Upgrade of Bioreactor System Providing Physiological Stimuli to Engineered Musculoskeletal Tissues

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Abstract – A novel central control interface (CCI) is developed to improve the modular bioreactor system with regard to extendability and modifiability in Tissue Engineering (TE) applications. This paper presents the results developed in the project with open-source hardware and the graphical programming system LabVIEW. A new platform independent User Interface was further developed to contribute to the new flexibility of the device.

Introduction: Bioreactors play a vital role in Tissue Engineering. While differing from common known bioreactors in the production industry, bioreactors in TE are used to "influence, support or mimic certain physical or physiological processes" [1]. The modular bioreactor system was developed to be a new device for the research and development of musculoskeletal tissue [2]. It is able to mimic the mechanical stress and the nervous stimulation occurring in the human body for a better growth and strength of the tissues [3]. While being a novel and universal device in this field of Tissue Engineering it comes with some disadvantages: The CCI can only control one bioreactor consisting of each one mechanical and one electrical stimulation module. Having in mind that the development of tissues can take months and contamination of one single tissue often results in an infection of all tissues in the bioreactor, the research can be very inefficient. Furthermore, the program running on the CCI was developed in the C programming language and is based on PIC microcontrollers. This makes it very hard to modify the code for attaching new sensors and other peripherals and thus creating a tailored device for every project. This paper describes a new approach of developing a new central control interface with a focal point on new hardware and programming systems to solve the current issues of the device.

Methodology: The bioreactor system consists of three core parts: The central control interface (CCI), the mechanical stimulation module (MMS) and the electrical stimulation module (MES). The MMS consists of a six-well plate and a geared down stepper motor equipped with a lead screw. The cell constructs are located in the wells and are anchored to two posts next to each well. One post is moved by the stepper motor and thus stretches the tissue. A potentiometer working as a displacement sensor is fixed to the actuator base and measures the potential backlash occurring when the force resistance of the tissues grows. The MES consists of 12 electrodes and a circuit that provides the electrical stimulus and is mounted on top of the MMS. The CCI was developed to control and observe the stimulation [1]. In order to improve the extendability and modifiability, the hardware of the CCI was changed from PIC microcontrollers to a Raspberry Pi 3. With the new hardware running Raspbian Jessie operating system (Release: 2016-09-23) new possibilities for alternative programming systems are available: The application running on the CCI was completely developed using the graphical programming system LabVIEW with the LINX Add-On. The stimulation parameters for the modular bioreactor system were configured either through a PC software running on Windows or on the device itself. While the Raspberry Pi and LabVIEW both are adaptable for internet applications, a new approach for a platform independent User Interface

was developed by creating a website with JavaScript (using the jQuery library), HTML and CSS that is hosted by the Raspberry Pi. The upgraded modular bioreactor system should be able to attach more than one bioreactor (MMS + MES). For this reason, a motor controller with a unique slave address was developed to be the interface between a MMS and the CCI. The motor controller consists of an Arduino Nano Rev 3 and an EasyDriver Stepper Motor Driver. The CCI communicates as a master to the motor controller slaves via the I²C-protocol.

Results: A breadboard-based prototype of the new modular bioreactor system was developed including a new CCI, a motor controller and one mechanical stimulation module. A new developed website based User Interface allows the user to configure the stimulation parameters. By the time the user filled out the necessary input fields and activated the “Apply Values” button in the User Interface, the LabVIEW application handles the HTTP request and writes the parameters into variables. By activating the “Start” button, the parameters are send to the motor controller with the respective slave address. Parallel to that a configuration file is written which contains the stimulation parameters for the respective MMS. The program running on the Arduino processes the values and controls the stepper motor with regard to the stimulation parameters: The configured stretch is calculated into steps the motor has to move depending on its gearhead and the lead of the leadscrew. Each step is made by toggling the STP pin of the EasyDriver. If the motor moved the actuator post to the desired position, the motor holds this position in the length of the pulse width value. After moving back to the zero position, another delay is executed in the length of the difference between period and pulse width. In the continuous mode, this procedure is executed continuously until the duration time elapsed. If the discontinuous mode is activated, the procedure is repeated depending on the repetitions value. After the repetitions the stimulation is paused depending on the rest time value. On the maximum point of every stretch operation, the Arduino reads the potentiometer value and converts the voltage to millimetres. The CCI requests this value every second and writes it with a time stamp in a separate log file to confirm if the tissue was stretched equally the whole time. Up to eight Mechanical Stimulation Modules with each a Motor Controller can be controlled and observed simultaneously with the upgraded CCI.

Discussion and Conclusion: Researchers working with the system are now able to apply mechanical stimulation up to 48 tissue specimens in eight separate modules. This upscaling reduces the risk of contamination of all tissues and increases the efficiency of the research and development. With LabVIEW as programming system of the CCI the application can be customized and modified to specific needs of various projects and applications in TE in an intuitive way. The new User Interface allows the researcher to control the bioreactor system with handheld devices like smartphones or tablets in the lab which bypasses the need of a space consuming computer.

References

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