoros, M.; Diaz-Parralejo, A.; Blas Pagador, J. Bioink Temperature Influence on Shear Stress, Pressure and Velocity Using Computational Simulation. *Processes* **2020**, *8*, 865. [CrossRef]
59. Gao, T.; Gillispie, G.J.; Copus, J.S.; Kumar, P.R.A.; Seol, Y.J.; Atala, A.; Yoo, J.J.; Lee, S.J. Optimization of gelatin-alginate composite bioink printability using rheological parameters: A systematic approach. *Biofabrication* **2018**, *10*, 34106. [CrossRef]
60. Strauß, S.; Meutelet, R.; Radosevic, L.; Gretzinger, S.; Hubbuch, J. Image analysis as PAT-Tool for use in extrusion-based bioprinting. *Bioprinting* **2021**, *21*, e00112. [CrossRef]
61. Matamoros, M.; Gómez-Blanco, J.C.; Sánchez, Á.J.; Mancha, E.; Marcos, A.C.; Carrasco-Amador, J.P.; Pagador, J.B. Temperature and Humidity PID Controller for a Bioprinter Atmospheric Enclosure System. *Micromachines* **2020**, *11*, 999. [CrossRef]
62. Shen, Z.; Shang, X.; Zhao, M.; Dong, X.; Xiong, G.; Wang, F.-Y. A Learning-Based Framework for Error Compensation in 3D Printing. *IEEE Trans. Cybern.* **2019**, *49*, 4042–4050. [CrossRef]
63. Gretzinger, S.; Beckert, N.; Gleadall, A.; Lee-Thedieck, C.; Hubbuch, J. 3D bioprinting—Flow cytometry as analytical strategy for 3D cell structures. *Bioprinting* **2018**, *11*, e00023. [CrossRef]
64. Schmieg, B.; Nguyen, M.; Franzreb, M. Simulative Minimization of Mass Transfer Limitations Within Hydrogel-Based 3D-Printed Enzyme Carriers. *Front. Bioeng. Biotechnol.* **2020**, *8*, 365. [CrossRef]
65. Kadi4Mat Team and Contributors. IAM-CMS/kadi-apy: Kadi4Mat API Library (0.21.0). Available online: https://zenodo.org/record/6623518 (accessed on 14 June 2022).
66. Kadi4Mat Team and Contributors. IAM-CMS/kadi: Kadi4Mat (kadi-v0.25.1). Available online: https://zenodo.org/record/6623521 (accessed on 14 June 2022).