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Bio-inspired control of automated stem cell production

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Abstract

The possible role of stem cells in medical treatments can hardly be overestimated. Today they are produced – almost without exemption – with significant human involvement using adaptive protocols that take the growth behavior of the biological material into account. Automated production platforms are being developed and tested in a number of research laboratories with the main goals of improving reproducibility, as well as increasing quality and throughput. However, automated stem cell production differs from the traditional manufacturing processes in (1) the inherent diversity of the products (stem cells), (2) their varying growth rates and process times, (3) the need for their regular observation and process adaptation, and, therefore, (4) for mixed-initiative production control. A distinctive feature of the domain is the symbiotic co-existence and co-evolution of the technical, ICT and biological ingredients in production structures. A challenging way to overcome these issues is the use of biologically-inspired control algorithms. In the paper the application of reinforcement learning is proposed for this purpose. As a first step, a digital simulation of the stem cell production was performed in order to generate patterns for the training process and to test the approach. In addition to the description of the concept, the paper also presents initial research results.

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Keywords: Stem cell production; Digital simulation; Machine learning; Reinforcement-based control; Biological transformation

1. Introduction

Stem cell based therapies hold much promise for the medicine of the future [1], [2] by providing new treatment modalities for chronic and life-threatening diseases. There is a common understanding that they represent a central element of regenerative medicine and therapy. For the reasons given in the abstract, the automatization of the stem cell production represents a real challenge.

As stated in [3], "increased understanding of the underlying biological processes and their interaction with approaches to manufacturing technology will be needed to create the step change required for the next generation of scalable precision production systems capable of more than replicating and incrementally improving the performance of the human operator".

As a further step in this process, a biologically inspired control approach, i.e. reinforcement learning (RL) is introduced in the paper for controlling automated stem cell production.

In Section 2, the problem of fully automatic stem cell production is presented and some such systems developed at Laboratory for Machine Tools and Production Engineering (WZL), RWTH Aachen University and at the Fraunhofer Institute for Production Technology, Aachen are highlighted. Modelling of the cell growth is introduced and the process and results of model fitting are outlined. The following sections introduce an agent-based simulation of the selected automated system and the control concept. The first results of the reinforcement learning based controller are described. Finally, some conclusions are drawn.

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2. Fully automated production of stem cells

In recent years, automated approaches towards manufacture of stem cells have been gaining importance. This includes both automation for scaled production of therapeutic cells as well as high-throughput generation of cell models for research and in vitro testing. In both cases, automation reduces the chance for human errors, provides more precision, repeatability, robustness and allows close monitoring and control of the process. Automation approaches that currently find application in the industry differ in the degree of automation and connectivity. In this paper, we will only focus on fully automated systems where no direct human interaction is necessary along the entire process. There are a number of examples for such systems:

- StemCellFactory – The StemCellFactory is an automated facility for the standardized and parallelized isolation and expansion of induced Pluripotent Stem Cells (iPSC) clones. The StemCellFactory is being upgraded by the possibility to generate iPSC by reprogramming blood cells and the technology for automated genome editing of iPSC clones [1].
- StemCellDiscovery – The StemCellDiscovery is a fully automated laboratory, which serves as a development environment for automating process protocols, new devices and novel software and algorithms.
- AUTOSTEM – In the interdisciplinary H2020-project AUTOSTEM, a closed, automated and sterile pipeline was developed for large-scale production of therapeutic stromal cells [5], [6].
- iCellFactory – The iCellFactory is a highly flexible automated research platform, serving as an environment to test new devices and approaches to control automated cultivation of different cell types and lines and to enable easy mechanical reconfiguration of the layout of automated cell culture platforms [7], [8], [9]. Current research focusses on Human Embryonic Kidney (HEK) 293 and induced Pluripotent Stem (iPS) cells.

The automation of these systems follows a service-oriented approach with highly modular control software that allows adaptive cell processing [10]. The machines represent fully automated laboratories, in which different automated laboratory devices are interconnected by a robot arm. In the following, we will use the StemCellDiscovery as a model representatives for those automated systems. Here, adherent mesenchymal stem cells (MSC) are grown in 2D on the surface of multiwell-plates in parallel.

The fully automated cultivation of donor- or patient-derived stem cells, however, bears certain challenges. Since the cells differ from batch to batch, they are prone to a high variability in quality and growth behavior [11], [12], [13]. This introduces the need for adaptive processing, which reacts to the cell behavior. For example, stem cell cultures are split into several new culture dishes once that the cells have covered most of the culture vessels surface. This is typically done when the cells reach 80% confluence [14]. Since the cell cultures grow differently from batch to batch, the time point for the split has to be determined based on the growth and is not fixed. The cultivation workflow is presented in Fig. 1.

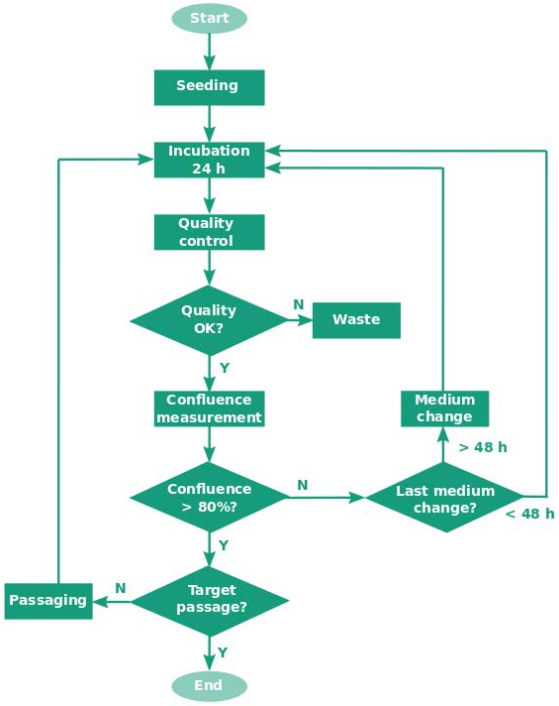

Fig. 1. The workflow of the process.

In order to realize full automation, the assessment of the culture status has to be transferred into the automated workflow. In this case, the cell growth (confluence) is measured repeatedly via microscopic imaging and the process is performed adaptively. Depending on the measurement result and culture time, either cells are directly returned to the incubator, a medium change is performed or if the cells reach a high growth density, the culture is split [15], [16], [7].

Though a certain adaptivity towards the cell growth behavior is key to the production of these cells, making decisions throughout the process introduces uncertainty into production planning and control. As the different processes such as medium change and splitting of the culture vary significantly in duration and utilized resources, bottlenecks can arise during high throughput operations. For this reason, the optimization of the process and production control strategies is a key issue.

2.1. Description of the cell growth

In order to simulate the production system, a cell growth model has to be selected in order to describe the product behavior.

Stem cells proliferate through symmetric division. When they grow unhindered, they exhibit exponential growth behavior. When grown in culture plates however, the cells are in the exponential growth phase only for a limited period of the culture. When they are seeded onto a new plate, they need to accustom to their surrounding and therefore exhibit a so-called lag phase. Once they have recovered, they start dividing at a maximum growth rate until their environmental conditions become limiting. In plate-based cultures where nutrients are replenished regularly through medium change,

the limiting factor is typically space. Once the cells cover most of the plate the growth slows down and cultures enter a stationary phase.

In reality therefore, growth curves typically resemble sigmoidal curves. This growth behavior is well-known also for other populations in biology and can be described using different mathematical models. For this paper, two different mathematical models were chosen and implemented into the simulation: the unified Gompertz model (1) and the Bertalanffy model (2) with confluence W, initial confluence W_0 at the time of seeding, upper growth limit A and growth constants k_G and k_B, respectively [17], [18]:

$$W_{(t)} = A\left(\frac{A}{W_0}\right)^{\exp(-e\cdot k_G\cdot t)} \quad (1)$$

$$W_{(t)} = A\left(1 + \left(\left(\frac{W_0}{A}\right)^{\frac{1}{3}} - 1\right)\cdot \exp(-k_B t)\right)^3 \quad (2)$$

In order to determine a parameter set for typical cultivation conditions, the functions were fitted to confluence data over time from cultivations of mesenchymal stem cells cultivated in 6-well plates. Cells were grown in Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin at 37°C in 5 % CO_2. A total of 72 growth curves from twelve plates were used to fit the curves. During cultivation, microscopic images were taken and the confluence was calculated using an image processing algorithm. These data were normalized in order to simulate growth as a person in the lab would describe the culture (range between 0 – 100% confluence). All data were normalized so that the highest confluence value measured was 100%. The growth functions were fit to the data set in order to determine a parameter. While A was fixed at 100%, k and W_0 depend on the individual culture. The resulting parameter set was rounded and the range extended to allow a simulation with a higher variability (as variability naturally occurs and the data set used was only from one donor – therefore, greater variability is expected when cultivating cells from different donors). The resulting two parameter sets used for simulation are given in Table 1.

Table 1. Parameter sets for simulation based on historical cell culture data (normalized for A = 100%:

	Low variability	Higher variability
W0	14 % (12 – 16.0%)	20 % (10 – 30%)
$k_{Gompertz}$ (k_G)	0.12 (0.09 – 0.15)	0.14 (0.08 – 0.2)
$k_{Bertalanffy}$ (k_B)	0.265 (0.2 – 0.33)	0.275 (0.15 – 0.4)
A	1 (100%)	1 (100%)
Threshold C_{Split}	0.8 (80%)	0.8 (80%)

3. Agent-based simulation of stem cell production

The simulation model of the stem cell production factory has been implemented in the AnyLogic Simulation Software [19]. An agent-based [20] modeling approach was applied, where both the plates and the equipment were modeled as agents. Nine pieces of equipment were included in the model: the processing equipment (liquid handling unit (LHU), decapper, plate reader, centrifuge, microscope), the storage equipment (incubator, storage, waste), and the transportation equipment (robot arm).

The five main processes of the production were implemented in the simulation system: seeding, quality control, confluence measurement, medium exchange and splitting of the cells (see Fig.1). Each process contains several steps and each step requires an equipment. Some steps are conditional, e.g. if a plate is waiting for a busy resource, it should be transported to the incubator until the required resource becomes available.

The process flows are fixed in the simulation, but their parameters can be modified externally. These include the duration of the operations, capacity of the factory, the growth models for the cell cultures, as well as the uncertainty model of the production system. In addition to the process parameters, the control of the system can be influenced externally. The control of the splitting can be defined by setting when, and into how many new plates the contents of a plate should be distributed. The processing order of the equipment requests are based on their priorities, which can be controlled by setting the weights of five components of the priority. Furthermore, there is a possibility to set the frequency of the medium exchange and the largest acceptable waiting time outside the incubator. All of the parameters can be set either in an input data file or dynamically from the external reinforcement learning program.

The simulation of the stem cell factory can be run in two different modes. Firstly, it can be used with the graphical user interface (GUI), which includes a 3D animation of the factory, see Fig. 2, Fig. 3 and Fig. 4. The GUI provides controls for the simulation runs, such as pausing the execution and setting the speed of the simulation. The current state of the factory—including the equipment, their waiting lines and the cell cultures—can be monitored, which is also supported with several charts and plot diagrams. The total amount of cell cultures can be easily observed, even if they are already distributed over several plates. In addition, the simulation produces detailed process logs that facilitate process tracking. The main purpose of the GUI is to support the evaluation of the simulation system and to allow manual experimentation with the different control settings.

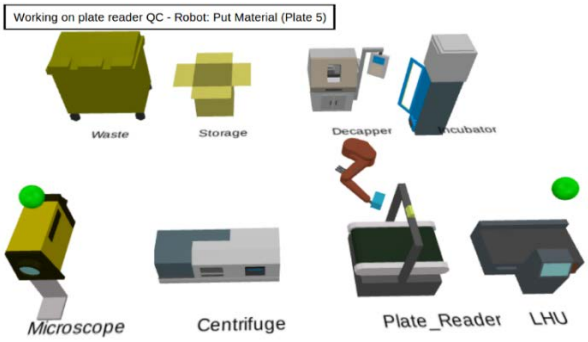

Fig. 2. Three dimensional animation of the cell.

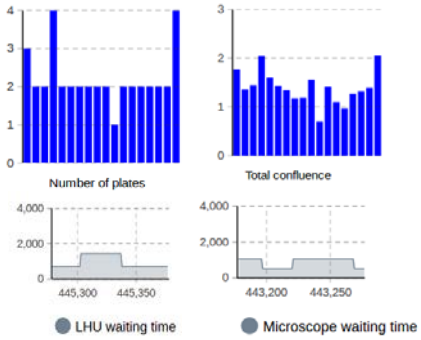

Fig. 3. The number of plates and total confluence of the cell cultures (up) and the expected waiting times in the queues (bottom).

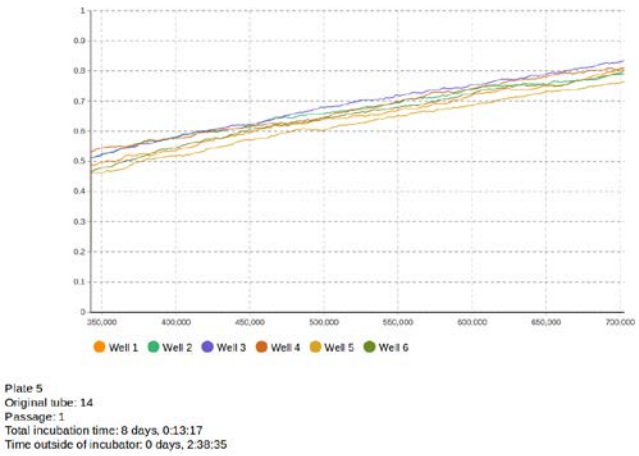

Fig. 4. Growth of the cell culture within a plate.

The second mode of simulation is designed to facilitate the optimization of the control policy. In order to do this, a large number of simulation runs are required for evaluating different policies. In this case, the GUI with animation and full monitoring capability of the simulated factory is not necessary. Instead, the simulation should run as fast as possible and should result only in some aggregated performance indicators. Such indicators are the output of the system (i.e., the average increase of the cell cultures' volume between entering and leaving the factory), the maximum waiting time required for the resources, or the quantity of the waste produced.

4. Biologically inspired control of stem cell production

One of the main aims of the project was to improve the controller of the current platform by bio-inspired computing methods. As reinforcement learning (RL) approaches are efficient in adaptive resource control [21], [22] such a method was chosen.

Reinforcement learning is a biologically-inspired machine learning approach to learn from interactions with a stochastic dynamic system based on feedbacks like rewards. An interpretation is to consider an agent (decision maker) interacting with an uncertain system and receiving information about the actual state and an immediate cost. The aim is to learn an efficient behavior (control policy), such that applying this strategy minimizes the expected cumulative costs in the long run. Let us quote R. Sutton and A. Barto, two prominent RL researchers and pioneers of the field, about the biological inspirations of RL: "Of all the forms of machine learning, reinforcement learning is the closest to the kind of learning that humans and other animals do, and many of the core algorithms of reinforcement learning were originally inspired by biological learning systems" [23].

4.1. Design concept of the RL based controller

A design concept was proposed for a centralized feedback controller which is optimized based on the simulation model, to compensate for the limited amount of empirical data.

The interaction diagram of the feedback controller and the simulation is presented in Fig. 5. The system state (vector), denoted by x_t, contains the properties of individual wells (medium, cell health, population, etc.), the states of the system resources (robot arm, LHU, microscope, centrifuge, incubator, waster, decapper, etc.), other environmental factors (temperature, humidity, etc.), any additional relevant properties of the automated cell platform.

The control input (vector), denoted by u_t, contain such parameters which directly influence the system (shaking, transportation, measurement, temperature control, etc.). The immediate cost (scalar), denoted by c_t, is a function describing the costs of states and/or actions (e.g., cell growth, cell health, etc.). There are some additional noises, denoted by n_t, which encode the stochastic nature of the process.

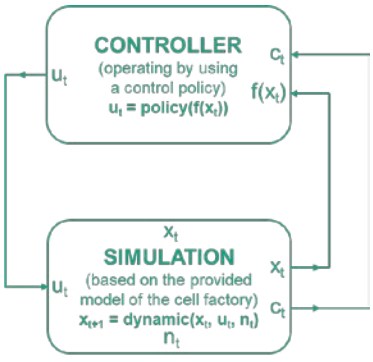

Fig. 5. Interaction diagram: The feedback controller and the simulation model.

Function $f(x_t)$ provides the available observations, as the system state is not fully observed, e.g., the cell growths are only measured at certain times. The controller can only take actions based on the observations. The simulation describes the state transition of the system to the next state (x_{t+1}) based on the current state (x_t), the control inputs (u_t) and an additional process noise (n_t). Meanwhile, the control policy determines the applied control input (u_t), typically, based on the most relevant features of the current state (x_t), in order to maximize the performance of the system over a given horizon.

4.2. Structure of the controller

The controller of the stem cell platform applies a *priority-based scheduling* mechanism, where the plate with the highest priority is served first. The (time-dependent) priority of a plate is computed as a linear combination of five features, listed below. The controller also depends on two other parameters: the confluence threshold for splitting and the time between measurements. Hence, the relevant parameters are:

- Priority of the plates:
  To prioritize the plates waiting for a resource, the weighted sum of the following parameters are calculated:
  - Process priority
  - Falcon tube priority (for the initial cell cultures)
  - Plate waiting time (changes during simulation)
  - Plate confluence weight (changes during simulation)
  - Time spent outside of the incubator (changes)
- Confluence threshold for splitting:
  If the measured confluence value is above this threshold, the cell culture in a plate is divided into two new plates.
- Incubation time between measurements:
  time spent in the incubator between confluence checks.

4.3. Optimization of the controller

The controller was optimized with RL to maximize the expected throughput (mean cell yield over a given horizon) of the system. During optimization, the seven parameters of the controller were adaptively tuned using an RL method, particularly a policy gradient algorithm, which is a variant of the so-called Kiefer-Wolfowitz method. A survey of RL based control methods, including policy gradient, can be found in [24].

The learning process starts with an initial state (x_0) and initial control policy (w_0). In the first step, multiple random perturbations ($w_{k,1}$, $w_{k,2}$, ..., $w_{k,m}$) of the control policy are generated (based on a parametric model of a policy), then in the second step these control policies are fed to the simulation, in order to evaluate each policy by multiple rollout simulations and estimate their cumulative costs. In the third step, these estimated costs ($c_{k,1}$, $c_{k,2}$, ..., $c_{k,m}$) are used to perform a gradient estimation and hence to calculate the policy modification vector (Δw_k). In the fourth, final step the policy modification is applied to the control policy, then the process repeats from the first step until a terminating condition is met. Policy gradient methods are guaranteed to converge (to a local minimum) under mild statistical assumptions [23].

5. First results of the reinforcement leaning based controller in a simulated environment

Numerical experiments were initiated and performed on the simulated system, to test the efficiency of the suggested RL based control method. The primary aim was to measure the speedup in the expected throughput (cell yield).

For the experiment setup, three different system sizes and four optimization scenarios were studied resulting in 12 experiments. Additionally, each system size was simulated with the currently implemented control mechanism (based on process priorities and waiting times) adding 3 further experiments for a total number of 15. Each simulation started with 18 falcon tubes (with varying cell growth parameters) and ran for 20 (virtual) days, the other parameters being the same as in the real system. The system sizes (maximum plate capacities of the system) were set to 50, 100 and 200 to represent different scales of which the largest was able to process all plates created by the splitting processes during the simulation. This latter variant is the closest approximation to the investigated platform for the real automated production of stem cells.

Each experiment ran for 100 iterations sufficient to stabilize the learning process in a small environment of the optimal setup, whose environment was determined by the noise level. In fact, in the case of the current system, usually only 50 iterations were enough for this stabilization.

A typical learning curve of an experiment is shown in Fig. 6. The curve illustrates how the optimization objective (throughput) stabilizes as the number of iterations grow.

The results of the numerical experiments showed that the most influential control parameter in this experimental setup was the confluence threshold. Optimizing only the five parameters of the priority based scheduling did not improve the throughput considerably, furthermore, optimizing just the incubation time only led to a slight improvement. However, optimizing the confluence threshold alone resulted in a 15-20% increase in throughput, while the full optimization (in which all seven parameters were optimized simultaneously) achieved up to 30% improvement in the largest system, with respect to the non-optimized system. We note that on the current experimental stem cell production platform the RL method resulted in about 30% average speedup, the smaller improvements were observed on smaller, restricted systems.

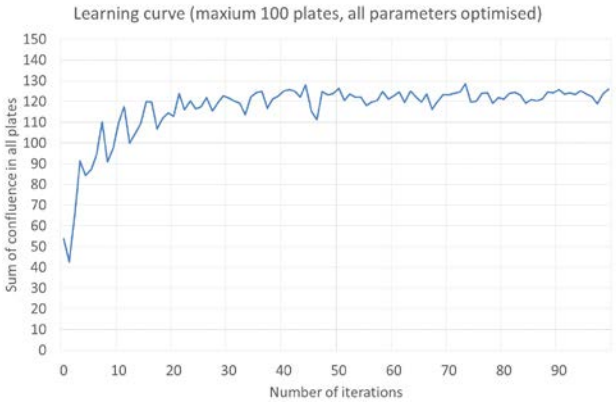

Fig. 6. Learning curve for a middle-sized system with full optimization.

6. Conclusions

The development of Cyber-Physical Production Systems (CPPS) presents new challenges to face and opportunities to manage – among other issues – the growing complexity of our systems by realizing control concepts which were hardly realizable before the era of Industry 4.0 [25].

One of the novel concepts is the biologicalisation, i.e. the biological transformation in manufacturing [26]. According to the authors of the referred paper, biologicalisation is "the use and integration of biological and bio-inspired principles, materials, functions, structures and resources for intelligent and sustainable manufacturing technologies and systems with the aim of achieving their full potential".

The research highlighted in the paper represents a field of biologicalisation in its own right, i.e. the use of biologically inspired algorithms for controlling manufacturing cells producing biological material.

The first results are promising, the adaptive stem cell processing on automated production platforms by reinforcement learning proved to be a viable alternative both for the traditional, manual stem cell processing, and for the actual automated solutions usually applying rule-based control algorithms realizing the protocols of the manual operations. Further works will include the implementation and testing of the novel control solution in the real physical environment of automated stem cell production, but also, in other fields of production, where similar challenges due to uncertainties appear.

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