Marc Wiartalla*, Frederik Berg, Jahn Kühn, Mateusz Buglowski, Christian Bleilevens, Stefan Kowalewski, and André Stollenwerk

A fully automated normothermic machine perfusion system for kidney grafts supporting physiological motivated flow profiles

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Abstract: Research showed that the normothermic machine perfusion of kidneys can enable prolonged storage and improve conditions compared to traditional cold storage. For research in this area, there is a demand for a long-term in vitro perfusion setup. In this work, we present a fully automated normothermic machine perfusion (NMP) system as an experimental research platform. The perfusion system is intended as a tool for researching the effects of different perfusion strategies on the kidney. To enable the automation, the NMP system consists of a blood pressure control, a circulation volume level control and a pH-regulation component. The setup is realized as a medical cyber-physical system consisting of networked embedded microcontroller nodes.

Keywords: Normothermic machine perfusion, long-term in vitro perfusion setup, medical cyber-physical system

1 Introduction

The preservation of human kidneys for transplantation is a relevant current research topic [14]. In the year 2021, there were 6593 patients in Germany on the active waiting list for a kidney transplantation [5]. While the clinical standard is the cold storage on ice, research shows that the normothermic machine perfusion (NMP) can improve the condition of the kidney and enable prolonged storage [8]. However, the optimal perfusion strategy and perfusate composition still needs to be researched. Relevant characteristics of the perfusion strategy are the decision on a constant or pulsatile perfusion strategy, the used pressure or flow profiles and the requirements for the gradient on pressure or flow. Thus, we need a system for the stable perfusion of organ grafts, specialized for the kidney, to enable research regarding the optimal perfusion strategy and perfusate composition. As we are interested in long-term perfusion, the system should be automated to relieve the medical personnel and reduce the potential for human errors during the manual control of medical devices. Furthermore, complex perfusion strategies require automation in the form of complex controllers as they are not realizable otherwise.

In this work, we present a fully automated long-term in vitro perfusion setup (mockloop) as a research platform. The mockloop is applicable as an alternative to animal experiments for the testing of medical devices and the preservation of kidney grafts. Using the system, the effects of different perfusion strategies on the kidney can be researched. For our research we used blood and organs from animals in approved in-house experiments to reduce the number of animal trials. To enable research, the system needs to be highly modular and configurable to support different perfusion strategies. Thus, it should be possible to change the components and perfusion parameters during runtime.

2 Related work

There already exist various NMP systems for different organs besides the kidney. Vogel et al. presented an automated perfusion device for the normothermic perfusion of discarded liver grafts [16]. The system includes an automated control for the regulation of temperature, blood flow, blood pressure, and oxygenation. In addition, multiple perfusion systems were already accepted for clinical use [11]. The OrganOx metra system is a mobile device for the normothermic machine preservation of livers [13]. TransMedics offers different portable organ care systems for the lung, heart, and liver [15]. However, to our best knowledge no detailed information is available on these devices. Finally, the XVIVO Liver Assist device can be used for the ex vivo perfusion of livers [19]. This system includes two pump units with pressure and temperature control. Multiple normothermic kidney perfusion systems can be found in the literature. Weissenbacher et al. developed an automated perfusion device for kidneys [17]. The device includes pressure control and a closed-loop controller for the oxygenation.

***Corresponding author: Marc Wiartalla,** Informatik 11 - Embedded Software, RWTH Aachen University, Ahornstraße 55, Aachen, Germany, e-mail: wiartalla@embedded.rwth-aachen.de
Frederik Berg, Jahn Kühn, Mateusz Buglowski, Stefan Kowalewski, André Stollenwerk, Informatik 11 - Embedded Software, RWTH Aachen University
Christian Bleilevens, Department of Anesthesiology, Medical Faculty RWTH Aachen University Hospital, Aachen, Germany

The commercial ex vivo kidney perfusion system XVIVO Kidney Assist can be used for hypothermic as well as normothermic perfusion [18]. It includes a pressure control for pulsatile perfusion. There is various literature on research regarding the strategy for the normothermic machine perfusion of kidneys [14]. In recent years, research has been done in the fields of the perfusion strategy, modification of the perfusate and assessment of graft quality during perfusion.
Most of the systems listed above are compact portable devices, that cannot be easily extended depending on the use. In contrast, our proposed perfusion system supports the dynamic configuration of components during runtime to enable more complex experiments and react to the condition of the perfused kidney. In addition, none of the listed systems includes an automated pH-regulation.

3 Concept

The mockloop consists of networked embedded microcontroller nodes, each connected to a medical device. For this, we make use of our developed hardware platform called ASMO-Boards, which is described in greater detail in [1]. Each ASMO-Board includes various interface for the connection to medical devices, as well as interfaces for the Controller Area Network (CAN) and Ethernet for the communication between nodes, resulting in a medical cyber-physical system. All algorithms are running on these ASMO-Boards. Therefore, instead of having one centralized complex system, we distribute the system among multiple smaller nodes, which reduces the software complexity on each node. Suited for this methodology, we developed a modular and verifiable software architecture for interconnected medical devices based on a real-time operating system. Our software architecture includes separate layers for the data retention and synchronization between nodes. In particular, the software architecture also includes a dedicated safety layer for different safety mechanisms, like control value limitations [10]. For the communication over Ethernet between nodes, we use the Data Distribution Service (DDS) [12]. Based on this hardware platform and software architecture, we present the mockloop concept for the extracorporeal kidney perfusion. Figure 1 shows a sketch of the setup. The basic NMP system consists of a reservoir, a diagonal pump (Affinity CP, Medtronic Inc. ,Minneapolis, USA), an oxygenator, a heat exchanger, a flow sensor (SonoTT, em-tec GmbH, Finning, Germany) and the needed tubing, which are common in these types of systems. Furthermore, the mockloop consists of three automation components: the blood pressure control, a circulation volume level control and pH-regulation.
As the kidney is sensitive to pressure disturbances, keeping

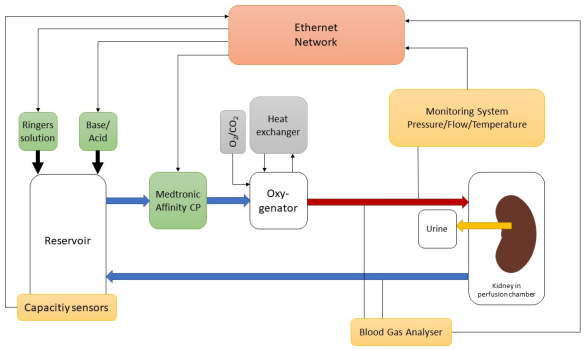

Fig. 1: NMP system with pressure control, pH-regulation and level control

a safe perfusion pressure is essential to preserve the kidney function. We therefore designed an automatic pressure control component, which allows for different perfusion strategies. For this, the mockloop includes a pressure sensor in the arterial cannula, connected to a patient monitor (Philips MX500, Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Germany). The developed blood pressure control includes different perfusion modes and is configurable during runtime. Firstly, the system should allow for pulsatile perfusion with different pressure profiles, which mimic the arterial pulse generated by the human heart. The pressure profile and parameters like period, amplitude and mean pressure have to be configurable to adjust the system to specific needs. Secondly, the system has to be able to provide a constant perfusion pressure with adjustable mean pressure. A manual perfusion mode also has to be included. The startup phase of the perfusion is of special interest. The system should allow for different startup procedures, e.g. a constant gradient until reaching the target pressure.
During long-term perfusion, the kidney can produce a significant amount of urine. This can result in the perfusate level in the system dropping, which in the worst case can lead to gas in the system. We therefore include a level control component in the mockloop, which automatically keeps a constant perfusate level in the system. The component includes discrete or continuous sensors that measure the perfusate level at the reservoir. A peristaltic pump (Ismatec Reglo ICC, Cole-Parmer GmbH, Wertheim, Germany) is used as an actuator to refill perfusate or Ringer's solution into the system.
The third automation component is the pH-regulation. Despite the regulatory capacities of the human kidney and buffer capacities of the perfusate, these might be insufficient in keeping the pH-value in the physiological range. Thus, we developed a flow-triggered pH-regulation component that injects acidic or basic solution during alkalemia and acidemia episodes. The component includes an online blood parameter system

(Terumo CDI 500, Terumo CV Group, Ann Arbor, USA) as a sensor for pH readings and a syringe pump (Cole-Parmer GmbH, Wertheim, Germany) as an actuator for the injections. To prevent high acid and base concentration in the perfusate, the injection is synchronized with high flow episodes.
Each of the mentioned medical devices are connected to an ASMO-Board, which communicate over Ethernet. We chose Ethernet to enable remote monitoring and feed the integrated data collection directly into an according data base.

4 Implementation

The implementation of the software architecture is based on the real-time operating system ChibiOS [7]. As the concrete DDS implementation, we use embeddedRTPS [9], because it is suited for the use in embedded systems. We combine manually implemented software components with model-based code generation. First, we describe the implementation of the pressure control algorithm, which was designed in Matlab Simulink (The Mathworks, Natick, MA). For the pressure control, the incoming data first has to be filtered, to reduce the noise in the measurements. We used Matlab Stateflow to model the different states of the perfusion like the startup and different modes for constant, pulsatile and manual perfusion. For the development of the controller, we created a system model. The rotary speed of the blood pump is used as an input and the arterial pressure is the simulated output. The model was identified via a step response at the end of animal experiments, and by using the response to a chirp signal in a simplified mockloop with a clamp instead of a kidney. The transfer function

$$G(s) = \frac{16}{s^2 + 18 \cdot s + 200} \cdot e^{-0.3 \cdot s}$$

represents the resulting system model. For the perfusion with constant pressure, we designed a proportional-integral controller (PI controller), which was parameterised using the given transfer function with a balance of performance and robustness. The determined parameters are $K_P = 10$ and $K_I = 7$. For the pulsatile perfusion with different pressure profiles, we designed an iterative learning control. For the controller output, the following formula is used:

$$u_{i+1}(k) = u_i(k) + learn_P \cdot e_i(k + T_d)$$

In the formula, the index i represents the period and index k is the step within one period. Furthermore, we use the controller output u_i, the measured control deviation e_i, the dead time T_d and the learning rate $learn_P$. All perfusion parameters, like target pressure, are adjustable during runtime by sending corresponding commands to the pump node. For the pulsatile perfusion, it is possible to define custom pressure profiles as integer arrays, to create different pressure curves.
In the first iterations of the mockloop we used continuous capacitive sensors to measure the perfusate level in the reservoir. However, the continuous sensors resulted in measurement problems during long-term perfusion due to changing behavior of the filters in the reservoir with soaking humidity during the circulation. In the later iterations, we used multiple discrete level sensors, which turned out to be more robust. The required injection volume is calculated based on the sensor level and sent to the peristaltic pump.
The third component is the pH-regulation [3]. The component is divided into two subsystems. The first subsystem measures the arterial pH value using an online blood parameter system and periodically computes the bolus to inject. The second subsystem controls the syringe pumps and synchronizes the injection with the pulsatile flow. This synchronization is done to avoid high local concentrations of base/acid due to insufficient dilution.
During perfusion not all components have to be used, for example during urine recirculation the level control component is not required. We therefore designed a modular system, such that it can be configured dynamically during runtime. The system automatically detects which components are connected to the system and thus which features can be used. Furthermore, we can notify the user via a user interface, which medical devices are missing in order to use a feature.

5 Results

The presented automated NMP system was used in multiple animal trials with different configurations for research regarding the normothermic kidney perfusion [2, 4, 6]. In total over 40 porcine kidneys were perfused using the presented system. In these experiments different configurations were utilized depending on the goals of the experiments. From these experiments we recorded around 100GB of data, storing all measurements and internal values for retrospective analysis. In the experiments different startup procedures were tested, e.g. a constant gradient until the target pressure is reached. The following figure 2 shows an example startup phase, which consists of an immediate jump to 25mmHg in under 13s without overshooting and a continuous increase over 5min to the target pressure of 75mmHg. During this 6h experiment, the blood pressure was kept in a safe range. The difference between the measured pressure and the target pressure of 75mmHg was less that 2mmHg for 98,12% of the measurements. For the calculation of this result the measured pressure data was not filtered and thus contains pressure disturbances, e.g. due to

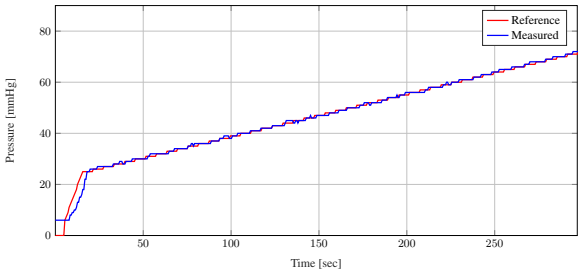

Fig. 2: Startup process during kidney experiment

perfusate sampling for blood gas analysis, which results in deviations from the target pressure.

6 Conclusion

In this work, we presented a fully automated normothermic machine perfusion system. The mockloop serves as a long-term in vitro perfusion setup for research regarding the normothermic kidney perfusion. The system consists of three automation components, which can be dynamically configured during runtime. The pressure control component enables constant and pulsatile perfusion with a configurable startup phases. The level control component automatically refills the perfusate level in the system based on the remaining reservoir level. Finally, the pH-regulation component can automatically keep the pH value in the physiological range by injecting boluses of base or acid. As an outlook, we plan to design different approaches for the sensor fault detection and diagnosis.

Author Statement

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References

[1] F. Berg, M. Wiartalla, M. Hüllmann, A. Derks, S. Kowalewski, and A. Stollenwerk. ASMO: a decentralized and verifiable interoperability platform in intensive care. *Proceedings on automation in medical engineering*, 2(1):724, Mar 2023.

[2] C. Bleilevens, B. M. Doorschodt, T. Fechter, T. Grzanna, A. Theißen, and E. A. Liehn et al. Influence of Vitamin C on Antioxidant Capacity of In Vitro Perfused Porcine Kidneys. *Nutrients*, 11(8), 2019.

[3] M. Buglowski, C. Bleilevens, G. Fabry, S. Kowalewski, and A. Stollenwerk. Flussgesteuerte ph-regulierung in einem automatisierten nierenperfusionssystem. *Proceedings on automation in medical engineering*, 1(1), 2020.

[4] E. Edgworth, L. Ernst, Z. Czigany, T. Saritas, L. S. Zarnitz, and M. Wiartalla et al. HBOC-301 in Porcine Kidney Normothermic Machine Perfusion and the Effect of Vitamin C on Methemoglobin Formation. *Antioxidants : open access journal*, 11(7):1329, 2022.

[5] Eurotransplant. Eurotransplant Annual Report 2021 https://www.eurotransplant.org/wp-content/uploads/2022/06/Annual-Report-2021_LR.pdf, accessed 10.04.2023.

[6] G. Fabry, B. Doorschodt, T. Grzanna, P. Boor, A. Elliott, and A. Stollenwerk et al. Cold preflush of porcine kidney grafts prior to normothermic machine perfusion aggravates ischemia reperfusion injury. *Scientific Reports*, 9:1–9, 09 2019.

[7] G. Di Sirio. ChibiOS. https://www.chibios.org, 2023.

[8] S. A. Hosgood, E. van, and M. L. Nicholson. Normothermic machine perfusion of the kidney: better conditioning and repair? *Transplant International*, 28(6):657–664, 2015.

[9] A. Kampmann, A. Wustenberg, B. Alrifaee, and S. Kowalewski. A portable implementation of the real-time publish-subscribe protocol for microcontrollers in distributed robotic applications. In *The 2019 IEEE Intelligent Transportation Systems Conference - ITSC*, pages 443–448, Piscataway, NJ, 2019. IEEE.

[10] J. Kühn, A. Stollenwerk, C. Brendle, T. Janisch, M. Walter, and R. Rossaint et al. Sensor supervision and control value limitations in networked intensive care. In *Gemeinsamer Tagungsband der Workshops der Tagung Software Engineering 2016 (SE 2016), Wien, 23.-26. Februar 2016*, volume 1559 of *CEUR Workshop Proceedings*, pages 187–194. CEUR-WS.org, 2016.

[11] H. Mergental and G. R. Roll. Normothermic machine perfusion of the liver. *Clinical Liver Disease*, 10(4):97–99, 2017.

[12] Object Management Group. Data distribution service specification, version 1.4, 10.04.2015.

[13] OrganOx Limited. OrganOx metra https://www.organox.com/metra-for-liver-transplantation, accessed 04.04.2023.

[14] T. B. Smith, M. L. Nicholson, and S. A. Hosgood. Advances in hypothermic and normothermic perfusion in kidney transplantation. *Transplantology*, 2(4):460–477, 2021.

[15] TransMedics, Inc. TransMedics Organ Care Systems https://www.transmedics.com/ocs-hcp/, accessed 04.04.2023.

[16] T. Vogel, J. G. Brockmann, A. Quaglia, A. Morovat, W. Jassem, and N. D. Heaton et. al. The 24-hour normothermic machine perfusion of discarded human liver grafts. *Liver Transplantation*, 23(2):207–220, 2017.

[17] A. Weissenbacher, L. Lo Faro, O. Boubriak, M. F. Soares, I. S. Roberts, and J. P. Hunter et al. Twenty-four–hour normothermic perfusion of discarded human kidneys with urine recirculation. *American Journal of Transplantation*, 19(1):178–192, 2019.

[18] XVIVO B.V. XVIVO Kidney Assist https://www.organ-assist.nl/wp-content/uploads/2021/08/Kidney_assist_TD-21_Brochure_KA.03.pdf, accessed 04.04.2023.

[19] XVIVO B.V. XVIVO Liver Assist https://www.organ-assist.nl/wp-content/uploads/2021/08/Liver_assist_TD-11_Brochure_LiA.08.pdf, accessed 04.04.2023.