Framework for Real-Time Control of Hidden Temperature Variables in Therapeutic Knee Cooling

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***Abstract*—The papers formalizes, implements and evaluates a framework for real-time control of hidden inner body temperature variables during therapeutic cooling or heating where the feedback cannot be obtained by measuring the controlled output variable either because the system is non-invasive, like most of the examples in biomedicine, or for any other reason. The control loop then uses the feedback information from other measurable variable/s of the system which can be used to estimate the controlled output variable of interest. We leverage three research areas from computer science and engineering for that purpose: computer simulations – to provide safe and inexpensive insight into the process/system to be controlled; machine learning – to provide methods for predicting the hidden controlled output from the measurable ones based on the data generated from the simulations; and control theory – to provide control techniques applicable in systems with constraints in the control input. The framework is evaluated on a real-world problem in the domain of biomedicine – real-time control of the inner knee temperature during cryotherapy after knee surgery. A fuzzy logic controller is designed to provide adequate real-time control of the inner knee temperature by controlling the cooling temperature. The framework is evaluated for robustness and controllability. The results show that the controlled cooling is essential for small or large sized knees, which are significantly more or less sensitive to the cooling compared to normal sized knees. Moreover, the framework recognizes dynamic physiological changes and potential changes in the system settings, like extreme changes in the blood flow or changed target inner knee temperature, and consequently adapts the cooling temperature. Controlled therapeutic cooling can contribute to the evaluation of various cryotherapeutic methods, and further development and standardization of cryotherapy, and most important, to smart and personalized cryotherapeutic treatments.**

***Index Terms*—Biomedical systems, Computer simulation, Fuzzy systems, Machine learning**

I. Introduction

The need for control of a process or a system is widely present, starting from a variety of situations in everyday life, like simple home thermostats that maintain a specified temperature, to applications in fields as diverse as electronics, aeronautics, chemical engineering, or biomedicine [1]. The field of biomedical control systems is relatively young compared to the others; nevertheless, some noteworthy recent developments have emerged in several key application areas [2]. There are variety of control mechanisms that can be used, but most often control systems are based on the principle of feedback [3] [4]. In feedback control, the variable being controlled is measured and compared with a target value. The difference between the measured and desired value is called error. Feedback control manipulates an input to the system to minimize this error. The key approach in feedback control is measuring the variable being controlled to compare it with a target value. However, there are examples where the variable to be controlled cannot be measured. Especially in biomedicine, measurements are often difficult to perform because human subjects are involved. Many examples can be found, particularly in clinical procedures, where in vivo measurements are often not as accurate as desired [5], difficult, dangerous or even impossible to perform [6], especially if deep tissues or vital organs are in question [7] [8]. Moreover, non-invasive medical procedures are emerging in the search for more reliable, less expensive, and risk-free medical technology for the future [9] [10] [11].

In this paper, we tackle a real-world problem in the domain of biomedicine – non-invasive real-time control of the inner knee temperature during cryotherapeutic treatment after anterior cruciate ligament (ACL) reconstructive surgery of a knee [12]. It is known, mostly from empirical evidence, that cryotherapy following reconstruction contributes to reduced tissue edema, inflammation, hematoma formation and pain, reducing the need for pain medication and enabling faster rehabilitation [13]. Various cooling modalities are routinely used in postoperative treatment in orthopedics, traumatology, facial surgery, pain prevention in sport, etc. [14]. In a previous study, we have shown that computer-controlled cryotherapy, with pre-programmed protocols in terms of heat extraction intensity and treatment time, is more effective and controllable than a conventional cooling with gel-packs [15]. We measured in vivo temperatures of the inner and outer knee parts and assessed the effectiveness of both methods. Moreover, we confirmed delayed and less severe pain in patients with the computer-controlled cryotherapy. However, a lack of uniformity in patients' response to the cooling was confirmed, which raises the need for "smart" cooling devices, i.e. personalized cryotherapy. Different patients need different cooling protocols, depending on their constitution and regulatory systems, and on environmental conditions. A "smart" cooling device would be able to perform cooling adapted to the individual patient's response. Therefore, we propose to upgrade the method for computer-controlled cryotherapy by introducing automatic control of the temperature inside the knee by changing the cooling temperature in the pad.

In case of biomedical systems, if the controlled output, i.e. inner knee temperature, cannot be measured because of the non-invasive nature of the system, then we should measure other non-invasive variables that can be used to estimate the output. Here we use computer simulation to estimate the hidden controlled variable based on other variables of

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the system/process whose measurement is more feasible – a concept known as soft or virtual sensing [16]. However, simulations are usually resource- and time-consuming, which is not acceptable in real-time control systems [17]. We assume that real-time control, especially in biomedical systems, requires a solution usually supported by a mini on-board computer that cannot process large amount of data nor perform computationally demanding operations. Therefore, we resort to machine learning methods [18] to construct a predictive model that will provide a prediction for the output in a much shorter time with satisfying accuracy. Namely, we use a validated simulation model of the cryotherapeutic treatment [19] to generate a substantial amount of diverse data from different simulation scenarios for the task of machine learning: capture the correlation between the hidden system variable and the noninvasive measurable ones.

Various machine learning techniques have proven to be adequate for extracting knowledge from data resulting from simulation models in various areas like medicine [20] [21], ecology [22], social sciences [23], etc. In a previous study, we have investigated the case of non-invasive real-time prediction of hidden temperature variables during therapeutic cooling [24]. The results have shown that using only temperatures from skin sensors as input attributes gives excellent prediction for the temperature in the knee center. Moreover, satisfying predictive accuracy is also achieved using short history of temperatures from just two skin sensors (placed anterior and posterior to the knee) as input variables. So, a few non-invasive temperature sensors on the knee surface provide an indirect feedback for the control process of therapeutic cooling. We have investigated the predictive performance and time/memory efficiency of several predictive modeling methods. Model trees have shown best predictive performance best with prediction error in the same range as the accuracy of the simulated data (0.1 °C). Moreover, they satisfy the requirements for small memory size and real-time response. The light-weighted predictive models will then correspond to the mini architecture of the computer that controls the cryotherapy.

The main part in the control process addressed in this paper – control of hidden temperature variables in therapeutic knee cooling, is the controller that will take corrective action to the inputs of the system based on the difference between the reference and the predicted output. There are various types of controllers proposed in the literature [25]. For feedback controllers, there are a few simple types, like on-off control and proportional controller. Alternates to the proportional control are the proportional-integral (PI) control and the proportional-integral-derivative (PID) control [26]. PID control is commonly used to implement a closed-loop control. While classical PID control does not incorporate any knowledge for the controlled system, another simple and practical control technique, which is based on the knowledge and expertise for the system, is the fuzzy logic [27]. In this paper, we use the fuzzy logic control technique since it is proven to be an excellent tool for designing intelligent systems in biomedicine [28] [29].

Fuzzy control is a practical alternative, not only for biomedicine but also for a variety of challenging control applications, because it provides a convenient method for constructing controllers via the use of heuristic information. The most attractive feature of the fuzzy theory for biomedical science researchers is the simplicity of fuzzy expressions (set of "rules", each in the IF-THEN form), which is extremely useful for reasoning and controlling in biomedical areas. Fuzzy logic has the advantage that the solution to the problem can be cast in terms that the knowledge of the system is used in the design of the controller. Furthermore, fuzzy logic is well suited for low-cost implementations and can easily be upgraded by adding new rules to improve performance or add new features. In the scope of the upgraded method for computer-controlled cryotherapy, a set of fuzzy logic rules is used to control the inner knee temperature by changing the temperature of the cooling liquid. Taking into account the limitations of biomedical systems, for example, acceptable extreme values or maximal gradients in the human temperature, we set up simple heuristic IF-THEN rules for an efficient fuzzy logic temperature control.

The rest of the paper is organized as follows. In Section II, we present the state-of-the-art in therapeutic devices with cooling or heating. After that, in Section III, we first describe the proposed framework for non-invasive real-time control of inner body temperature variables during therapeutic knee cooling. The framework as such has been protected with a patent at the Slovenian patent office from November 2014 [30]. Furthermore, we present the design of the fuzzy logic controller. In Section IV, the experimental evaluation of the framework as a whole is performed. The experimental design is first described, and then the results of the evaluation are presented. Finally, the paper concludes in Section V with a summary and discussion of the results, and directions for further work .

II. Background and Related Work

Therapeutic cooling is often performed using either ice chips or refrigerated gel-packs, or a cryotherapeutic cuff cooled by a liquid with a specified flow rate and temperature maintained by an external cooling device or by a container with ice water. Therapeutic heating is performed similarly, but at a different temperature. The shape and type of the cooling/heating cuff and the temperature and/or flow rate of the cooling/heating liquid can influence the amount of extracted/added energy from/to the treated part of the body. Different devices for therapeutic cooling are already known. Most of them are based on a circulating cooling liquid in a pad/cuff and incorporate temperature, flow, or pressure control of the cooling liquid, but not for means of controlling the treatment depending on the patient's response. They are flexible and adaptive to the cooled portion of the body [31], or fitted around a joint for applying therapeutic temperature-regulated compression to the joint and providing support for the limb [32].

Some form of a temperature control using feedback from the temperature of the outgoing circulating liquid has been subject of inventions [33] [34]. The subject of the invention in [34] is an improved temperature control fluid circulating system for automatic cooling that uses temperature control fluid in a thermal blanket. The thermoelectric cooling device has a cold side and a hot side. The temperature control fluid is cooled by the cold side of the cooling device and its temperature is modified depending on the sensed temperatures of the fluid flowing within the blanket. Similar, in [33], a device therapeutically treating a desired region of a patient's body uses a non-ambient temperature fluid circulating through a pad having a tortuous fluid pathway positioned on the treatment region. The device has fluid inlet and outlet lines, each having an end connected to the pad and an opposite end positioned in a reservoir containing the non-ambient temperature fluid. Temperature control of the pad is enabled by an in-line valve and temperature monitor positioned in the outlet line.

Other therapeutic devices control the cooling based on the measured temperature of the cooled body surface. In [35], the therapeutic device includes: a shield adapted to be placed in intimate surface to surface contact with the body portion to be cooled, a regulator for passing a fluid through the shield at a regulated temperature and/or flow rate, a control for the flow and temperature of the fluid, and a temperature sensor for modifying the temperature and flow of the fluid in response to the monitored temperature of the body portion. A similar apparatus for controlling the temperature of an area of the body is the subject of the invention in [36].

Finally, invasive control therapeutic methods and devices are also known. In [37], the automatic cooling device is an automatic blood circulation therapeutic machine. Blood circulation is kept under appropriate environmental temperature, and auto chemotherapy is ensured when the blood is transfused back. Another invasive therapeutic treatment has been subject of an invention [38], where embodiments of a temperature control case and related methods and systems are disclosed. Some embodiments include both internal and external temperature sensors to allow the device to predict internal temperature changes and adjust heating/cooling elements accordingly before the internal temperature is unduly impacted by the ambient temperature.

However, none of the above-mentioned therapeutic devices incorporate a method for non-invasive real-time control of inner temperatures during the therapeutic treatment with cooling or heating. To the best of our knowledge, a concrete technical solution for therapeutic cooling or heating, which incorporates control of inner temperature variables whose measurement is not feasible or would introduce invasiveness into the system, is not known so far. Moreover, the use of simulation or predictive modeling, or the combination of the two, for estimation of controlled inner temperature variables in therapeutic control systems, has not yet been known.

III. Methods

A. *Framework for Real-Time Control of Hidden Body Temperature Variables*

The framework for non-invasive real-time control of hidden inner body temperature variables during therapeutic cooling or heating uses cross-fertilization of computer simulations, machine learning and control techniques [30]. The application of the framework for non-invasive real-time control of inner knee temperature variable during therapeutic cooling is schematically presented in Fig. 1 and Fig. 2. According to Fig. 1, first we generate a large amount of simulation results E by performing preliminary simulations of the system with different values of the input simulation parameters P. The simulated data contain values for a large number of inner and outer system variables. We analyze the simulated results and describe the system with a smaller set of significant inner and outer variables, thus forming dataset F. Then, we build a predictive model D from the dataset F using methods for advanced data analytics, like machine learning. The predictive model captures the correlation between the inner variables that cannot be measured and the outer variables that can be measured with sensors. We select a subset of the measured variables that performs the best in predicting the value of the controlled inner variable. The predicted value of the controlled variable with satisfying accuracy replaces the value of the input variable in the control loop. In general, there can be more than one controlled inner variable.

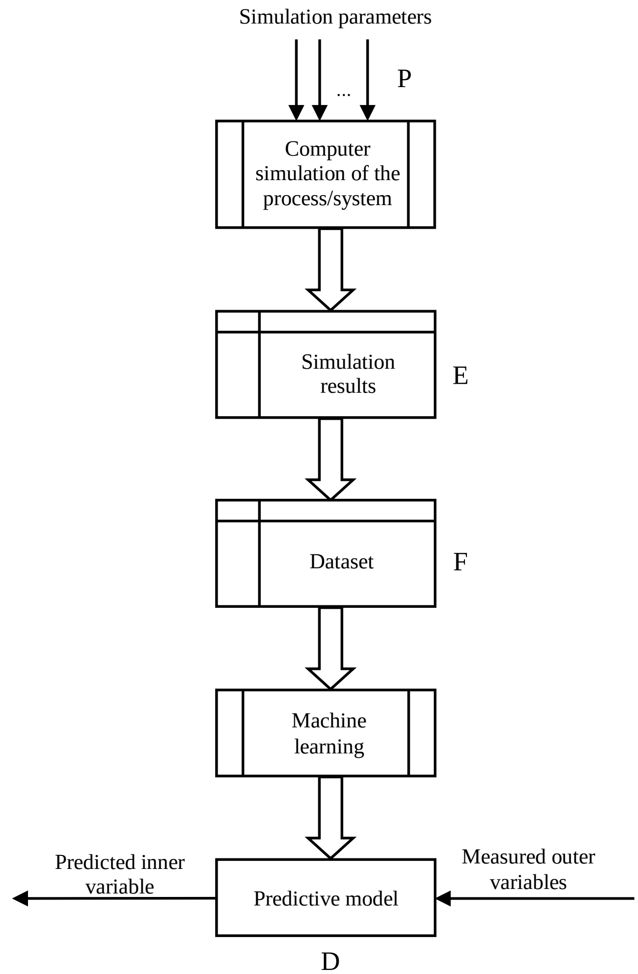

Fig. 1. Schematic diagram of the construction of the predictive model.

The feedback loop for real-time control of inner (hidden) temperatures during therapeutic knee cooling is schematically shown in Fig. 2. If the controlled output variable cannot be measured, for example, the temperature inside a knee, the so-

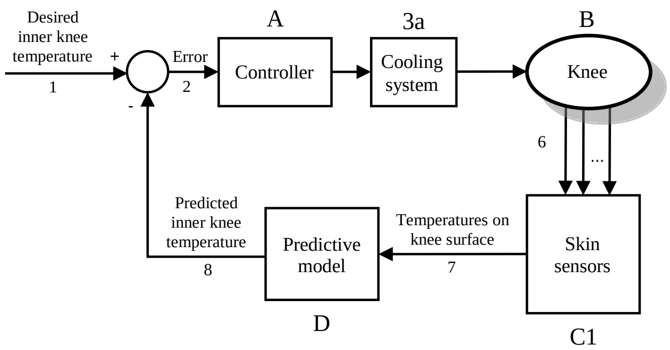

Fig. 2. Schematic diagram of the feedback control loop.

lution that is the subject of the invention is to add a predictive model D to the feedback control loop to obtain estimation of the inner knee temperature (8) instead of the actual inner knee temperature that cannot be measured non-invasively. The predicted inner knee temperature (8) is estimated based on the measured values (7) of other outer system/process variables whose measurement is more feasible. Sensors C1 are added for non-invasive measurement of the outer variables (6) (for example, temperature on the body surface). Preliminary, a simulation model of the system/process is used to provide reliable data for different input simulation parameters to build the predictive model D using machine learning methods. The controller A, based on the difference (2) between the desired value (1) and the predicted value (8) of the inner knee temperature, controls the cooling temperature in the pad (representing the cooling system 3a) wrapped around the knee (representing the plant B).

The method for control of the inner knee temperature is based on computer-controlled cryotherapy with pre-programmed protocols in terms of heat extraction intensity and treatment time. The goal is automatic control of the temperature inside the knee, representing the plant B, by changing the cooling temperature in the pad, representing the cooling system 3a. The cooling temperature of the pad is changed according to the output of the controller A. The controlled inner knee temperature is a hidden system variable since we aim to achieve non-invasiveness of the biomedical system. Therefore, a few non-invasive temperature sensors C1 on the knee surface measure the values of outer variables, like the value (7) of the temperature on the skin or the actual heat flux between the knee and the cooling pad, and provide feedback for the physiological response of the patient. The sufficient number of sensors is determined using machine learning methods. To control the deep knee temperature successfully in an arbitrary knee without measuring it, we need to predict the value of the inner variable, i.e. the value (8) of the deep temperature, from the non-invasively measured outer variables (7), i.e. the temperatures on the knee skin, using predictive model D obtained by knowledge extraction from the simulated data E. The light-weighted predictive models can be now implemented on a low performance computer that controls the cryotherapy. Computer simulations of heat transfer in biological tissues, using spatial models of human knee, form the ground base for providing the simulated data E.

The implementation of the framework for the case of real-time control of inner knee temperatures during therapeutic cooling starts with the computer simulation of the system. First, we simulate topical cooling of a human knee after ACL reconstructive surgery using cryoceutical pad cooled by a liquid at constant temperature maintained by an external cooling device (computer-controlled cryotherapy). The heat transfer in biological tissues is modeled with the Bio-heat equation that incorporates heat conduction, heat transfer between blood and tissues, and heat production by metabolism [39] [40]. A three-dimensional geometric model of the knee is derived from cross sections available from the Visible Human Dataset [41]. The Bio-heat equation is numerically solved on parallel computers through time and spatial discretization with the explicit finite difference method [17]. Next, the numerical solution procedure for the treatment of heat transfer in biological tissues is validated with extensive in vivo measurements during computer-controlled cryotherapy [19]. The validation results confirm that the used model and numerical procedure are appropriate for the simulation of heat transfer in bio-tissues. The validated simulation model is then used to generate an extensive amount of simulated data from different simulation scenarios with variation of the simulation parameters, namely knee dimension, blood flow rate and cooling temperature. Previous evaluations [19] have shown that variations in the knee dimension and the blood flow rate have the most important impact on the temperature profiles.

We then perform predictive modeling using the dataset from the simulated results. First, feature ranking using the RReliefF method [42] revealed that the most important features for predicting the inner knee temperature are the skin temperatures that correspond to the temperatures of skin sensors placed anterior and posterior to the knee. Next, based on the feature ranking results, we investigate several scenarios for the performance of several methods for predictive modeling: linear regression, regression trees, model trees, and ensembles of regression and model trees [43] [44]. The model trees perform the best with prediction error in the same range as the accuracy of the simulated data (0.1 °C). Furthermore, they satisfy the framework requirements for small memory size and real-time response. Results have shown that using only temperatures from skin sensors as input attributes gives excellent prediction for the temperature in the knee center. Moreover, satisfying predictive accuracy is also achieved using short history of temperatures from just two skin sensors (placed anterior and posterior to the knee) as input variables. The simulation and predictive modeling part of the framework have been already covered in details in [24]. In this paper, the focus is on the control part of the framework.

B. Fuzzy Logic Controller

Fuzzy logic applies the easy design of logic controllers for the control of complex continuously-varying systems. The term ”fuzzy” means that the logic involved deals with concepts that cannot be expressed as ”true” or ”false” but rather as ”partially true”. Fuzzy logic was first proposed by

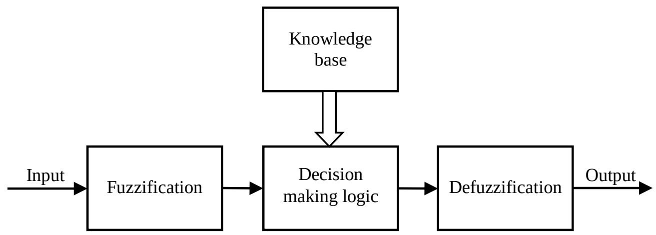

Fig. 3. Block diagram of a fuzzy logic controller.

Prof. Zadeh from the University of California at Berkeley in 1965 in his paper [45] where the concept of ”linguistic variables” or ”fuzzy sets” was introduced. His invention was not well recognized for almost ten years, until Prof. Dr. Mamdani from London University applied the fuzzy logic in a practical application for control of an automatic steam engine in 1974 [46]. Many more fuzzy implementations followed since then, including applications in industrial manufacturing, automatic control, automobile production, banks, hospitals, etc. Furthermore, fuzzy logic techniques have been widely applied in commercial appliances for everyday use, such as heating ventilation and air conditioning systems.

Fuzzy controllers are conceptually very simple. The block diagram of the fuzzy controller is shown in Fig. 3. First, the crisp input variables in a fuzzy control system are mapped by sets of membership functions known as ”fuzzy sets”. The process of converting an input value to a fuzzy value is called ”fuzzification”. Then, based on the knowledge for the system, the rules written in natural language are translated into fuzzy logic rules in the form of IF-THEN statements. Given ”mappings” of input variables into membership functions and truth values, the fuzzy controller then makes decisions for the action based on a set of rules. Next, all the rules that apply are invoked and their results are combined. Finally, the combined result is converted from the fuzzy domain back into a specific control output value, a procedure known as ”defuzzification”.

The most common shapes of membership functions are triangular or trapezoidal, although bell curves are also used. The shape is generally less important than the number of curves and their placement. It is recommended for the membership functions to overlap in order to allow smooth mapping. The IF-THEN rules have two parts: the IF part is called the ”antecedent” and the THEN part is called the ”consequent”. The fuzzy rule sets usually have several antecedents that are combined using fuzzy operators, such as AND, OR, and NOT. AND uses the minimum weight of all the antecedents, OR uses the maximum value, and NOT operator gives the ”complementary” of the membership function. There are several ways to define the result of a rule, but one of the most common and simplest is the ”max-min” inference method, in which the output membership function is given the truth value generated by the premise.

The results of all the rules that have fired are ”defuzzified” to a crisp value by one of several methods. There are dozens of methods for ”defuzzification” proposed in the literature, each with various advantages or drawbacks (Shaw, 1998). The following ”defuzzification” methods are of practical importance:

- Center-of-Area (CoA) - The ”centroid” method, in which the ”center of mass” of the result provides the crisp value, is the most popular ”defuzzification” method. The CoA method is often referred to as the Center-of-Gravity method because it computes the centroid of the composite area representing the output fuzzy term.
- Center-of-Maximum (CoM) - In the CoM method, only the peaks of the membership functions are used. The ”defuzzified” crisp compromise value is determined by the place where the weights are balanced. Thus the areas of the membership functions play no role and only the maxima (singleton memberships) are used.
- Mean-of-Maximum (MoM) – The MoM method is used only in some cases where the CoM approach does not work. This occurs whenever the maxima of the membership functions are not unique.

However, the fuzzy logic paradigm may provide scalability for large control systems where conventional methods become unwieldy or costly.

The decision to implement fuzzy logic controller was motivated from the following several features of the system/process that we want to control - therapeutic cooling of a knee:

- The framework requires light and low-cost implementation controller that can easily upgrade the mini-computer of existing computer-supported cryotherapeutic devices.
- The controlled output - the cooling temperature - can have a small set of possible discrete values.
- The controlled system is non-linear and can easily be distressed, for example, sudden blood flow rate changes or other types of physiological changes.
- We take advantage of our knowledge for cooling of body parts. This includes the knowledge gathered from the clinical study of cryotherapy effects after knee surgery [15] and the computer simulation of heat transfer in biotissues [19].

Considering the framework design for control of the inner knee temperature shown in Fig. 2, we define the input to the controller (the error) as the difference between the desired and the predicted inner knee temperature, and the output of the controller as the change in the cooling temperature. Further, we define the sampling interval as the time interval when the controller invokes a control action. We define fuzzy sets for two inputs – the ”error” and the derived change in error, ”delta”, defined as the difference between the error in the previous and the current sampling interval, as well as the output - ”cooling”. The definition of the fuzzy sets is given in Table I. The membership functions are defined for the inputs as in Fig. 4 and for the output as in Fig. 5. The following reasoning is behind the definition of the fuzzy sets as such:

- The zero fuzzy sets for the error and delta must not be very small, because we have to also encounter the possible errors made by the predictive model. If these fuzzy sets are very small, the chance for wrong control actions because of prediction error will increase.
- The cooling fuzzy set is defined according to the specifications of existing cryotherapeutic devices, namely, the

TABLE I
FUZZY SETS.

error		delta		cooling	
P:	Large Positive	P:	Positive	Dec:	Decrease
SP:	Small Positive	Z:	Zero	Z:	Hold
Z:	Zero	N:	Negative	Inc:	Increase
SN:	Small Negative				
N:	Large Negative				

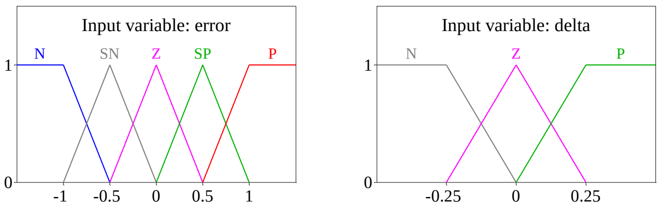

Fig. 4. Membership functions for the controller input variables.

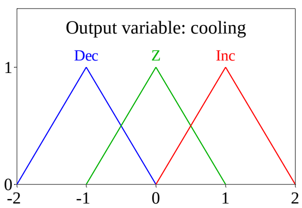

Fig. 5. Membership functions for the controller output variable.

cryotherapeutic device used in the clinical study in [15]. The decrease and increase of the cooling temperature is set to the minimal accuracy of the device, i.e. 1 °C.

- Larger fluctuations of the cooling temperature can cool or warm the knee to an extent that reversing back to a previous temperature state can take longer.

The rules of the fuzzy logic controller are given in Table II. The presented rule set resulted from a trial-and-error approach while designing the controller. Namely, the design of fuzzy logic controller as such is a result of previous evaluations of several variations of the rule sets and fuzzy sets; especially the input fuzzy sets, since the output set is more or less determined by the performances of cryotherapeutic devices. Similar to PID controllers, fuzzy controllers also need to be tuned for optimal performance. The tuning involves the selection of fuzzy sets and the definition of their membership function, as well as the minimal set of rules that results in a desired behavior of the controlled system for different scenarios.

The reasoning for the present rule set originates mostly from our knowledge of the system operation, i.e. therapeutic knee cooling. Specific considerations in the design include the following:

- The cooling temperature should be changed as little as possible, i.e., cooling with a constant temperature as long as the inner temperature is distant from the target value and the error decreases (Rule 9). The reasoning behind this rule is not to cool the knee to a large extent because if warming is later needed, the knee will warm up very slowly since it will possess significant stored self-cooling energy.

TABLE II
FUZZY SYSTEM RULES.

1.	IF	error is P			THEN	Cooling is Inc
2.	IF	error is SP			THEN	Cooling is Inc
3.	IF	error is Z	AND	delta is P	THEN	Cooling is Inc
4.	IF	error is Z	AND	delta is Z	THEN	Cooling is Z
5.	IF	error is Z	AND	delta is N	THEN	Cooling is Dec
6.	IF	error is SN	AND	delta is P	THEN	Cooling is Inc
7.	IF	error is SN	AND	delta is Z	THEN	Cooling is Dec
8.	IF	error is SN	AND	delta is N	THEN	Cooling is Dec
9.	IF	error is N	AND	delta is P	THEN	Cooling is Z
10.	IF	error is N	AND	delta is Z	THEN	Cooling is Dec
11.	IF	error is N	AND	delta is N	THEN	Cooling is Dec

- The reasoning behind Rule 6 (that on first looks like opposite reasoning) is that it takes time to achieve significant change of the temperature in the knee center when the cooling temperature is changed. With this rule, we act preventive in order not to allow the controlled temperature to go much above/below the target. This is also closely related to the previously discussed Rule 9. The question that can be asked here is why not also opposite reasoning for Rule 2. The answer is that the knee cools faster than it warms and if Rule 2 decreases instead of increases the cooling temperature, the target temperature may not be reached.

Additional specific implementation settings of the controller include the following:

- The cooling temperature has a lower limit at 2 °C, which is the minimal temperature that can be set in the cooling pad of existing cryoceutical devices. Constant cooling with very low temperatures can be harmful for the treated tissues and can increase the risk for frostbite and nerve damage [47]. Therefore, the cooling temperature must be bounded from below.
- The minimal sampling interval of the controller should not be below the time needed for the cryotherapeutic devices to change the temperature of the cooling liquid, i.e. 2 minutes. Moreover, the cooling temperature should not be changed too frequently because frequent changes can cause possible complications on the treated tissues. On the other hand, the sampling interval should not be too large – larger sampling interval can cause the response time of the control system to be prolonged, i.e., the controlled output will be reaching the target very slowly. The decision for the value of the sampling interval has to balance between these limitations.
- The error and delta input values are rounded to the accuracy of the simulation data, i.e. 0.1 °C. This is also the reasonable minimum accuracy of medical temperature measurements.

The fuzzy logic controller has been implemented using the Fuzzy Logic Toolbox in MATLAB (www.mathworks.com/products/matlab/). The inference method used is max-min. Because of the discrete nature of the controlled output, the MoM (Middle of Maximum) ”defuzzification” method is used.

IV. Results

The experimental evaluation of the proposed framework for real-time control of inner knee temperatures during therapeutic cooling is performed with simulated instead of measured knee temperatures. The evaluation with measured values would require a new clinical study for invasive in vivo knee temperature measurements. When evaluating the framework on a real case, the cooling conditions should be strongly administered. This includes unified preparations of each knee for cooling (predefined bandage thickness and positions of the skin sensors), as well as unified conditions during the cooling (uniform coverage of the knee with the cooling pad).

The performance of the framework has been evaluated with a custom-made evaluation engine designed in MATLAB. The engine combines the numerical solver of the computer simulation implemented in C++, the predictive model implementation in Java, and the fuzzy logic controller implemented in MATLAB. The best performing model tree with input attributes – temperatures on four locations on the knee skin [24], has been used as predictive model in the framework.

The evaluation results are presented as temperature evolution in the knee center during controlled cooling treatment. In addition, the temperature evolution in the knee center during uncontrolled cooling treatment with constant cooling temperature is presented for comparison. Both cooling methods start at cooling temperature of 9 °C – the initial cooling temperature of the Waegener cooling protocol used in [15]. The sampling interval is set to 10 minutes, but it is a user-defined value that can be set as desired or needed. The target inner knee temperature has been set to 27 °C, but can also be set to any desired or required value. The framework was evaluated for 9 hours of controlled cooling treatment for several scenarios to test the robustness and controllability of the system. All scenarios use the same fuzzy logic controller designed in Section III-B.

A. Robustness

First, we evaluate the framework for small, normal and large sized knee with normal and constant blood flow rate. The results are presented in Fig. 6, Fig. 7 and Fig. 8, respectively. The blood flow parameters for different tissues are set as in [24].

The results confirm stability of the system for different settings of the knee size. In all scenarios, the predicted inner knee temperature follows the simulated inner knee temperature very well. The results show that the control of the cooling temperature is much more needed with small and big knees, especially in the case of a smaller knee. Smaller knees respond faster and to a larger extent to temperature changes in the cooling compared to bigger knees. The controlled cooling protocol does not allow for a small knee to be cooled below the target inner knee temperature. For a large sized knee, the uncontrolled cooling protocol does not lower the inner knee temperature, while the controlled cooling protocol succeeds to bring the inner knee temperature closer to the target value. For normal sized knees, both cooling protocols – controlled and uncontrolled - perform approximately the same. However, if

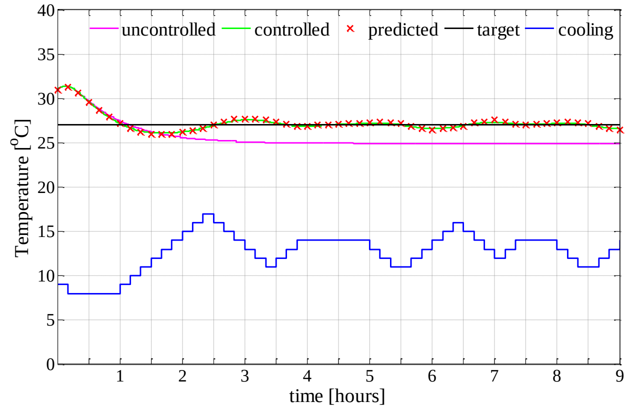

Fig. 6. Control of inner knee temperature during therapeutic cooling of a small knee with normal blood flow rate. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

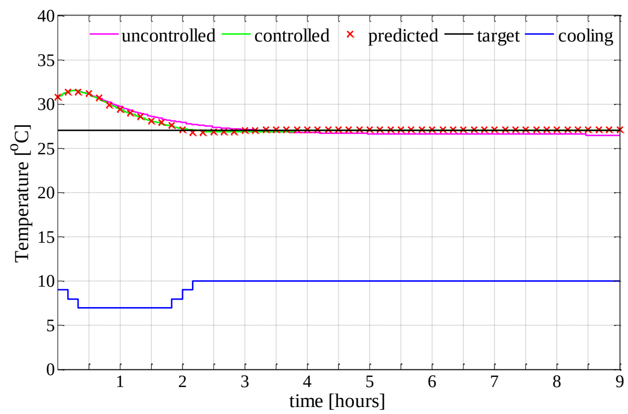

Fig. 7. Control of inner knee temperature during therapeutic cooling of a knee with normal size and normal blood flow rate. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

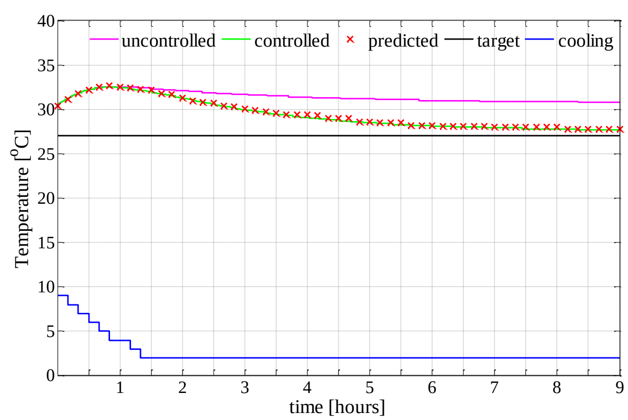

Fig. 8. Control of inner knee temperature during therapeutic cooling of a big knee with normal blood flow rate. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

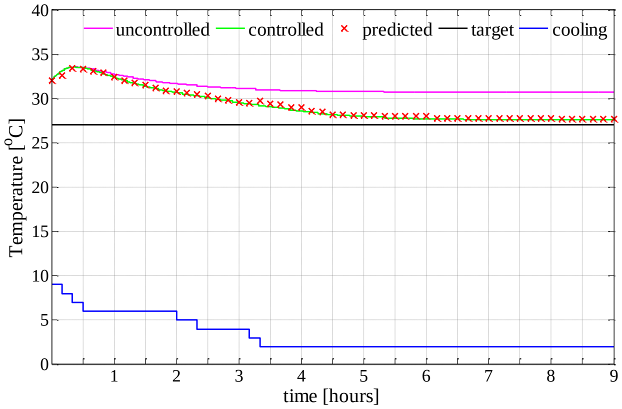

Fig. 9. Control of inner knee temperature during therapeutic cooling of a knee with normal size and large blood flow rate. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

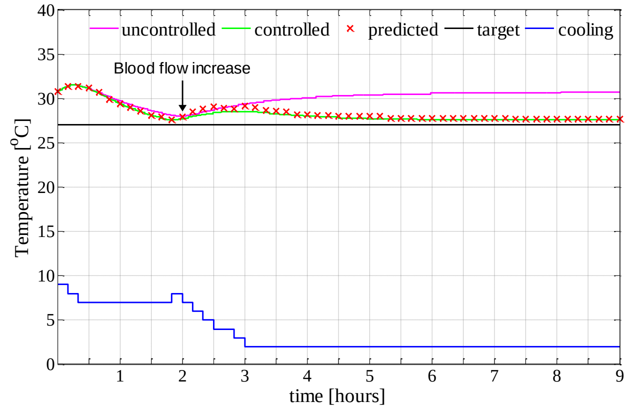

Fig. 10. Control of inner knee temperature during therapeutic cooling of a knee with normal size and sudden change in the blood flow rate from normal to large after 2 hours of cooling. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

the blood flow rate in a normal sized knee is for any reason larger, then controlled cooling is required. Fig. 9 shows the results for a scenario with a normal sized knee and 100 % larger blood flow rate than the nominal blood flow rate.

In the case of large sized knee with normal blood flow (Fig. 8) and normal sized knee with larger blood flow (Fig. 9), the controlled inner knee temperature at the end of the cooling has not reached the target value: there is an offset of 0.7 °C for large sized knee with normal blood flow and offset of 0.6 °C for normal sized knee with larger blood flow. In these cases, the cooling temperature at some point reaches its minimum and the cooling continues with constant temperature of 2 °C. Several hours of cooling at the minimal temperature are still not enough to lower the controlled temperature to the target value. However, the offsets from the target value are acceptable. Lowering the cooling temperature even more in order to reach the exact target value is not a solution since it can increase the risk for frostbite and nerve damage.

Next, we evaluate the framework in the case of immeasurable disturbance, such as sudden change in the blood flow rate. The results for scenarios with blood flow rate suddenly increased after 2 hours and after 4 hours of cooling are presented in Fig. 10 and Fig. 11. In both scenarios, the predicted inner knee temperature follows the simulated inner knee temperature adequately. Therefore, the framework succeeds to recognize the physiological change in the knee and consequently adapts the cooling temperate. On the other hand, the uncontrolled cooling protocol allows for the temperature inside the knee to increase dramatically. Again, in both scenarios, an offset (0.6 °C) from the target value can be observed at the end of the cooling. The reason is the same as the one stated above: the cooling temperature reaches its minimum that is not enough to lower the controlled inner temperature to the target value.

B. Controllability

Finally, we investigate the response of the framework to a deliberate change of the target inner knee temperature. The results for a scenario with change of the target inner knee temperature from 27 °C to 29 °C after 3 hours of cooling

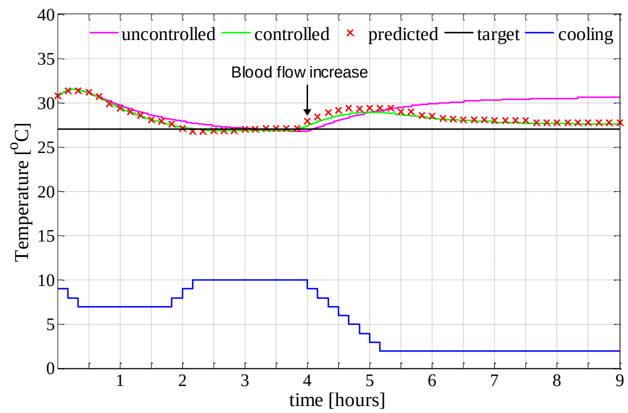

Fig. 11. Control of inner knee temperature during therapeutic cooling of a knee with normal size and sudden change in the blood flow rate from normal to large after 4 hours of cooling. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C.

are presented in Fig. 12. Here, the comparison is made with an uncontrolled cooling treatment with a constant cooling temperature of 9 °C until the target is changed. Because the change of the target temperature is a known input to the system, after the target temperature is changed by 2 °C, the constant cooling temperature of the uncontrolled cooling treatment is also increased by 2 °C. Such a scenario will allow for a more proper comparison of the controlled and uncontrolled cooling therapies.

The results show that the framework manages to follow the change in the target temperature and the inner knee temperature again reaches its target after 4 hours of controlled cooling. On the other hand, the uncontrolled cooling protocol does not succeed to increase the inner knee temperature towards the target, although the cooling temperature was increased appropriately. In this scenario, larger prediction errors can be noticed around 4 hours. The cooling temperature at that time is set to the value of 17 °C. Simulation settings for cooling temperatures higher than 15 °C have not been included in the simulation dataset. Therefore, the predictive model does not perform as good as for simulation settings that have

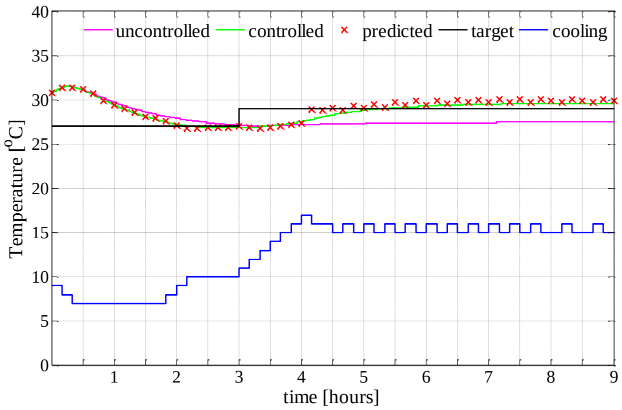

Fig. 12. Control of inner knee temperature during therapeutic cooling of a knee with normal size and normal blood flow rate with change in the target temperature after 3 hours of cooling. The controlled cooling is compared with uncontrolled cooling, i.e. cooling with constant temperature of 9 °C until the target is changed, and cooling with constant temperature of 11 °C after the target is changed by 2 °C.

been included in the dataset. However, besides the errors in prediction, the controller still takes good corrective control actions. An offset of 0.6 °C from the target value can be observed at the end of the cooling because of the prediction errors. In future work, the dataset should be extended with simulation settings with a larger range of cooling temperatures in order to improve the performance of the predictive model in such scenarios.

In all scenarios, the sampling time of the controller has been set to 10 minutes. The sampling time dictates the response time of the control system. If the response time of the system needs to be prolonged or shortened, the sampling time should be set to larger or smaller time intervals. The framework implementation allows for the sampling time to be custom set. This feature of the framework can be used to investigate different types of controlled cooling protocols and contribute to standardization of cryotherapeutic methods.

V. Discussion and Conclusions

The paper formalizes, implements and evaluates a framework for real-time control of hidden inner body temperature variables during therapeutic cooling where the feedback cannot be obtained by measuring the controlled output variable either because the system is non-invasive, like most of the examples in biomedicine, or for any other reason. The control loop then uses the feedback information from other measurable variable/s of the system that can be used to estimate the controlled output variable of interest. The work leverages three research areas from computer science and engineering for that purpose: computer simulations – to provide safe and inexpensive insight into the process/system to be controlled; machine learning – to provide methods for predicting the hidden controlled output from the measurable ones based on the data generated from the simulations; and control theory – to provide control techniques applicable in systems with constraints in the control input. The framework is evaluated on a real-world problem in the domain of biomedicine – real-time control of the inner knee temperature during cryotherapy after surgery.

The need for non-invasive control of inner knee temperature during therapeutic cooling is based on the finding that the cryotherapy should be controlled depending on the individual patient's response, which raises the need for "smart" cooling devices for personalized therapy. In ordinary control systems, based on the principle of feedback, the variable to be controlled is measured and compared to a desired reference, and the discrepancy is used to compute a corrective control action. The proposed solution is a method for non-invasive real-time control of inner temperature variables during therapeutic cooling or heating, based on the feedback control loop that uses predicted, instead of measured, inner temperatures because measurements are not feasible or would introduce invasiveness into the system. The method uses machine learning to construct a predictive model for estimation of the controlled inner temperature variable based on other variables whose measurement is more feasible, i.e. temperatures on the body surface. The machine learning method uses data generated from computer simulation of the therapeutic treatment for different input simulation parameters.

We have performed experimental evaluation of the proposed framework for real-time control of inner knee temperature during therapeutic cooling. A fuzzy logic controller was designed to provide adequate real-time control of the inner knee temperature by controlling the cooling temperature. The framework was evaluated for robustness and controllability. The results showed that the controlled cooling is essential for small or large sized knees, which are significantly more or less sensitive to the cooling compared to normal sized knees. Moreover, the framework recognizes dynamic physiological changes or potential changes in the system settings, like extreme changes in the blood flow or changed target inner knee temperature, and consequently adapts the cooling temperature.

The proposed solution is based on currently available computer-controlled cryotherapeutic devices with the ability to control the cooling intensity. Computer-supported cryotherapeutic devices are becoming more common and are replacing the classical passive therapies based on ice. These growing trends are stimulated by the higher efficiency and controllability of the heat extraction or heat supply, the shorter treatment time, and the possibility to introduce an external pressure on the injured body part provided by computer-supported cryotherapeutic devices. We use these abilities of such devices furthermore in order to adjust the cooling intensity based on a personal feedback for the cooling treatment of each patient and achieve non-invasive control of inner temperatures according to predefined trajectory. Our solution involves an upgrade of the current cryotherapeutic devices with few small thermo sensors (thermistors) and a support mini on-board computer with very little additional cost. The light-weighted predictive model and a set of fuzzy logic rules for control correspond to the mini-computer architecture of such devices. Much more sophisticated cryotherapeutic devices, based on the proposed principles, would have the ability to control cooling not only in term of intensity but also in term of locality. The cooling pad could have more inputs in order to maintain specified temperatures in different regions of the cooled part of the body. Such a ”smart” cooling device would be able to perform cooling adapted to the individual patient's response and contribute to improved postoperative or post injury treatment. Moreover, controlled therapeutic cooling can contribute to the evaluation of various cryotherapeutic methods, and further development and standardization of cryotherapy. We believe that the above-listed potentials will increase the interest for the results of this paper.

The work presented in this paper can be extended in several directions. First, the evaluation of the framework for real-time control of inner knee temperature during therapeutic cooling is performed with simulated instead of measured knee temperatures since the evaluation with measured values would require a new clinical study for invasive in vivo knee temperature measurements. The clinical evaluation of the framework is a major step in the direction of future work. For that purpose, a prototype of a computer-controlled cryotherapeutic device with the means of controlling the inner knee temperature should be first implemented using current implementations of computer-supported therapeutic devices. Next, for achieving even better predictive performance in real-life therapeutic cooling, the dataset can be extended with simulated data for a wider range and/or higher resolution of already varied input parameters (cooling temperature, knee dimension and blood flow rate), or variations of other input simulation parameters, such as initial temperature state, thermo-physical parameters of substances, etc., the proposed framework for non-invasive real-time control of hidden inner body temperature variables can be applied for control of inner temperatures during therapeutic cooling or heating of any part of the body. The application includes using already developed valid simulation model of bio-heat transfer in the treated body part. The modular design and implementation of the framework allow for easy inclusion of different simulation or predictive models, which does not affect the basic idea for control of inner body temperature variables that are difficult or impossible to be measured based on outer variables whose measurement is more feasible. The results of the paper confirm that the proposed framework for control of inner body temperatures can significantly improve the process of therapeutic cooling or heating.

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