Óbuda University

PhD Thesis

Design of processes supporting the development of medical devices

by

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1. Scope of Research

1.1. Kidney disease

This doctoral thesis is related to hemodialysis machines, their operation and their development. Hemodialysis machines are used to replace or support the kidney functionality during malfunction which process is known as blood purification. Renal replacement therapies are required in case of kidney malfunction which can be grouped as acute and chronic kidney failure. It is also used to improve living conditions until the kidney of the patient could be transplanted. The need for such machines is well demonstrated by showing that chronic disease is the 9th leading death cause in the United States [1].

Chronic kidney disease is built up over a longer period of time while the glomerular filtration ratio (blood purification capability of kidney) is gradually decreasing. After a certain threshold, the kidney cannot remove enough metabolic waste products and it begins to accumulate in the body. The accumulation of these waste materials results unpleasant symptoms (fatigue, drowsiness, itching, joint pain) in the beginning but it could achieve life threatening conditions as well [2]. The chronic kidney disease is spreading, estimated to affect more than 10% of adults in the United States, elder people over 70 years are especially threatened [3].

On the other hand, acute kidney injury is the rapid loss of kidney functionality. It is caused by a trauma with a variety of backgrounds [4]. According to Susan et al. [5] every one in five adults and one in three children experiences acute kidney injury in hospital care. Critically ill patients are especially threatened and their mortality is significantly affected by the presence or absence of renal replacement therapy [4]. Acute kidney injury typically lasts for hours or days. If the injury does not recover (at least partially) within 3 weeks then it is considered chronic kidney disease.

Different machines are utilized for the treatment of these illnesses, though their basic principles are the same.

1.2. Basics of hemodialysis machines

In hemodialysis machines peristaltic pumps are responsible for fluid transportation including blood of the patient [6]. They are transporting liquids by repeatedly compressing an elastic tube(segment) without getting in contact of the transferred fluid. Peristaltic pumps can be operated with disposable tubing which is practical as the treated blood gets in contact only with the sanitized kit. This way infection and contamination can be avoided. Furthermore, peristaltic pumps are gentle to the transported fluid. This is especially important in case of blood, as the breakdown of corpuscles (formed elements) should be avoided. From medical point of view the only drawback of peristaltic pumps is their inaccuracy. Hemodialysis machines typically operate with two roller peristaltic pumps (at least for the main pumps).

During treatment the blood is flown through a semi-permeable capillary system, which is responsible for removing the metabolic waste materials. Furthermore, it can be used to remove excess fluid if it is required for the vitality of the patient. On the other hand, removing too much fluid can lead to dehydration which might increase to a life threatening level. Moreover, in certain machines peristaltic pumps are also used for transporting drugs. In such cases the precise transfer is even more crucial due to the possible overdosing.

The inaccuracy of peristaltic pumps is the main reason of feedback control [7]. The elasticity of tube segment may result approximately ±10% in total transferred volume due to deviation of production [8]. Furthermore, the transferred volume is depending on pressure ratio which might further worsen the fluid balance. The accumulation over the long therapy time (up to and over 72 hours) could further increase these effects.

The fatigue of tubing material has to be also mentioned. The continuous repeated squeezing of the material will make it stiffer over time. Thus, it will be unable to reshape completely to its original form which also means that the inner volume (thus the transfer volume) gets decreased. One purpose of the current thesis is to propose solutions on this problem.

1.3. Importance of development processes

However, it is not enough to design and integrate every components into the system, but also it has to be ensured that the machine is safe for every intended application. Safety-critical systems have so high risk of causing harm that this risk must always be reduced to a level “as low as reasonably practicable” (ALARP) required by ethics, regulatory regimes, and standards (IEC 61508). Here, the manufacturer promises the guarantee via statements and external certification bodies while authorities are responsible for its inspection.

With the growing complexity of software it is getting harder to test it exhaustively to explore every malfunction. This way only a majority of problems will be revealed and the possible occurrence of errors cannot be specified exactly only statistically. Therefore, not the software itself is the main target of inspections but the development process instead. It is more important to have a well-established workflow, which contains steps not only for developing but for controlling as well. According to studies [5, 9, 10] it is more effective to have a well-designed and executed process than committed people.

The required processes, including prescriptions from standards and directives, mean significant documentation burden and practically compliance is impossible without the use of supporting tools. These tools support various fields of development: requirement management, change management, etc. Altogether, they are called application lifecycle management (ALM) tools or ALM system, where transparency and interoperability are key features.

Here traceability and lately consistency are playing key roles. The maintenance of these measures are crucial to minimize the introduced errors, because 50-60% of software defects are related to requirements development [11]. Here, the rate of leakage (inherited defect which is detected only at a later stage) is 53% in the requirements phase and 68% in the design phase [12]. Altogether this raise the need for automations which support both the everyday job and the assessments as well. The second purpose of the thesis refers to this problem.

2. Aim of the Thesis

The dissertation is organized around the two described problems in Section 1.2. and 1.3. First, it is discussed how the patient fluid balance can be kept by controlling the fluid pumps in the machine, linking the problem to control theory.

The aim was to show for the industrial users the benefits of control engineering applications, but proposing instead of classical control algorithms (i.e. PID-type), advanced and cost-effective solutions, like soft-computing methods and other non-conventional techniques. According to this, different fuzzy controllers (Mamdani-type, integro, adaptive, AFNIS) controllers were developed. Furthermore, tensor-product (TP) based PI-control was developed in order to compare TP control possibilities with classical methodologies. .

Due to the demonstration nature of this research, it was not the only expectation to simulate and model the behavior of controller, but to prove their applicability in reality as well. Therefore, controllers providing the best performances have been implemented and verified.

The second part of the thesis investigates how it is possible to improve the software quality through the manipulation of tools in Application Lifecycle Management (ALM) system. The focus was on traceability and consistency related problems from this extensive topic.

The novel idea of Augmented Lifecycle Space (ALS) method by Biro et al. [KJ10] was targeted to be demonstrated here first. With its help it is possible to generate/affect automatically workflows to get rid of traceability gaps and inconsistencies. Its operation was proved both for homogeneous system, where the transparency and interoperability of the system is good, and for heterogeneous system where the direct accessibility is problematic.

3. Materials and Methods

3.1. Fluid balance control

3.1.1. Used model and evaluation criteria

One pump and its related tubing together with fluid bag and its weighting scale was separated as a subsystem. The correlations between the pumps can be neglected as a good approximation without risking the compliance of performance requirements. This subsystem was identified with specific regards to insecurity in fluid transport volume, quantitation error of weighting scale and the insecurity of rotation of pump head [KJ1].

For evaluation of the behavior of controllers, a model was created, based on the identification, which not only mimics the real machine, but the controller has a dedicated place, thus it can be always updated with the analyzed one [KJ2]. Here, one branch is responsible for the calculation of ideal transfer volume, while the other branch with the same plant is responsible for the real transfer volume calculation. The difference is the error signal used by the controllers. It is possible to introduce various errors in this second branch: Slope error can be introduced which simulates the tube related errors (such as fatigue, pressure dependency, tube inaccuracies, etc.). Offset error can be introduced to simulate bag and weight measurement related problems (weighting error, bag swinging, etc.).

For analysis, the following properties of the controllers were analyzed: settling time, overshoot, accuracy, and robustness, while considering their physiological meaning and relevance. The features of the controllers were evaluated with simulation of models

The aim of this research was to show industrial users that soft computing methods and other non-conventional development methods can be used also in safety-critical applications. Therefore, the benefits of fuzzy controller and ANFIS based controllers were shown. Moreover, tensor product based design of a PI controller has demonstrated that it is worthy to consider using sophisticated design methods instead of the common ones.

3.1.2. Fuzzy controllers

I have created a regular fuzzy controller which uses the error signal as its input. Secondly, I have created a fuzzy controller which uses the integral of the error signal as its input (Integro Fuzzy). Finally, I have created a fuzzy controller which uses the error signal as its input, but here iterative learning control method was used to provide a basic adaptivity for the controller (Adaptive Fuzzy) [KJ3].

After comparison, it can be stated that the settling time of the integro fuzzy controller was the slowest, which was followed by the regular fuzzy controller. The settling time was very similar for the reference PID controller and the adaptive fuzzy controller. This latter was faster at higher flows, while the PID controller was faster at lower flows.

According to the results, it could be concluded that the adaptive fuzzy controller was capable to replace the reference PID controller, however its performance was a bit worse. Still, the adaptive fuzzy controller contained additional expert knowledge and it could adapt to the changing tube segment caused by fatigue or pressure changes. Altogether, this makes it beneficial to use it in real systems.

3.1.3. ANFIS controllers

I have also designed controllers using adaptive neuro-inference systems [KJ4, KJ5]. I have compared a regular ANFIS controller and an ANFIS controller completed with iterative learning control to test against the reference PID controller. The training data sets were created to mimic the behavior of a PID controller but the overshoot was removed together with some minor modifications to improve the performance.

It has the beneficial properties to incorporate expert knowledge and to outperform the other solution by improving the training data set. When combined with iterative learning control method, it is a potent solution capable to adapt the changes of the system.

3.1.4. LMI-based feedback regulator

It can be valid to use classical PID controllers in certain circumstances. This includes when the developed system has limited resources and the implementation of controller developed by soft computing methods cannot fit in. Furthermore, the lack of knowledge regarding soft computing methods may validate this if there is not enough time or a professional cannot be trained/hired.

I have created a PI controller for such cases to demonstrate the application of less known development methods [KJ7]. Here, I have used tensor product model transformation. The resulted weighting functions were used to get the parameters of full state feedback control.

The controller had no derivative term because the quantitation error of weighting scale is in the range of error and it cannot be distinguished from it. The settling time was comparable with the reference PID controller, while the PI controller had only minimal overshoot. The accuracy was close to zero for both controllers and both of them passed the robustness tests. This way it was proved that the design method is effective, and it can be advised to use in industrial applications.

3.2. Improving traceability and consistency

3.2.1. Augmented Lifecycle Space method

It is demanding to provide automated methods for detecting process related problems during development [KJ7, KJ8]. In this research the aim was to find traceability and consistency related problems automatically and give a method to eliminate them. Lifecycle space is the summary of stored artifacts in a selected ALM system together with their relationships. The mentioned artifacts include but are not limited to requirements, test cases, test results, workflows, reviews and the code itself.

The idea of Augmented Lifecycle Space (ALS) method is to check this existing system and complete first virtually with the missing artifacts and relationships [KJ10]. This augmentation results an improved system where analyses can be re-executed which may detect further problems. In the end, every missing artifact and relationship can be explored and workflows can be generated for fixing these problems.

3.2.2. Demonstration in homogeneous and heterogeneous system

To demonstrate the applicability of ALS approach, I have created a test environment [KJ9, KJ12]. Here, a homogeneous system was created first which means practically perfect transparency. The only used tool was JIRA, where the artifacts were created. The AutomotiveSPICE model was used for creating the test system, as it already emphasize the importance of both traceability and consistency. It is expected that in the future such expectations will appear in the medical domain as well.

Separate projects were filled with sample issues to simulate system requirements and software requirements and software detailed design. An additional project was created to each of the aforementioned ones, where the test cases were created. This was completed with an independent project which was empty at the beginning and this was later used for augmentation. Relationships were added to the system to show the decomposition of artifacts beginning from system requirements until software detailed designs.

If any problem was found then an issue (missing link, missing test cases, outdated requirements) was created in the project responsible for augmentation. Here, issues had the same workflow as in the real development. This workflow was transited automatically to a state where the issue can be fixed (requirement review was prescribed for outdate issue as an example). According to the decision of stakeholders, these issues can be approved and executed to get rid of the problems. Result were evaluated according to Technical Action Research [13].

The same experiment was executed for heterogeneous case [KJ11, KJ14]. The difference was that requirements were stored in separate formal modules in IBM Rational DOORS instead of JIRA projects. The linking was created via unique identifiers, and the information was passed between the two components via CSV file. The analyzer program was executed with DOORS DXL scripts instead of JIRA REST API.

4. New Scientific Results

Thesis group 1: Non-conventional control methods of hemodialysis machines

Thesis 1
I have designed and compared multiple controllers for the transfer volume control of hemodialysis machines. These controllers were compared with a classical PID controller in terms of settling time, overshoot and accuracy.

Thesis 1.1
I have created and demonstrated the applicability of a fuzzy inference system where the error signal and the integral of the error signal were used to create the control signal. Furthermore, I have created an adaptive fuzzy controller with the help of iterative learning control method. This latter adaptive fuzzy controller is comparable to the reference PID controller in terms of accuracy and settling time, but is more cost-effective. It has no overshoot and it is capable to adapt the changes of the tube segment such as fatigue. The applicability was verified with testing the controller on a target machine which confirmed the results of simulation.

Thesis 1.2
I have created two ANFIS based controllers and demonstrated their usability considering practical implementation. One of them was a classical ANFIS system, while the other was completed with an anti-windup system and an iterative learning control circuit. This latter modified ANFIS system is comparable to the reference PID controller in terms of accuracy and settling time. Moreover, it has no overshoot and it is capable to adapt the changes of the tube segment such as fatigue. The applicability was verified with testing the controller on a target machine which confirmed the results of simulation.

Thesis 1.3
As PID controller is still commonly used in industrial application it is vital to provide design methods to find optimal control. In this part I have implemented and demonstrated how an LMI-based feedback regulator can be designed with the help of tensor product transformation. The design controller had satisfactory results both in terms of accuracy, settling time and overshoot when implemented on a hemodialysis. It proved to be applicable as a systemic design method which can be utilized in other safety-critical applications as well.

Relevant own publications pertaining to this thesis group (1 journal and 5 international conference publications):

[KJ1], [KJ2], [KJ3], [KJ4], [KJ5], [KJ6]

Thesis group 2: Practical application of Augmented Lifecycle Space approach

Thesis 2
I have created custom application lifecycle management system in order to prove the applicability of Augmented Lifecycle Space approach. Result has shown that it can be used practically both in homogeneous and heterogeneous system and with modification it can be beneficiary for software development companies.

Thesis 2.1
I have proven the applicability of ALS method for homogeneous systems. The implemented solution is capable to find traceability missing traceability links, detect chronological inconsistencies and provide basic measures regarding test coverage. For the according type of found deficiencies the program generates a workflow automatically which should be followed in order to fix the problems.

Thesis 2.2
I have proven the applicability of ALS method for heterogeneous systems as well. The solution is capable to find traceability gaps, major inconsistencies and it also provides basic measures. The implemented solution also realizes a minimal point to point integration between the two system components to provide a platform form information sharing. Similarly, this solution also generates workflow to make possible the correction of found deficiencies.

Relevant own publications pertaining to this thesis group 2 journal and 6 international conference publications):

[KJ7], [KJ8], [KJ9], [KJ10], [KJ11], [KJ12], [KJ13], [KJ14]

5. Discussion and Practical Applicability of Results

I have created different controllers to control peristaltic pumps in hemodialysis machines. The aim of this research was to demonstrate to industrial users that soft computing methods and non-conventional controller development methods could be beneficial in safety-critical products.

According to the simulations and verifications the following conclusion can be stated: The adaptive fuzzy controller is beneficial in systems which are less resource demanding. With its help the changes of the peristaltic pump can be handled (adaptivity) while it is also possible to utilize the expert knowledge accumulated by the company. If the system is not resource demanding then the modified ANFIS controller is the best choice as it is outperforming every other controller which was analyzed. This controller also benefits from expert knowledge, and it is also capable to adapt to the changes of the used tube segment. If the system is really resource demanding it is advised to use PID controller with proper tuning instead of the conventional tuning methods. It was shown that the PI controller designed via tensor product transformation has outperformed the original PID controller (created with conventional methods).

According to both simulation and verification with a target machine, it can be stated that the above mentioned controllers are practically applicable.

I have demonstrated the applicability of augmented lifecycle space in the practice. With its help I was able to detect missing requirement links, find outdated requirements, and explore missing test cases and provide some minor indicators (test coverage).

The experiments were executed first in homogeneous system, where the only used tool was JIRA and they were also performed for heterogeneous system, where JIRA and DOORS were responsible for information storage. As a result a single workflow was generated for each found deficiency. This workflow is set programmatically depending on the type of found problem. By performing these workflows the detected issues can be fixed.

The results are promising and they can be already used in real developments. However, improvements are inevitable. These already implemented simple checks detect only a minority of problems. Formal methods and machine learning could be utilized to execute more improved analysis which would boost the usefulness.

The industrial recommendations shall be also considered in the future to improve usability next to efficiency. Thus, it has to be solved to affect directly the workflow instead of generating additional ones. Furthermore, it has to be solved to limit the analysis to a lifecycle space which is really required and to neglect items which are already baselined.

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