

ABSTRACT

# Patient-specific modelling & bioinformatics in PPPM

## PATIENT SPECIFIC MODELLING AND MODEL GUIDED THERAPY

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A Therapy Imaging and Model Management System (TIMMS) is an information technology (IT) concept and framework for the collection, organization, and utilization of medical information from sources such as the Electronic Medical Record (EMR), PACS, etc. TIMMS was originally designed as a surgical assist system, but has many general medical uses as well, including all forms of Model-Guided Medicine and may therefore be generalized to a medical information and model management system [1].

Functionally, a TIMMS provides the following functionalities throughout the course of medical or therapeutic

treatment (by means of interconnected engines, agents, repositories, and IT infrastructure) (Fig. 1):

- a) Creation and maintenance of a Patient-Specific Model, thereby providing a multi-scalar, comprehensive, precise, personalized representation of the patient,
- b) Real-time knowledge management and decision support system thereby promoting optimized diagnostic, prognostic and therapeutic decisions throughout the treatment workflow,
- c) Validation system thereby providing quality assurance, patient safety, system security and processing of medical evidence, and
- d) Standardized interfaces for communication and mechatronics, thereby creating a unified environment for the input and output of data (including the representation and display of information and images, as well as the electromechanical control of interventional and navigational devices).

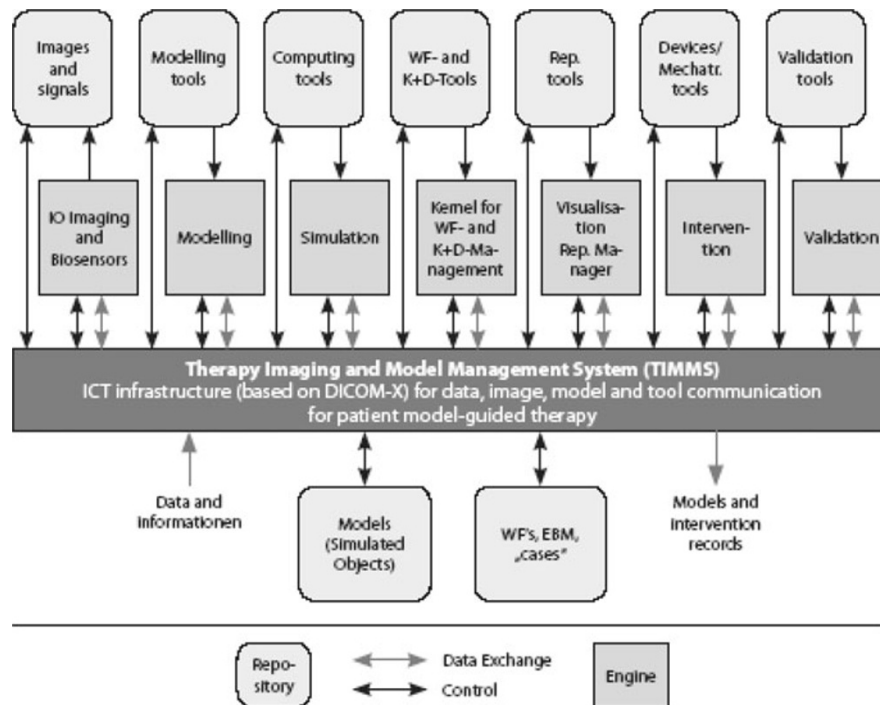


Fig. 1 TIMMS IT Reference Architecture (WF: workflow, EBM: evidence based medicine)

The Patient-Specific Model (PSM) is the central construct for a patient within a personalized medicine environment, in order to provide a clinician with a real-time representation of critical information about the patient. The data of the Patient-Specific Model reside within a Probabilistic Patient-Specific Database (PPD) [2]. The fields of the database consist of

- absolute patient attributes such as name, medical record number, etc.,
- descriptive patient attributes, such as medical images; graphical physiological information, such as ECG or EEG; physiological values within expected value ranges; results of biochemical and biomedical modeling, in the form of results of equations; pathological findings, etc.; and,
- probabilistic patient attributes, such as probability of tumor response to treatment, which are expressed in terms of probability and confidence level; conditional tables; etc.

A multi entity Bayesian network (MEBN) allows the graphing of an unlimited number of relationships between the fields within the PPD. Real-time function of a Patient-Specific Model will require the development or modification of a new form of database: a probabilistic database which will allow the utilization of probabilistic data structure, which will incorporate a database design and a database management system which allows probabilistic database functions and storage capabilities.

A probabilistic database is a database representing uncertainties in which the possible worlds have associated probabilities. Probabilistic database management systems

are an active area of research. While there are currently no commercial probabilistic database systems, several research prototypes exist [2].

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## MEDICAL AND INFORMATION TECHNOLOGY ASPECTS FOR PERSONALISED MEDICINE

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The individualization of medicine and healthcare appears to be following a general societal trend [1]. The terms “personalised medicine” and “personal health” are used to describe this process. It must be emphasised, however, that personalised medicine is not limited to pharmacogenomics as it is sometimes defined [2], but that the spectrum of methods and tools for personalised medicine is much broader, see Fig 1.

Applications range from individualised diagnostics, patient-specific pharmacological therapy, therapy with individual prostheses and implants, Fig. 2, to therapy approaches using autologous cells, and from patient model-based

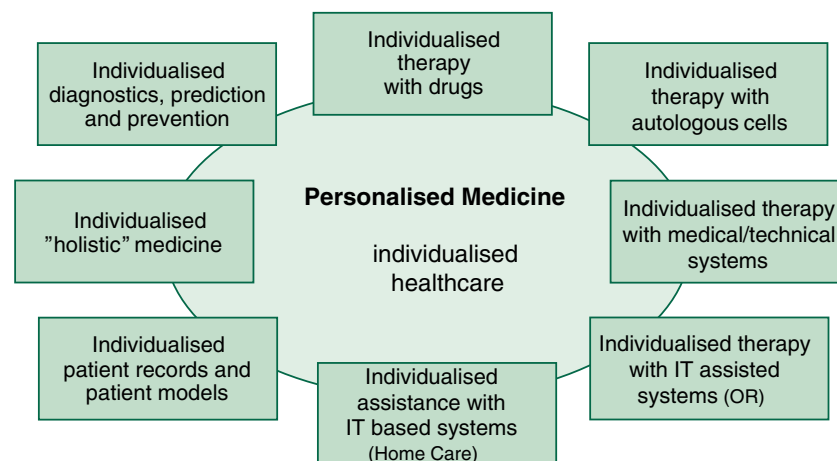


Fig. 1. Spectrum of methods and tools for personalised medicine

therapy in the operating room, Fig 3, including electronic patient records [3] to the individual care of patients in their

home environment [4] with the use of technical systems and services.

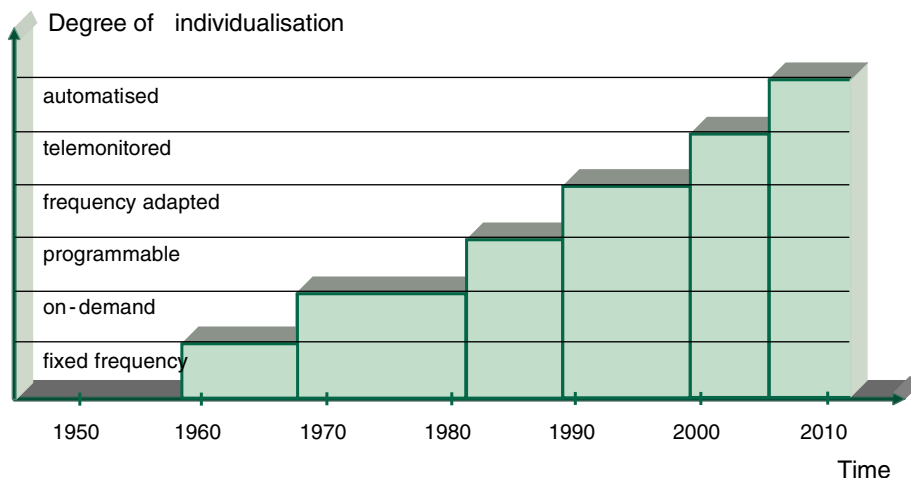


Fig. 2. Individualisation of active implant: example heart pace maker

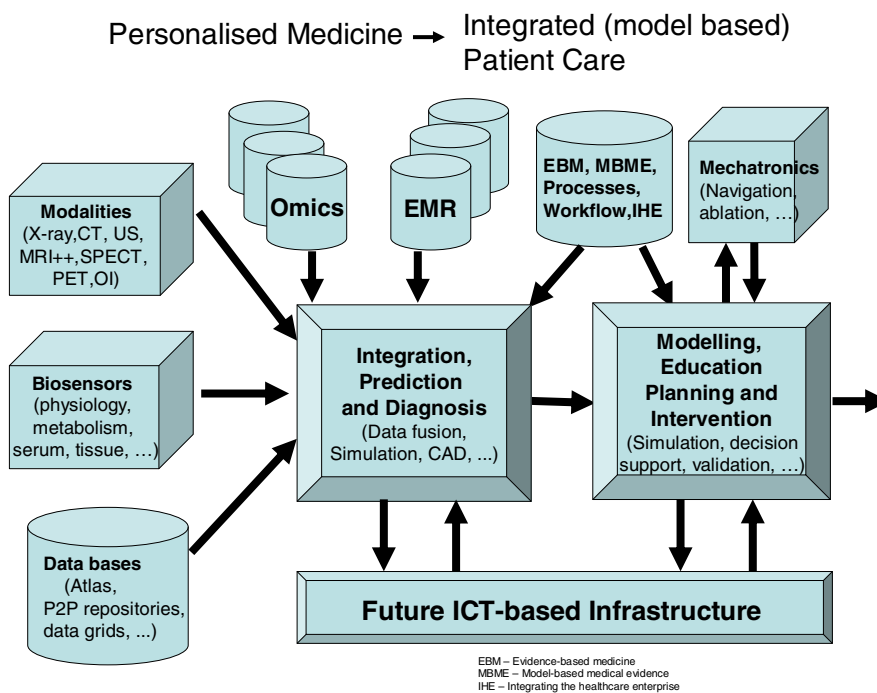


Fig. 3. Patient specific modelling for a model based medicine

Although in some areas practical solutions have already been developed, most applications will not have fully evolved for many years to come. Medical and information technologies are essential to personalised medicine and personal health. The syner-

gy of these two technologies provides the basis for most tools and systems employed in individualised medicine. Based on an overview on methods and tools and the general application fields of personalised medicine [5], the potential

beneficial applications of ICT in personalised medicine are exemplified in this paper.

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## COMPUTER-ASSISTED MODELING OF OCULAR PARAMETERS FOR PERSONALIZED TREATMENT IN OPHTHALMOLOGY

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The refractive surgery is well established treatment of various vision lesions. In spite of tremendous technological developments, not always the results are satisfactory. Computer-assisted modeling of ocular parameters can be used to estimate results of refractive surgery. Laser in situ keratomileusis (LASIK) is the most widely used ophthalmic surgical technique to correct refractive errors. The technique is mainly used to treat myopia, hyperopia and astigmatism. The goal of refractive surgery is to reduce the refractive error and correct vision. Even though LASIK outcomes are usually quite satisfactory, complications like uncompensated refractive errors, visual aberrations or irregular astigmatism may occur. Usually, before the procedure refractive error, ocular astigmatism, corneal topography and central corneal thickness of the eye, are measured. However, the surgery is usually based on general, averaged statistical data from wider population. Individual features of human eyes such as rigidity of ocular tissues can also influence the surgery outcomes. Therefore some uncompensated refractive errors may occur after LASIK procedure.

Development of numerical analysis methods creates possibility to individualize LASIK procedure. Finite elements method was used to analyze the influence of individual corneal properties on the effect of LASIK surgery. Corneal geometry including radii and pachymetry, as well as biomechanical properties of the tissue were taken into account during modeling. The photoablation process cause changes in geometry of the anterior corneal surface and the corneal thickness. However, medical procedures do not consider the influence of intraocular pressure (IOP) on geometry of postoperated cornea. Our calculations predict how different values of IOP influence the geometry of corneal surface before and after LASIK. Nonlinear stress-strain characteristics of cornea were taking to account. In the physiological range of the intraocular pressure (10–20 mmHg), a linear relationship between IOP value and the cornea displacement was found. For modeling of the optical properties of human eye, the software ZEMAX® was applied. Quality of retinal image was assessed for modeling of the individualized eye before and after LASIK. Spot-diagrams and optical transfer functions (OTFs) were analyzed, as well. Combining mechanical and optical modeling of human eye may lead to better understanding of the relations existing between IOP, corneal geometry and rigidity, as well as retinal image quality. Our investigation can help to improve process of planning LASIK surgery. Taking into the consideration individual properties of human eye, it may help minimize postoperative refractive errors.

## MEANINGFUL USE OF PATIENT-CENTRIC HEALTH RECORDS FOR PERSONALIZED MEDICINE

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The success of personalized medicine (PM) for the care of a patient is dependent on effective use of PM knowledge (e.g., pharmacogenomic interpretation of somatic mutations in tumor tissues) while considering the full-blown description of the patient's past medical history (e.g., existing mutations associated with observed responsiveness to certain drugs). In order for PM knowledge to be effectively applied to the patient medical records, the latter needs to be as rich as possible and more importantly, semantics of medical data should be made explicit and machine-processable [1]. Often, semantics of research & clinical data is represented implicitly, and is hidden in unstructured and disconnected descriptions of the data or just in the heads of human experts (researchers and caregivers). Meaningful semantics includes rich metadata, i.e., the predefined structure of data in medical records. In addition, it is extremely important to explicitly represent the patient-specific context of each discrete data item and how it

relates to other data items, as well as how it fits within the entire health history of an individual. Dispersed and disparate medical records of a patient are often inconsistent and incoherent. A patient-centric longitudinal electronic health record (EHR) based on international standards (e.g., CEN EHR 13606 [2]) could provide coherent and explicit representation of the data semantics. New PM evidences generated by clinical research and validated in clinical trials should be represented in alignment with clinical data representations in a way that lends itself to personalized medicine realization. A constantly growing stream of raw data is available today in both research and clinical environments, e.g., DNA sequences along with rare variants in research and sensor data along with personal alerts in healthcare. The representation of such raw data should adhere as much as possible to common and agreed-upon reference models (e.g., HL7/ISO RIM – Reference Information Model [3]) so that, for example, any observation is represented in the same way in terms of its attributes such as id, timing, code, value, method and status, as well as standard representation of clinical statements (e.g., observation of gall bladder acute inflammation indicated procedure of cholecystectomy or EGFR variations cause resistance to Gefitinib), where implicit semantics can become explicit and thus processable by decision support applications.

A patient-centric EHR could span across the individual's lifetime but is practically nonexistent today because none of the existing stakeholders in the health world (i.e., healthcare providers, insurers, government agencies and the patients) can sustain such an information entity due to lack of information technologies expertise as well as conflict of interests. The inevitable solution is for healthcare providers to stop being the legal record keepers and let new entities (independent health record banks - IHRB) be the sole health record keepers, sustaining a single EHR for an individual no matter where this individual has been treated. There should be multiple and competing IHRBs that will be regulated by new legislation that shifts the obligation of medical record keeping from healthcare providers to IHRBs [4].

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## INTERPRETATION OF LABORATORY RESULTS IN THE COMPLEX PREDICTIVE DIAGNOSTICS: STATUS QUO AND PERSPECTIVES

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Predictive, preventive and personalised medicine (PPPM) has emerged as the advanced concept for the medicine of the 21st century and it receives widespread international acceptance. The information gathered in the healthcare and related fields becomes more complex than any time in the history of medicine, and it is expected to encompass even more data thanks to the “omics” fields, complemented by the data on the nutrition components, herbal components, medical drugs, and the data on the particular interrelations between all the components. Continually increasing complexity of medical information in healthcare together with the rising impact of the PPPM clearly catalyses closer cooperation between medicine, informatics, mathematics, software engineering, communication technology, statistics, complexity science, linguistics, ethics and other the related fields.

Due to the amount of the relevant medical data on the particular patient produced in the process of the analysis of the patient's biological material, the role of laboratory diagnostics in the PPPM is fundamental and it is potentiated by the latest information technology which must be actively engaged in the process of computer assisted diagnostics, decision making, data and knowledge mining, text mining, knowledge semantics and knowledge structuring, model-based prediction, individual prevention and treatment suggestions. More active assistance in data processing is essentially needed in the preanalytical and postanalytical phases, both of which are vital for the reliable result interpretation in the laboratory diagnostics. By complex analysing of the patient's results and related data, the computers should be able to offer “second opinion”, based on the relevant knowledge traceable in the scientific literature and the referential knowledge bases. In the future, we should have functional interactive models for an individual patient's health, allowing us to predict potential health problems under diverse model situations.

The active processing of complex information in healthcare and life sciences is crucial and provides reliable knowledge for understanding the complexity of interactions among all components of an individual human body, thus facilitating the potential for plausible predictions, prevention and

consequent medical decisions related to the individual patient. Any potential success in this respect, on the other hand, brings considerable ethical questions we have to solve, prior to ever taking the “wrong path”.

The investigation of the predictive and preventive potential of the new tools in *in-vitro* and *in-vivo* diagnostics, and consequent evaluation and implementation of these tools in the daily healthcare, must progress in concert with *in-silico* diagnostics - active computer processing of acquired analytical data, patient profile data, medical information and other related data in order to suggest reliable prediction for the benefit of the patient, or better say for the benefit of an individual person who, thanks to the prediction and preventive actions, may, hopefully, avoid the state of being called “a patient”.

### **MULTILEVEL, MULTISOURCE BIO- MEDICAL RULE DISCOVERY SYSTEM – ESSENTIAL ENABLER TO PREVENTIVE, PREDICTIVE AND PERSONALIZED MEDICINE**

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The revolutionary trends in scientific research in general, and Bio-Medical research in particular, have provided new and profound insights into multiple levels and various degrees of sensitivity to the human body functioning in its surroundings. Newly developed invasive and non-invasive tools based on “**converging technologies**” and the capturing of massive amounts of information have created a crucial need for advanced, innovative and specially tailored analysis tools. That is in order to utilize all available knowledge and translate it into the optimum practice of **preventive, predictive & personalized medicine**.

The analytical tools that coincided with a spectacular progress in the quality and accuracy of health care must adjust, for example, to the unexpected predominance of chronic degenerative disease characterized by high complexity, non-linearity, etc.

New philosophical approach as well as new innovative analysis tools specially developed to meet these needs has to be taken. The goal is to enable the “whole approach” - a **simultaneous systematic analysis** providing the broad insight on various phenomena in order to reveal the underlying rules. The coupling of computer sciences, complexity theory, non linear dynamics and logic theory lead to the development of learning machine that extract the underlying rules and thus facilitates prediction that improves its accuracy while in usage.

A new Data Mining rule discovery tool was specially developed to meet these goals and the above mentioned

needs and constrains in Bio-Medical applications. The tool enables simultaneous analysis of multilevel, multi-source data (images, numeric, signals, categorical, descriptive data, etc) while relating to the whole data set as is – which is crucial to the “whole system” approach. Further more it minimizes over- fitting, usually a major barrier - small data sets with many parameters.

Following these constrains the patented algorithm is proven to reveal:

- All *If Than* tools and all *If than Not* tools that meets the predefined threshold
- An optimal subset of *If and Only If* (necessary and sufficient conditions)
- A subset of *If and Only If Not* rules utilized as a screening tool to identify specific targets.
- A set of unexpected rules and cases.

The tool was already applied successfully to autoimmune diseases, degenerative diseases, ethnic group analysis as well as structural biology, drug development, personalized skin treatment, drug penetration, neuronal biomarkers, etc. In Alzheimer patients, for example, the tool enables combined analysis of imaging data, signals, numerical and categorical data (laboratory tests) descriptive data (patient history), etc.

A special example of the Cerebellar conditioning modelling was applied providing insight into the learning mechanism - “BCI accelerates learning by timing the delivery of stimuli”.

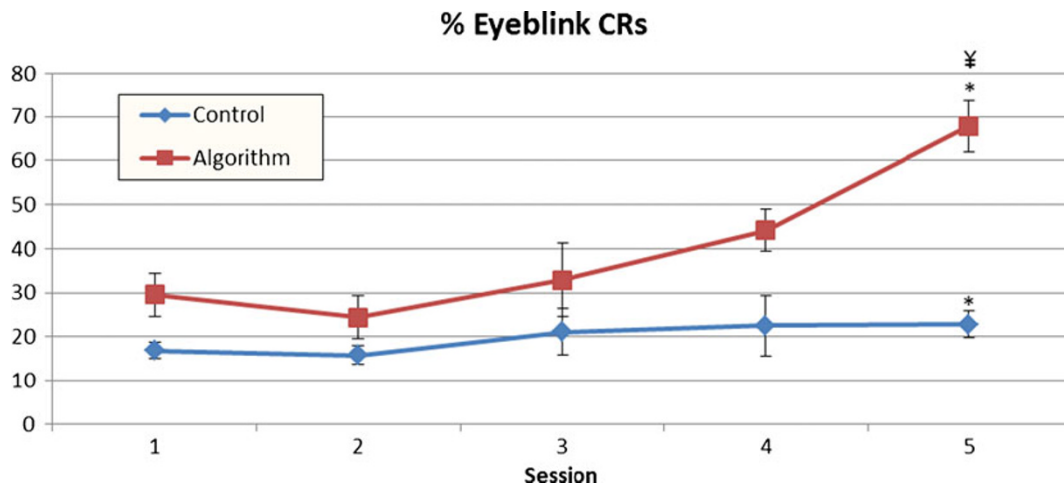
Understanding of the neuronal coding of sensory events holds the opportunity to bi-directionally interface the brain sensory system to a smart BCI, with the objective to rehabilitate or enhance the learning of sensory events. The bi-directional interface may be beneficial for individuals with localized neuronal degeneration or brain injury. At the present study motor learning was accelerated by online BCI tuned to deliver sensory events during the ‘optimal’ brain state.

### **QUESTION OF CHOISE, DECISION MAKING IN DIAGNOSTIC IMAGING AND INTERVENTION MISTAKE PREDICTION MATHEMATICAL MODELING APPROACH**

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**Fig. 1** % Eyblink CRs (Mean  $\pm$  SE) along five sessions of eyeblink conditioning in algorithm treated group and yoked control group. The algorithm group significantly outperformed the conditioning in the control group. (all comparisons are Bonferroni corrected)

\* Significant increase in comparison to the 1st session,  $p < 0.02$ .

¥ Significant increase in comparison to the control group,  $p < 0.001$ .

The majority of processes found in medicine are nonlinear, chaotic, have a high level of complexity. The decisions in healthcare are often stereotyped, managed by habits preferences, previous experience and official directives. These decisions might be not completely conscious.

In our current study, we made attempts to bring a system into this process. Each stage requires creation some mathematical models that might be described by generalized equation. These equations can be could be solved in closed system. We do not aim at finding absolute solutions, its statistically calculated optimal way of solution, but accent on a special mood, the state of expert, which could give a possibility to make only one correct decision with failure in input parameters. In such cases the lack of prior data is compensated by doctor's experience. A great value for our vision had a study of neurophysiological mechanisms of perception and decision making by medical practitioner. For example, at **stage of visual diagnostics** in order to expand its diagnostic capabilities, to reduce subjectivity in the perception and interpretation, we implemented the method of fractal analysis the medical images. It becomes a highly informative indicator of pathological formations, using nonlinear mathematical parameters of structure. This method requires expert medical approach, which is more objective than existing automated. It can be

applied in all areas of medicine, where the visual information is used, mostly in oncology. Fractal analysis may become a dominant factor in predicting outcome of doubtful clinical conditions. According to preliminary results, the malignant formations have higher fractal dimension. For modeling the **stage of decision making**, errors analysis and for predicting procedure risk we studied the negative selection of variants of prognostic indicators of interventional sonography mistakes as a combinatorial optimization problem (as the task on the graph) and was solved, using algorithmic scheme for the method of branches and boundaries using own designed phantoms. In the absence of experimental data the expert method of assessment by independent specialists was applied. Studying the error on phantoms, we concluded that in some situations that anyway mistake was admitted by performers, regardless of adherence to conventional methods. The reason for such errors can be called fatigue, coordination disorders etc. These parameters could not amenable to analysis and interpreted using linear methods. In this case we suggest to explore the problem using the method of diffusion equation of bifurcation. The reproducible errors model could potentially help to prevent iatrogenic injury in clinical situations, excluding any stereotypical, unconscious decision, to formulate methodological aspects of intervention and initiate flexible upgrading of clinical protocols.