PATIENT INDIVIDUAL PARAMETERIZATION OF CARDIAC VENTRICULAR TACHYCARDIA TERMINATION ALGORITHM

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Abstract: Implantable cardioverter defibrillators (ICD) are devices capable of terminating ventricular fibrillations with a defibrillation and ventricular tachycardia (VTs) with antitachycardia pacing (ATP).

This work presents a computer model that can be parameterized for each patient individually in order to simulate several VTs and different ATP protocols with the aim to find the optimal parameter settings of the patient’s ICD device. Based on CT images, a 3D hybrid automation (HA) of the left ventricle was modeled and a reentry cycle with pathologically altered cells was included in the model. Overall, 192 scenarios were simulated with different origins of the VTs, cycle lengths of the VTs, lengths of the action potential, ATP protocols and timings of the first stimulus.

The simulation results show that the effectivity of an ATP protocol in terminating a VT strongly depends on the characteristics of the underlying VT.

Keywords: implantable cardioverter defibrillator, antitachycardia pacing, hybrid automaton, computer simulation

Introduction

Sudden cardiac death is responsible for 20% of all cases of death in industrialized countries. In 80% of these cases a coronary heart disease is present which, if left untreated, may likely lead to cardiac arrest. The probability of survival decreases by 10% every second, so an immediate defibrillation is vitally important. An implantable cardioverter defibrillator (ICD) is a common method to monitor and treat tachycardic events for the prevention of sudden cardiac death. [1, 2]

ICDs permit various therapy strategies. They try to terminate ventricular fibrillations with a defibrillation, which is a painful experience for the patient. Otherwise they are able to terminate a ventricular tachycardia (VT) with antitachycardia pacing (ATP). Untreated VTs can lead to ventricular defibrillation hence the ATP therapy is of great importance. ATP is completely painless for the patient and effective in 88%, preventing the patient from a defibrillation. [3]

The ADVANCE CRT-D trial demonstrated that different ATP configurations have a varying effectivity while treating VTs of various lengths [4]. The key question is the configuration for an individual patient. The more successful ATP is, the more painful defibrillations can be avoided and, as a consequence, the patient’s quality of life could be enhanced as well as the mortality and hospitalization rate could be decreased.

The purpose of this work was to develop a computer model of the individual patient’s left ventricle based on CT images in order to simulate numerous VTs and different ATP therapies to find the optimal parameter settings of the patient’s ICD device.

Methods

A three-dimensional hybrid automaton (HA) with a 3D Moore neighborhood and a cell size of 1 mm x 1 mm x 1 mm was implemented. The HA comprises background cells and four different types of myocardial cells: healthy cells, cells with a delayed conduction, cells with a delayed conduction and an elongated action potential and cells with no conduction. For modeling the action potentials of the myocardial cells the implementation of the Beeler-Reuter Model of the CESE framework [5] was used.

The model of the left ventricle was constructed from the patient’s CT images by employing the "Seeded Region Growing Tool" from ImageJ. The results were saved as TIFFs. An import tool was implemented to fill the HA with cells based on the TIFFs.

To generate a VT a reentry circuit was modeled according to Fig. 1. This reentry circuit represents a model of a scar caused by a myocardial infarction. By editing the length of the scar and the parameters of the cells the cycle length of the VTs could be adjusted. The scar was located one time near the apex and another time in the middle of the ventricle.

In the model the two electrodes of the ICD were located in the apex and in the middle of the free lateral septum. With the described model right ventricular (RV) and biventricular (BV) ATP protocols of type scan, ramp and scan+ramp were simulated. The ATP protocols comprised three bursts with five stimuli each and with burst cycle lengths (BCL) of 82% and 88%. Overall, 192 simulations and two series of 96 scenarios were executed: series 1 with the first stimulus when the apex was no longer absolutely refractory and series 2 with the first stimulus when the apex turned into the resting phase.

All VTs (cycle length: 408 ms, 340 ms and 288 ms) were simulated for a time period of 30 s to ensure they were sustained VTs. The ATP protocols were simulated for 8 s with a step size of 0,5 s. If there was no action potential after 7,5 s the ATP protocol terminated the VT.
Figure 1: Reentry circuit for the generation of the VTs successfully.

Results

On an AMD Phenom(tm) II X6 1090T Processor with 3.20 GHz, 8GB RAM one simulation lasted approximately 1 h.

Choice of the ATP protocol: In simulation series 1, with the early first stimulus, 33 VTs were terminated successfully. Scan was most effective with 15 terminations followed by ramp and scan+ramp with 9 terminations. In series 2, with a well-timed first stimulus, 72 VTs (27 scan+ramp, 26 ramp and 19 scan) were terminated. Summing up, scan RV (BCL 88%) with 12 terminations turned out to be the most successful ATP protocol.

Frequenz dependency: Disregarding VT 408 ms(1) which was designed to be difficult to be interrupted, in series 1 the effectivity was affected by the frequency. The shorter the cycle length was, the less ATP therapies were successful (13 terminations by 408 ms(1), 9 by 340 ms and 8 by 288 ms). In series 2, the ATP protocol’s effectivity was almost independent of the cycle length. Altogether, most VTs were terminated with a cycle length of 408 ms(1).

Location of the reentry circuit: VTs generated in the two different locations were terminated almost equally often. In some cases VTs originating from the two different locations with the same parametrization were terminated for one location only.

Influence of the BCL: Series 1 showed a significant difference in the ATP’s effectivity for a BCL of 82% (11 terminations) and a BCL of 88% (22 terminations). Series 2 showed also a higher effectivity for a BCL of 88% (58 terminations) compared to a BCL of 82% (47 terminations). The three most effective ATP protocols scan RV, ramp BV, and scan+ramp BV had a BCL of 88%.

RV versus BV: Overall, RV and BV ATP were equally effective. In series 1 the BV ATP led to poorer results if scan was used.

Discussion

A reentry circuits’ parameterization with almost similar cycle lengths of the reentry circuit and the myocardial cell revealed an interesting property: the more similar the paths of the reentry circuits were, the more difficult it was to generate or terminate the VT. VT 408 ms(1) was designed to demonstrate this property. On the other hand, the more diverse the paths were, the easier it was to generate or terminate a VT. ATP in series 1 was not nearly as effective as in series 2. The reason for this is, that in series 1, the first stimulus of the ATP protocol was poorly timed and, as a consequence, many stimuli encountered refractory cells. The finding that RV and BV were equally effective is in accordance with the results of the ADVANCE CRT-D trial. In summary, no ATP configuration prevailed. For circumscribed situations predictions could be made. The vision for the future is a model for the individual patient including information about location and size of the scar and the occurring VTs. With this model a variety of simulations are supposed to find the optimal ATP configuration for the patient’s device.

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Bibliography


Model-based Decision Support: Requirements and Future for its Application in Surgery

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Abstract: Making decisions in surgical planning and treatment becomes challenging given the increasing number and complexity of information entities to be considered (e.g. omics data, radiological images). Decision support systems are required that support in understanding and interpreting the data and allow for reproducible decisions of high quality. In this paper, we provide a vision of model-based surgical decision support systems. Such systems base upon a digital patient model that integrates all information entities relevant for an organ or disease. We will further collect requirements to be considered when developing digital patient models and model-based surgical decision support systems.

Keywords: Model-based Decision Support, Patient Modelling, Standardization

Introduction
The digital patient record consists of a large number of isolated data entries that are provided by various information systems and medical devices. Through the developments in medical image processing, genome and proteome analysis, even more complex data items become available for their consideration in diagnosis and treatment. Considering such complex information during surgical planning and treatment requires besides availability of the data, its aggregation and presentation in an understandable, clear and timely manner.

Clinical decision support systems aim at making the optimum use of patient data and are supposed to support in this process of information management and interpretation. They should lead to high percentages of appropriate treatment and reduce mortality and complications. However, such systems did not yet arrived sufficiently in clinical practice, since approaches often lack relationships to scientific evidence and are poorly integrated with clinician’s workflow [4]. Clinical decision support systems (CDS) often learn and predict from large sets of patient data using supervised machine learning. Other systems follow a rule-based approach. In the last years, the idea of model-based decision support came up [5]. Research and available systems following that approach are still limited, and for the complex domain of surgery completely missing.

The objective of this paper is to present the vision of model-based decision support in surgery, and to collect requirements and future issues to be addressed. We are summarizing the requirements after describing the main vision and ideas behind model-based decision support.

Methods
In surgical planning and treatment as well as in other clinical decision processes, a physician has to perform mainly two tasks: Assess the health status of a patient (situation assessment) and propose or decide for a therapy (decision making). A model-based decision support system supports these tasks. It bases upon two assumptions: 1) Medical knowledge can be modelled including diagnosis, treatment, and decision making processes, i.e. it can be formally described which parameter characterize a specific diagnosis or which steps are performed within a decision-making process. We refer to this medical knowledge as domain theory. 2) The observations made during physical or other clinical assessment of a patient can be described and instantiates the formal patient model. We refer to this by the term situation description.

The domain theory can be described in a structural model by structural elements (objects and relations between objects) and constraints on quantities (e.g. values, intervals). The specific state of a patient or organ (i.e. the situation) is described in terms of perceivable objects, their interrelationships and quantity value assignments (e.g. measurements).

Consider the following example: A decision support system for treatment decisions of Larynx carcinoma bases upon a structural model describing parameters to be considered in decision making (e.g. information entities such as age or extracapsular spread of lymph node metastasis). For each information entity (attribute) a value describing the normal state is assigned and also probabilities to what extent the entity contributes to the decision process. During situation assessment, the attributes of the model are instantiated with the measured data. A decision support system could use that information, and the structural model to predict the outcome for various treatment options.

In the following, we will concentrate on patient models for outcome prediction, surgical planning and treatment and describe requirements.

Results
Given the two tasks in surgical planning and treatment (see before), a model-based decision support system comprises two components: situation assessment component and therapy proposal or prognosis component. Within situation assessment, hypotheses are determined about the current situation based on the available data items, i.e. the observations. The therapy proposal
component determines which procedures need to be taken to achieve some defined treatment goal.

Situation assessment requires on the one hand information on the observations made, i.e. the patient data collected during examinations need to be available. Different kinds of data need to be considered, ranging from radiological images, to textual reports and omics data. A digital patient model is supposed to offer an integrated view on the information related to an organ or disease [1]. On the other hand, a structural model of (patho-) physiology needs to be available with which the observations made can be matched, i.e. observations made are linked to the information entities defined in the patient model. Each information entity in the digital patient model needs to provide a description of

- its semantic content (category of the image „X-Ray“, kind of procedure „X-ray of thorax“),
- the requestor and recipient of some the information entity,
- the temporal context (e.g. year, day, time of an examination),
- code and name of a procedure, underlying protocol and guideline,
- reasons for an examination.

Making data available requires methods for gathering the data from the various information systems, for fusing and integrating data of different type, and in particular to identify semantic links between information entities. In order to get an additional value from the data integrated in the patient model and also to identify links between information entities, methods for semantic analysis, text mining, information retrieval and knowledge management are required. Those technologies connect information entities automatically and make them available among others for automatic interpretation and reasoning purposes. For example, integration of functional and morphological image data can offer an additional value relevant for interpretation, e.g. by connecting image data with electrophysiological data acquired during the surgery with electric stimulation. Important questions in this context concern data storage and data representation. To enable automatic interpretation and re-use of data, data items need to be described in a standardized way, i.e. by ontologies.

The therapy proposal or prediction component bases upon a decision model, that contains for a concrete disease the possible treatments and information to what extent the single entities contribute to a specific decision. It also needs the patient model instantiated during the situation assessment stage. Before and after a surgery, decisions are made that require awareness of all relevant information on a patient and their disease. Methods for automatic reasoning and inference are necessary to build predictive patient models. They allow to make predictions on the course of disease given several treatment options. Mathematical models were already suggested for this purpose [3, 5]. Further, reasoning methods need to be robust against missing data and observations and should consider all relevant information. Another crucial aspect is to decide situation specific about the amount and kind of information to be considered in the decision support system: During a surgery, the time aspect is critical; therefore only a subset of relevant information can be considered. In contrast in therapy planning, all patient model information can be assessed since more time for data processing and interpretation is available. To suggest treatments, a system needs to be equipped with information on costs and benefits. Costs could comprise estimated risk of complications of some surgery or navigation path; benefit could be the increase of the survival rate.

To enable users to assess the proposals and predictions made by the system, appropriate visualisations need to be available. The variety of information entities that are stored in the patient model and that are considered in a decision process are often complex. The data needs to be prepared and visualized in a way that allows to quickly realise the dependencies. This includes preparing methods for managing the patient and decision model and verifying and adapting the models.

**Discussion**

Model-based decision support in surgery is still at the very beginning, but is crucial for ensuring quality of medical treatment; allow for simulation and training, support in research and development of new or improved therapies; optimizing decision making and therapy. This paper presented a vision of such decision support. A next step would be to work towards a digital patient model. A data structure and representation format needs to be established. A big problem is the distributed information in hospitals, where various information systems exist that contain relevant patient data. The problem of data gathering still exists and need to be addressed in order to be able to consider all relevant patient data in decision making processes.

**Bibliography**

WORKFLOW-SUPPORTED BIOSIGNAL INTEGRATION IN MULTIMODAL CLINICAL TRIALS

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Abstract: This work aims to describe the IT architecture of a multimodal clinical trial, in which workflow supported biosignal integration to several usually isolated IT systems had been implemented.

Keywords: Biosignals, Telemedicine, eHealth, Clinical Database, Clinical Trials

Introduction

In multimodal clinical trials various biosignals from different sources like medical devices or a telemonitoring system have to be collected and combined with information of case report forms. The INTENSE-HF study is one example for a clinical trial in which biosignal data acquired by patients and medical staff are integrated from different sources into one clinical database. The primary objective of the study is to determine the effectiveness of combined intervention of telemonitoring plus home visits of a heart failure nurse compared to a control group without telemonitoring. In this study, patients are equipped with a telemonitoring set and transmit their vital parameters every day. In addition, patients get visited once a month by a special trained mobile heart failure nurse. During the home visit, the nurse takes blood samples and the patient has to fill out questionnaires regarding his health status. Beside the main study, there is an electrocardiography (ECG)-substudy and a nourishment-substudy, where a body-impedance analysis (BIA) is being done. If the patient takes part in one of the substudies, the heart failure nurse also records the relevant biosignals during the home visit and the patient has to fill out questionnaires concerning his nourishment.

Aim of this work is to design and implement the IT architecture of the INTENSE-HF study and to support workflows that guide the user through the data-capturing and –integration process.

Methods

First we identified the processes and setup the IT subsystems that were involved in the clinical trial (Error! Reference source not found.). These are the telemonitoring-system [1], which is used by patients and physicians to integrate vital parameters, lab and medication data on a daily basis. The case report forms (CRF) for the study have been implemented with the electronic data capture (EDC) system OpenClinica [2]. In addition to the EDC, there is the questionnaire tool LimeSurvey [3], where patients and relatives fill out standardized questionnaires.

To capture biosignals the heart failure nurses have been equipped with tablet computers, a mobile ECG-device and a mobile BIA-device. The devices are connected to the tablet computer via universal serial bus (USB). A biosignal repository has been setup for archiving the ECG and BIA measurements and is implemented as subversion (SVN) repository. To alleviate the biosignal integration-process and ensure the correct integration in the biosignal repository, a workflow-supporting biosignal-integration-software has been implemented. We designed this software as a client/server application. The client part of the software is installed on the tablet computers and supports offline data capturing and automatic data synchronization with the server, if a network connection is available.

Pacemaker-data are manually integrated to the biosignal-repository from the cardiac rhythm management database HELGA [4] or the clinical information system. For intermediate data analysis, like recruitment statistics, we setup the reporting system Pentaho [5], which imports data from the IT subsystems and generates predefined reports.

Results

To alleviate registration of new subjects we implemented a web application, which guides the user through this multi-step-process of pseudonymization, randomization and registration of the subject in the involved subsystems. A pseudonymization web-service is used to generate a subject ID (SID) from the clinical information system ID (CIS ID).

For capturing biosignals with the tablet computers during home visits, the workflow-support-client system is used, which is able to control the ECG-recording software and also takes care about pseudonymization and uploading the captured signals to the biosignal-repository. The data integration process consists of the following steps:

1. Workflow-support-client synchronizes with EDC to retrieve subject and event list on a regular basis
2. User opens workflow-support-client on tablet computer to select subject and visit from list of subjects
3. Workflow-support-client reads meta-information about substudies of selected subject and displays dynamic graphical user interface based on the substudies in which the subject takes part and based on the particular visit:

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a. If ECG has to be done, the subject is automatically registered in ECG-software with SID
b. If BIA has to be done, the hyperlink for starting the BIA software gets rendered
c. If questionnaires have to be filled out, the hyperlinks for accessing these questionnaires are rendered

4. After finishing the necessary examinations, biosignals are uploaded if an internet connection is available
   a. If an ECG-Report was uploaded, a notification is send to the physician to review the ECG. The notification contains the hyperlink to the ECG-PDF-Report and the hyperlink to the subject/visit in the EDC system

Figure 1: IT-architecture of the INTENSE-HF study

Discussion

One of the challenges in a multimodal clinical trial is to find a trade-off between loose-coupled and tight-coupled systems, in order to support workflows within the clinical trial best. Not all subsystems have been integrated in the workflow-support-system, e.g. the randomizer, the tele-monitoring system and the BIA-software are just linked with the other systems by the SID, because effort for complete integration would have exceeded the benefits.

When integrating biosignals from various sources, there is the demand for a secure IT architecture which takes care of keeping identification attributes, performs identity management and connects healthcare data across several systems.

As for now the first patients of the INTENSE-HF study have been enrolled and the integration of their biosignals in our database is working as expected. Nevertheless, the workflow-support and usability of the IT-system have to be evaluated during the course of the study.

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Bibliography


AN EXPERIMENTAL SETUP FOR INSTRUMENTAL ANALYSIS OF FEMORAL DEROTATION OSTEOTOMY

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Abstract: Femoral derotation osteotomy (FDO) is an established surgical procedure to recover physiological gait of patients with torsional bony malalignment. Yet in many cases, therapeutic outcome after functional rehabilitation is well behind expectations. Our investigations have revealed methodical problems of the procedure leading to significant measurement bias and poorly reproducible surgical results. Targeting to improve outcome quality, we developed a prototype system to quantify anatomically relevant parameters in FDO using a bone phantom. Using electromagnetic tracking and geometric reconstruction, we achieved accurate and precise measurement of anatomically relevant parameters. Considerations for intraoperative application promise a successful implementation into a CAS system.

Keywords: computer model, gait, osteotomy, femur, electromagnetic tracking, measurement, CAS

Introduction

Patients with torsional bony malalignment showing gait abnormalities usually receive surgical treatment to recover physiological gait. In specialized centers, these procedures are preceded by sophisticated diagnostics utilizing instrumental 3D gait analysis. An important surgical standard procedure to treat outwards rotated gait is the femoral derotation osteotomy, which readjusts the hip joint angle. The distal femoral bone is cut through and the lower segment is rotated by the diagnostically specified angle around the bone shaft axis. Finally the segments are mechanically fixed with a support plate. To keep track of the rotation, two parallel K-wires are drilled into the bone above and below the cutting location. The adjusted rotation angle is measured by the surgeon using a Moeltgen goniometer to read the angle enclosed by the K-wires [1]. Therapeutic success monitored after one year often falls well behind expectations, not leading to functional improvement for a significant number of patients. The estimated error of adjustment ranges from 10 to 20 degrees. Furthermore a systematic loss of functional correction is evident [2].

Our preliminary research on possible causes of error by means of computer simulation revealed methodical problems of the procedure that potentially lead to either a false estimation of the adjustment or leave functionally relevant side effects on the leg anatomy out of consideration. Results indicate that unwanted tilt of the (ideally perpendicular) cut plane and manual angle readings from a variable and inconvenient point of view have the most significant impact on surgical results. We concluded that supporting the intervention with accurate measurement devices is essential to improve the quality of femoral derotation osteotomy. This work investigates the simulation results in a real world scenario with the aid of a tracking system, aiming to provide a prototype measurement setup for intraoperative usage in a CAS system.

Methods

In order to accomplish our objective, we developed a data acquisition system and protocol to take and record measurements from bone phantoms specifically modified for the purpose of femoral derotation (fig. 1). Considering intraoperative application in a future stage, we chose an NDI Aurora electromagnetic (EM) tracking system to acquire accurate 6-DoF data samples. Small sensors and easy mountability proved suitable for the constrained accessibility of the area of operation. Precautions were taken to avoid electromagnetic induction in the working environment.
volume that may interfere with the measurement. Offline analysis was subsequently accomplished in Matlab to reconstruct anatomically relevant parameters such as adjusted rotation angle, displacement of the distal bone segment, etc.

**Execution**

Prior to data acquisition, the sensors are mounted to the k-wires. The exposed bone surface in between is then sampled sparsely with the pointer-tool. By taking additional samples along the boundary of the cut plane, its (often oblique) orientation is characterized. After derotational adjustment of the distal segment, the separated bone segments are screwed tightly together to fix them. The initial and final positions and orientations of the sensors are recorded by the measuring system.

**Analysis**

Using numerical optimization, the bone shaft axis is reconstructed. An initial approximation of the shaft orientation is obtained by principal component analysis of the surface samples. Femoral cross sections change shape and size along the shaft, rendering the reconstruction nontrivial. By grouping the sampling points into a number of equally spaced segments along the shaft and then projecting them onto (virtual) planes perpendicular to the shaft, a center point is determined for each segment (Fig. 2). A subdivision into 4 to 6 segments delivers best results while retaining enough samples per segment. The bone shaft axis is finally fitted to the calculated center points. Knowing its exact orientation is of central importance for further parameter reconstruction. Including the orientation of the cut plane, calculation of the rotational axis, tilt and displacement of the knee segment is possible. The resulting adjustment angle is defined by the effective enclosed displacement of the knee segment along the bone shaft axis relative to its initial magnitude prior to adjustment.

Validation of the results is performed by comparing the computed adjustment to an analog angle scale on the experimental setup (see Fig. 1) and simulated results from our computer model.

![Fig. 2: Reconstruction of bone shaft axis](image)

**Results**

Our approach to quantify anatomically relevant parameters in femoral derotation osteotomy by means of a measurement system and geometric reconstruction has shown promising results: We achieved an accurate and precise characterization of the anatomical modifications applied to the bone phantom.

While constraining the measurement locations to the intraoperatively accessible area of operation, reconstructing the adjustment angle was possible for several typical configurations of cut plane, k-wire placement and extends of rotation up to the clinically reasonable maximum of 30°. Deviations to the analog scale remained within 1°, indicating a valid reconstruction of the bone shaft axis. Displacement of the knee joint was observed to behave according to simulation, shifting out of the bone shaft axis by up to 15 mm in cases of large adjustment angles and tilts of the cut plane nearby 15°.

Preliminary simulation has shown that surgeons may overestimate the adjustment angle by up to 7° solely due to measurement inaccuracy, which may be further compromised by high observer bias of the manual reading. The complete process of sensor attachment, measurement execution and recording took 5 minutes on average, with the rigid attachment of the sensors to the k-wires consuming the largest amount of time.

Analysis of the measurement data is available almost instantly after import into Matlab, yet relying on a complete dataset which does not permit real time computation during execution.

**Discussion**

The presented prototype measurement setup has shown to provide objective and valid results in a laboratory environment. Due to its considerate design, it can easily complement the established surgical procedure without major modifications or higher invasiveness.

Intraoperative application, however, requires further development to address limitations of the current setup: High reliability and sufficient accuracy of electromagnetic tracking needs to be guaranteed under surgical conditions with several metal tools involved. This has already been successfully achieved in other surgical domains by suitable calibration methods [3]. Also, additional sensors may be required to allow for passive movement of the patient’s leg.

The available, cubic tracking volume with an edge length of 40 cm leaves little margin for movement or tall patients. Beyond that, a just in time analysis of acquired data is required to provide feedback to the surgeon during execution.

**Bibliography**


A HEALTHCARE SUPPLY CHAIN SOLUTION FOR DENTAL PURPOSES

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Abstract: This paper introduces a Supply Chain Platform to improve the process quality and reducing the costs in dentistry. The platform supports the dental based processes and provides the deployment of specific workflows rested on a generic workflow process.

Keywords: DI-GI-DENT, healthcare supply chain, dentistry, dental platform

Introduction

In dentistry the conventional manufacturing is not yet fully replaced by the CAD/CAM technology. As a consequence, the manual manufacturing process for dental prosthesis is very imprecisely and costly in this case [1][2]. This leads to a lack of wearing comfort and high prices for the patient. Furthermore the quality problems decrease the lifespan of the denture.

Nevertheless if the CAD/CAM technology is used in the dentistry industry especially the reverse engineering process is reviewed; see [3], [4], [5]. The data and workflow process is only partly supported. In this field exists a variety of export format and interfaces. A successfully production of artificial teeth needs a defined healthcare supply chain to define the interfaces and combine isolated applications. The objective is to reduce the manufacturing time, the resources and to increase the quality of a therapy [6]. This supply chain has to include the dental site, like CAD/CAM models or dental data, and the logistic site, like job data, material data, expenses or other important information beyond the medical data.

This abstract describes a healthcare supply chain solution for dental purposes called DDI Healthcare Supply Chain. The approach becomes developed in the project “Erforschung und Entwicklung einer integrierten, digitalen Versorgungskette für dezentral verteilte Diagnostik-, Therapie- Wertschöpfungs-Logistikprozesse in der Dentalmedizin (DI-GI-DENT)”.

DDI Healthcare Supply Chain

In healthcare, supply chain management is a relative new topic, because most people think that the National Health Service and the industry are not comparable and therefore the solutions are not usable. But in [7] it is shown that there exist high potential. In dentistry such an approach is not yet examined.

To develop an efficient supply chain we analysed the process steps of every associate in the manufacturing process of dentures. It has been shown that the conventional process between the parties is unstructured, i.e. it is not always clear which data are needed. The results helped to describe interfaces and form workflows. In some cases a process step like “scan the dentition” can be done by the dentist or the laboratory because they could work close together. This means that every step has to be independent by the institution. Not every defined step hast to be completed in the process chain. To make this generic and partly reusable every step in the supply chain needs input and output data (except for the first step) with a defined (but extensible) data type (figure 1). With a generic workflow it possible to model i.e. manufacturing or service processes.

Figure 1: Process step chain

Scenario

A typical procedure starts by the dentist, see figure 2. He looks at a patient and makes the diagnosis. Then he forms a therapeutic and cost schedule. If the patient is willing to get a dental prosthesis, the dentist creates a new job and releases it on the platform. The doctor can choose different tasks like scanning the teeth or manufacture the den-
ture. The tasks are defined in a workflow and differ for every workflow.

After the publication dental labs search for jobs or provide the tasks: scanning the teeth, building a digital model and manufacturing the prosthesis. The dentist grants a lab to do the business and commit the relevant patient data for the first process step. Then the lab scans the teeth and models the denture. If the dental lab is not able to produce the denture the workflow step can be released again over the platform. The procedure is the same as for the dentist. The lab delegates the manufacturing process to a milling center. Therefore the dental lab provides CAM data.

After production the milling center reports to the laboratory and the lab notifies the dentist over the DI-GI-DENT platform.

Figure 2: DDI Healthcare Supply Chain Scenario

Results

This paper introduces a healthcare supply chain platform for the dentistry. With this platform it is possible to choose the best contractor or request a contractor directly. The consideration of the associates builds a generic and modular process workflow. Important is that every workflow process has defined input and output data. With this condition it is simple to add new workflows for different platform users. This leads to a time efficient and cost reducing manufacturing process.

Discussion

It is shown that an optimized medical process is able to reduce costs, increase the reliability for value, quality and time. The support of such a process is done by the platform, but it is not defined how the semantic can be provided. This point needs to be focused in further studies and has to be an extension for the platform.

Except for the semantic integration, the platform offers a high potential to reduce costs and increase process quality for companies in the dental industry, because it is a new consideration in healthcare.

Bibliography

REGULATORY GENOMICS – DECODING DROSOPHILA
REGULATORY SEQUENCES

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Abstract: The precise regulation of gene expression is crucial for all animals. The regulatory information about when and where genes are to be expressed is located in defined genomic elements called enhancers that are able to activate gene expression in precise spatial and temporal patterns. We have developed a novel method to find such enhancers and measure their activity quantitatively across entire genomes. This allows us to trace enhancer activity across evolution and study its sequence basis.

Keywords: transcriptional regulation, enhancers, genomics, computational biology, transcription factors & motifs

Introduction

In higher eukaryotes, genes are expressed dynamically in complex spatial and temporal patterns, which are progressively refined to set up body plans and define specific cell-types.

Transcriptional regulatory information is encoded in enhancers, discrete regions within the non-coding part of the genome. As enhancers lie at variable positions within and around genes their discovery has been challenging and only relatively few enhancers has been described and functionally characterized.

Methods

As methods to identify transcriptional enhancers genome-wide based on their activity have been lacking, we developed STARR-seq (self-transcribing active regulatory region sequencing, [1]). In STARR-seq, candidate sequences are positioned downstream of a minimal or core promoter such that sequences with enhancer activity transcribe themselves and enhancer activity is reflected by the sequences’ presence among cellular RNA. This allows the quantification of enhancer activity for millions of candidate sequences from arbitrary sources of input DNA and enables screens across entire genomes.

We applied STARR-seq to the Drosophila melanogaster genome in two different Drosophila cell lines and to a 1 megabase (Mb) region of the human genome in human HeLa cells.

Results

Applied to two Drosophila cell-types, STARR-seq reveals thousands of enhancers with cell-type specific activity across a wide range of strengths. Surprisingly, about one third of the enhancers lie in inaccessible chromatin and are marked by H3K27me3, suggesting that their endogenous loci are silenced or correspond to a poised enhancer state – even though such enhancers function in luciferase assays using ectopic or genomically integrated reporters.

STARR-seq reveals a surprising complexity of gene regulation with several independently functioning enhancers for single genes, including both developmental regulators (e.g. transcription factors) and broadly expressed genes such as actin. Similarly, the genome-wide strongest enhancers are located near both functional classes of genes.

Using STARR-seq, we are screening the genomes of five closely related Drosophila species in Drosophila melanogaster S2 cells to trace cis-regulatory function across evolution in a constant trans-regulatory environment. This will allow us to assess conservation of enhancer function in orthologous sequences as well as the number of enhancers that emerged de novo since the D. melanogaster and yakuba split about 10 million years ago.

Finally, we compare the sequences of enhancers with similar and different activities across different cell-types and tissues to determine regulatory motifs that are shared in functionally related sequences and are required for regulatory function.

Discussion

STARR-seq will be widely applicable to screen DNA from arbitrary sources in any cell-type of interest. This includes human HeLa cells, for which we demonstrated that STARR-seq detects enhancers that function in classical luciferase assays independent of their chromatin states and thus more reliably than previous methods.

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Bibliography

A CLINICAL METABOLOMICS STRATEGY TO DISCOVER NEW BIOMARKERS IN COMPLEX DISEASE: AN OVERVIEW

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Abstract: In clinical metabolomics biomarker discovery is conducted by the complementary power of clinical study design and execution, molecular profiling technologies and an efficient bioinformatics strategy for biomarker search, verification and interpretation. This survey article gives a review of useful bioinformatics methods for biomarker discovery, addressing the problem of data preprocessing, the data-driven search, prioritization and biological interpretation of metabolic biomarkers candidates in disease. Advanced data mining approaches and new strategies using network-based methods are discussed in more detail.

Keywords: Biomarker discovery, metabolomics, bioinformatics, complex disease

Introduction

Rapid progress in high-throughput technologies such as next generation sequencing or MS-based profiling techniques like GC or LC-MS/MS and in the development of related bioinformatics methods allow the systemic analysis and characterization of alterations in genes, proteins and metabolites. These technologies offer a broad spectrum of approaches to discover novel biomarkers and pathways activated in complex diseases. Since clinically relevant biomarkers are still lacking for aiding in diagnosis, disease screening or treatment, the complementary power of modern profiling techniques and powerful bioinformatics tools is applied for the discovery of new biomarker candidates. This large interest in biomarker discovery originates from their broad range of clinical applications and their fundamental impact on pharmaceutical industry [1].

In this contribution, emerging bioinformatics methods for biomarker discovery in metabolomics, i.e. the systematic search of low molecular weight biochemical compounds in complex biological mixtures, their selection and application to the problem of identifying, prioritizing, interpreting and validating metabolic biomarkers suitable for the clinical application are discussed.

Methods

In general, human biomarker discovery studies comprise a variety of experimental designs, including most frequently used retrospective case-control or more complex cohort study designs such as crossover or serial sampling designs. Latter, so-called longitudinal cohort studies allow patients to serve as their own biological control, which enable to study thoroughly the kinetics of circulating analytes by reducing the interindividual variability observed in multiple cohort studies. In metabolomic biomarker discovery bioinformatics plays a major role because this process is highly data-driven and, thus, constitutes the missing link between the initial discovery phases including experimental design, study execution and bioanalytics (i.e. sample preparation, separation and high-throughput profiling) and the search, verification and independent validation of biomarker candidates (see Figure 1).

Once sample collection, preparation, separation and MS analysis have been carried out, technical reviewing of generated data is essential to ensure a high degree of completeness, consistency and reproducibility. Data preprocessing is an additional necessary step to transform data into a format suitable for subsequent targeted analyses. This includes tasks such as data transformation and normalization, data sampling and outlier detection [2]. A pool of statistical bioinformatics methods is nowadays available for identifying, prioritizing and classifying robust and generalizable biomarker candidates, showing a high predictive value in terms of sensitivity and specificity. In general, data analysis tasks for the search of biomarker candidates in experimental data are “supervised” because study cohorts are typically well-phenotyped in carefully designed and controlled clinical trials. Commonly used supervised data mining methods for the search and prioritization of biomarker candidates in both, independent and dependent samples, include paired/unpaired null hypothesis testing, principal component analysis (PCA), uni- and multivariate feature selection methods.
such as the information gain, reliefF, associative voting, the biomarker identifier, guilt-by-association feature selection, repeated measure analysis as well as more advanced methods like embedded or ensemble-based techniques (e.g., support vector machine recursive feature elimination, stacked feature ranking or the wrapper approach) [2]. Very recently, we proposed a prioritization model for classifying metabolic biomarker candidates according to their discriminatory ability by coupling a feature selection modality with a network-based approach to review and interpret major hubs (key metabolites) and their interactions and correlations in the network. In particular, the quantitative analysis of networks has become a novel technique for the biological and biochemical interpretation of alterations in disease-associated pathways. Therein, different types of topological graph descriptors, e.g., parametric or partition-based entropy measures are suggested to be used for analyzing such complex metabolic networks [3]. Generalizability and validation of biomarker candidates is a crucial step of the entire biomarker discovery process. Objective measures to assess the discriminatory or predictive value and the generalizable power of identified biomarker candidates are sensitivity and specificity or the area under the receiver operating curve (AUC). In longitudinal time series studies, alternative measures can be used to assess the predictive value of biomarkers in a similar manner, as described in [4]. In general, identified biomarker candidates need to be validated using larger sample sets, covering a more comprehensive cross-section of patients or populations. If such data is unavailable or impossible to collect, computational cross-validation strategies can be performed to assess generalizability on a single cohort. Usually, stratified n-fold cross-validation, bootstrapping or permutation analysis can be applied to overcome this problem. Nevertheless, prospective clinical studies are finally needed to verify and validate the clinical benefit of the selected panel of biomarker candidates before they can be applied to clinical applications.

A challenging discovery step is the biological and biochemical interpretation of putative metabolic biomarker candidates. In metabolomics, pathway mining tools are usually used to map, visualize and reconstruct a list of possible pathways by extracting metabolic information from network databases like KEGG. Such tools allow a direct functional annotation of metabolites, enzymes or reactions related to experimental findings. Hyperlinks to comprehensive databases such as OMIM or Swiss-Prot bring forth supplementary information about the underlying biochemical and biological mechanisms.

Applications

In a recent longitudinal biomarker cohort study we were able to identify, categorize, and profile kinetic patterns of early metabolic biomarkers of myocardial infarction using a bioinformatic-driven discovery strategy as described above. A panel of new metabolic signatures could be identified that appears as early as 10 minutes after the event. Some of them are promising candidates that may be useful in developing future diagnostic tests [4]. A new computational approach by coupling a generic search and prioritization strategy with a network-based approach was performed for profiling the human response to physical exercise. In this study a group of known, but also unexpected metabolic signatures were identified by studying the analyte kinetics at rest versus stress [3]. Figure 2 demonstrates figuratively this two step discovery strategy.

Figure 2: Coupled network-based computational strategy for biomarker search, prioritization and interpretation in time series data. The pBI feature selection algorithm preselects major metabolites, which are subsequently used for inferring a kinetic network for studying metabolite interactions.

Conclusion

Major interest in metabolomics biomarker discovery studies originates from their broad range of medical applications - as clinically validated biomarkers can aid in diagnosis and disease prediction or serve as indicators of treatment efficiency, their impact on pharmaceutical industry and the public health system. Therein, bioinformatics is an essential tool for the biomarker search, bridging the gap between complex raw data generated by MS analysis and the data-driven search and verification of new biomarkers and pathways associated with disease.

Bibliography