

Chapter 2

The Digital Patient Model and Model Guided Therapy

Leonard Berliner and Heinz U. Lemke

Abstract One of the goals of this book is to provide a roadmap for the development of information technology (IT) tools to facilitate Predictive, Preventive, and Personalized Medicine (PPPM). Our approach to the management of medical information is based on model theory that has arisen from a conceptual transformation from image-guided patient management to a model-centric world-view or model-guided patient management. This approach seeks to implement a comprehensive form of Model-Guided Therapy (MGT) through the use of a Therapy Imaging and Model Management System (TIMMS), and its application as a decision support system for achieving MGT. It is our hypothesis that if we can utilize patient-specific modeling techniques to generate valid Digital Patient Models (DPMs) we may be able to develop a statistically valid methodology for predicting diseases and treatment outcomes, preventing diseases or complications, and developing personalized treatment regimens. We are calling this proposed system Model-Based Medical Evidence (MBME) and are engaged in its development. It is further postulated that Multi-Entity Bayesian Networks (MEBN) used in the construction of the DPM will be utilized in the development of a practical decision support system.

Keywords Personalized medicine · Hepatocellular carcinoma · Information technology · Model guided therapy · Therapy imaging and model management system (TIMMS) · Digital patient model · Patient-specific model · Model-based medical evidence · Bayesian network

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2.1 Introduction

As stated in Chap. 1, one of the goals of this book is to provide a roadmap for the development of information technology (IT) tools to facilitate Predictive, Preventive, and Personalized Medicine (PPPM). Our approach to the management of medical information is based on model theory that has arisen from a conceptual transformation from image-guided patient management to a model-centric world-view or model-guided patient management. This approach seeks to implement a comprehensive form of Model-Guided Therapy (MGT) that extends beyond the scope of image guidance and can be used as a decision support system in the treatment of patients. There are three basic domains of discourse that need to be managed by a comprehensive medical and surgical MGT system: data, workflow, and synthesis of information. The two basic functions of such a system are Patient-Specific Modeling (which is involved with data collection, synthesis, and simulation) and Process Modeling (which is related to the execution of a surgical workflow).

2.1.1 *Therapy Imaging and Model Management System*

A Therapy Imaging and Model Management System (TIMMS) and its application as a surgical assist system for achieving MGT has been described [1]. A TIMMS is a comprehensive medical-surgical communication and assist system (Fig. 2.1) that is composed of interconnected computer hardware and software components such as Engines, Agents, Repositories, and IT infrastructure, and provides the following features and functions throughout the course of medical and surgical treatment:

1. Standardized interfaces for communication and mechatronics (such as robotics), 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 surgical and navigational devices);
2. Creation and maintenance of a Digital Patient Model (DPM) based on generic Patient-Specific Models (PSMs) modified by the addition of patient-specific data, thereby providing a multi-scalar, comprehensive, precise, personalized representation of the patient;
3. Creation and maintenance of a system for Process Modeling of all aspects of the surgical workflow, to ensure efficiency, learning, and safety throughout operative procedures.
4. Real-time knowledge management and decision support system (Kernel for Workflow and Knowledge and Decision Management) thereby promoting optimized diagnostic, prognostic, and therapeutic decisions throughout the treatment workflow. The key role here is to assist and optimize the practice of medicine in the face of incomplete medical knowledge, which is an inherent part of clinical practice.

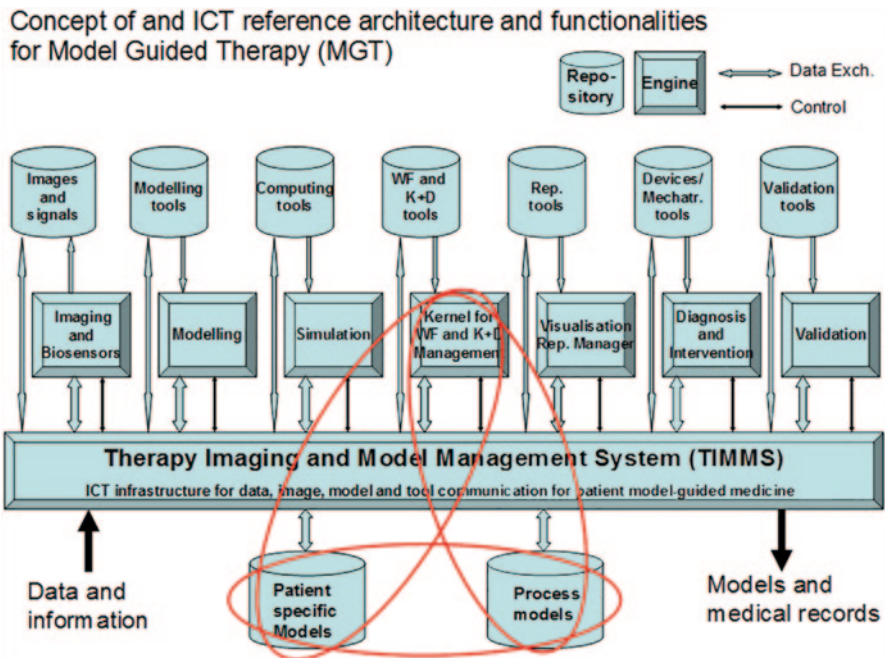


Fig. 2.1 The structure of the therapy imaging and model management system (TIMMS) that may provide much of the IT framework for personalized medicine. The kernel for workflow and knowledge and decision management, the patient specific models repository and the process models repository are the central components for the development of digital patient models through the process of patient-specific modeling (Lemke and Golubnitschaja The EPMA Journal 2014, 5, p. 8). (Legend: *ICT* Information and Communication Technology; *WF* Workflow; *K + D* knowledge and decision; *Rep* Representation; *Mechatr* Mechatronic)

5. Validation system, thereby providing quality assurance, patient safety, system security, and processing of medical evidence.

There are seven TIMMS engines that may be defined as software modules that can be executed on an appropriate computing machine to provide functionalities. These engines relate to imaging and biosensor data acquisition, modeling, simulation, workflow and knowledge and decision management, visualization, intervention, and validation.

The TIMMS engines, repositories, and IT infrastructure initially were designed to facilitate model-guided surgical therapy. Subsequently, the TIMMS structures and functions have been generalized to apply to all forms of model-based medical management (suitable for patients with cancer, diabetes, etc.) and may be abbreviated MIMMS (Medical Imaging and Model Management System).

For the purposes of developing a working TIMMS or MIMMS for PPPM, it is necessary to understand the functions of the central TIMMS engine (Kernel for Workflow and Knowledge and Decision Management; Kernel), the Modeling Engine, and their substrate, the DPM.

The Kernel provides the strategic intelligence for therapeutic planning and workflow execution. Often this module (or parts thereof) is integrated into some of the other engines, as the need demands. This important computing Kernel (or “brain”) of the system may use different forms of logic, different database structuring, agents, machine learning, and other forms of artificial intelligence, depending on the specific applications of the procedure or procedures being performed. Agents may be defined as software modules, containing some form of intelligence, which, with some degree of autonomy and adaptability, carry out functions or tasks. A full description of the role of the Kernel is beyond the scope of this book, but attention will be focused on the design, development, and management of the DPM. The use-case, as developed in this book, will focus on the requirements for a DPM to facilitate the management of patients with HCC.

2.1.2 Digital Patient Model

In every day terms, the DPM may be thought of as a representation of the patient, composed of both the static and dynamic features of the human organism, maintained within a multi-layered database structure [2]. Certain features are relatively stable, such as the DNA sequence within the chromosomes, or a radiograph of an extremity, while other features are in a constant state of fluctuation, such as pulse and respiration. In addition, the clinical significance of physiologic fluctuations may vary in different clinical settings. Thus, the DPM must be capable of managing a constellation of interacting static and fluctuating causes and effects of varying degrees of certainty, predictability, and significance. As the database of knowledge underlying the creation and maintenance of DPMs increases, a statistically valid tool that increases in accuracy as more data are added (to be discussed below), will be available for assistance in medical and surgical management in the face of incomplete medical knowledge.

Ideally, the DPM has the capabilities to capture patient specific information in a way that facilitates evaluation and application of that information:

- a. The DPM can receive and process information from an unlimited number of sources, and at a rate required for real-time activity.
- b. The DPM is comprehensive, yet flexible enough to be extensible at any time.
- c. The information contained within the DPM can be extracted by a wide variety of selection parameters, templates, and constellations.
- d. Extraction is flexible and controllable by the end-user and researchers.
- e. Extraction may take in a variety of formats or representations—charts, tables, lists, images, graphs, and models.
- f. The DPM allows and facilitates simulations, prognosis, prediction, and therapy planning. One of the key functions of the DPM is to allow simulated evaluation of hypothetical, alternative therapies to predict and optimize patient outcomes, and to anticipate adverse effects of the proposed therapies.

- g. The DPM allows comparisons and compilations with other DPMs to collect Model-Based Medical Evidence, Population-Based Medical Evidence, and Disease-Based Medical Evidence.
- h. The DPM facilitates actions with workflows, algorithms, and databases.

Features of the patient that are amenable to graphical representation are maintained as references within the DPM database structure to Picture Archiving and Communications Systems (PACS) and repositories that allow access to the actual images, for example, through functionalities of a suitable IT infrastructure for simulations and interventions. This allows medical images to be loaded into advanced medical workstations for purposes of treatment planning and simulation, as well as allowing real-time interaction with hardware and software for image-guided interventions, such as radiation therapy and minimally invasive therapies.

Those features of the DPM that are measurable and/or have cause-and-effect relationships, and can be quantified may be dealt with in a different manner than non-quantifiable features, such as constitution and appearance. In Bayesian terms, these quantifiable features, or entities, may be thought of as a dynamic set of data elements, i.e. attributes with interconnected and fluctuating probability distributions.

The probability distribution of each attribute or variable reflects and represents the state of uncertainty associated with the knowledge about a particular feature of an individual patient. The existence of relationships among attributes, represented by appropriate links and their binding strength, are also subject to probability distributions. The value of each attribute probability distribution lies within a statistically definable range of normal and abnormal values. The boundaries of the values for each attribute, and the volatility of the changes of these values, vary in health and disease, and at different ages, and may be subject to further alterations based on the body's homeostatic mechanisms, as well as constitutional, genetic and epigenetic, and environmental factors, including prior medical and surgical interventions. It is therefore reasonable to assume that the described situation surrounding the patient is amenable to be represented by a form of Bayesian Network. However, standard Bayesian Networks that have been utilized in previous medical decision support and knowledge management systems are inadequate for this purpose. A Multi-Entity Bayesian Network (MEBN) [3] is available that can overcome the limitations of standard Bayesian Networks.

A MEBN is a logic system that integrates first-order logic with Bayesian probability theory and can provide a descriptive and functional framework for the quantifiable components or entities of the DPM. These entities of the DPM will be stored as attributes within both a PSM Database (to be described below) and the appropriate nodes of the graph created for the MEBN.

The First and Second Order Information Entities (IEs) for the generic PSM may relate to the entities listed in Tables 2.1 and 2.2. The attributes of these IEs may be obtained through links with the appropriate databases, spreadsheets, Electronic Medical Records (EMRs), and repositories, for example by means of the functionalities of a suitable MIMMS. These Primary and Secondary IEs are broken down

Table 2.1 First order information entities

First and second order information entities	
1	Genome
2	Proteome
3	Cellular
4	Tissue
5	Organ
6	Organism

Table 2.2 Second order information entities

Second order information entities	
1	General health status
2	Central nervous system
3	Sensory organs
4	Cardiovascular
5	Gastrointestinal
6	Respiratory
7	Genitourinary
8	Endocrine
9	Nutritional/metabolic
10	Hematological/lymphatic
11	Musculoskeletal
12	Integument
13	Psychological
14	Genetic/proteomic
15	Prostheses/devices
16	Growth/development
17	Aging
18	Environmental factors

into Third Order IEs and further subdivisions that include the vast, and continually expanding, list of patient-related information.

A finer granularity is developed and refined as more patient and disease specific attributes are enumerated as third and fourth order (and beyond) IEs. A general template for a range of attributes of a generic PSM is presented in Fig. 2.2. The central area of the template represents the current status of the generic PSM, and is divided into three categories: pre-determined factors, anatomic factors, and physiologic/functional factors. Allowances are made for those influences that have a direct role on altering the PSM—processes, such as aging, development, diseases, surgical procedures; extrinsic inputs or interventions; intrinsic mediators. A separate section of the template displays the PSM output that generates the current or working model of the actual patient, or the DPM.

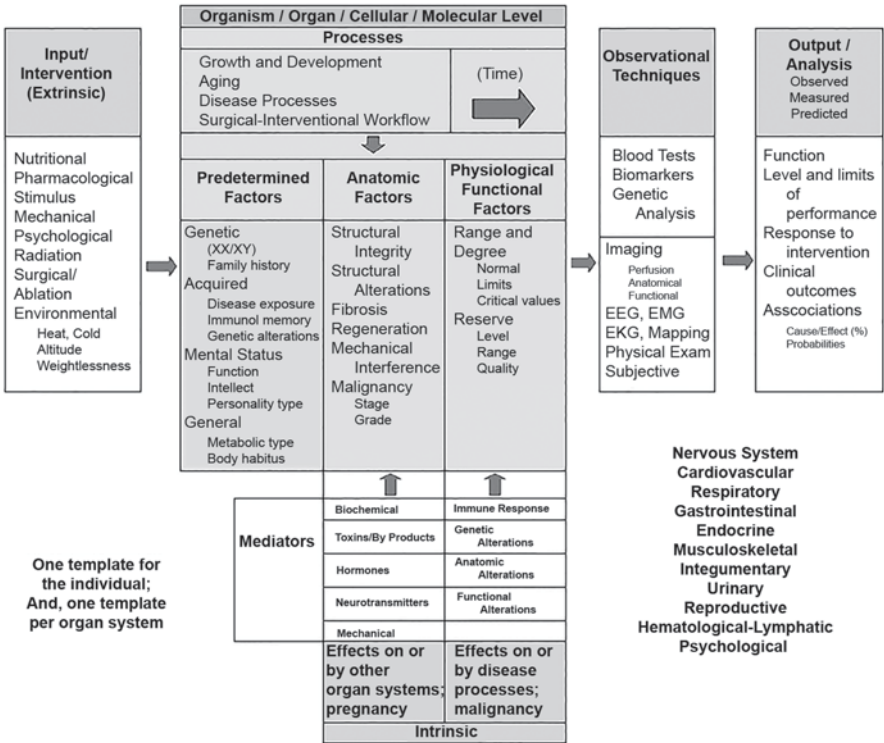


Fig. 2.2 A generic PSM template. The DPM is generated when the specific factors and values are entered into the full set of templates and the output is analyzed and may be used for prediction

It can be surmised that the full collection of templates that includes each of the First and Second Order IEs represents a vast amount of information that would be overwhelming for rapid clinical problem solving, given the capabilities of today’s computer systems. It would, however, be possible to store this information in properly designed database systems with the appropriate database architecture. It is also proposed that for management of clinical problems in a feasible manner, a specific selection of PSM attributes (or PSM Constellation) relevant to the clinical problem at hand, can be identified and formed into a limited or working DPM. The attributes of the DPM would be available to the clinician in whatever forms are desired and useful—graphic, tabular, descriptive, and 3-D model. The ability to make queries regarding patient status, diagnosis, treatment plans, and prognosis would be provided. (This approach would not preclude independent, separate, and deeper database queries and data-mining from the complete PSM database [or, databases] to detect as yet unrecognized causes, effects, and outcomes, and for other forms of research.)

The PSM Constellation may be presented as a pictorial representation, as in Fig. 2.3, with only the First-Order IEs being shown. However, the PSM Constellation is multi-scalar and contains, within the computer structure the active entities of

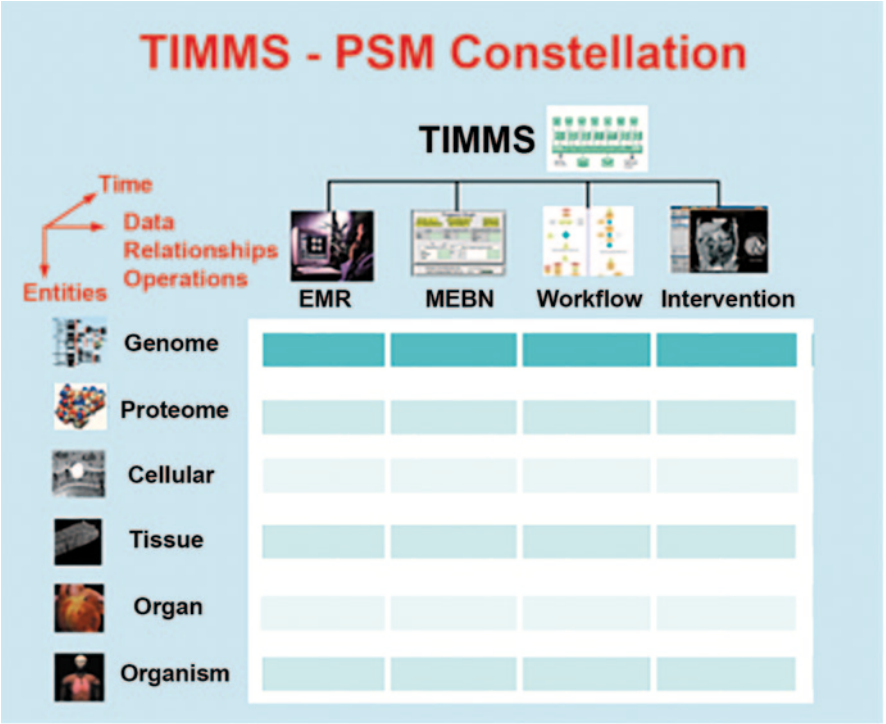


Fig. 2.3 Generic PSM constellation grid showing first order information entities

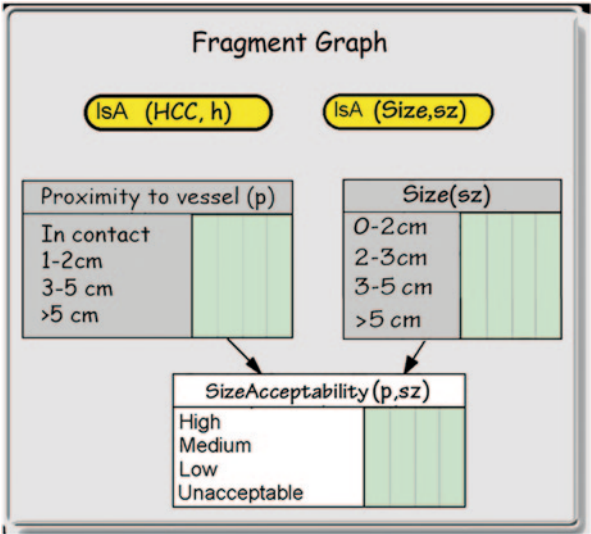
all orders. Linkages between any entity, of any order, (on the y-axis) and an associated TIMMS Component (on the x-axis) may be displayed as needed.

The attributes defining the DPM will change over time, especially during the course of a medical treatment or surgical intervention. It is one of the roles of the DPM and associated software tools to gather, calculate, record, tabulate, or otherwise organize, maintain, and communicate values for each of these entities, and to predict and record the changes in values brought about through the interactions with the entities. These changes over time would be reflected in changes to the grid along the z-axis.

2.1.3 Multi-Entity Bayesian Network (MEBN)

A MEBN [3] is a logic system that integrates first-order logic with Bayesian probability theory and can provide a descriptive and functional framework for the DPM. It is the nature of a MEBN to increase in overall accuracy as the precision of the data used to generate the various component probabilities increases (see below).

Fig. 2.4 MFragment. This MFragment demonstrates the relationships between the **a** proximity of a discrete HCC lesion, **b** a nearby vessel, and **c** the size of the lesion. (Preliminary draft; under development)



With the addition of sufficient context-appropriate patient-specific data, it is hypothesized that the MEBN will provide a flexible and sufficiently accurate model of a patient, and will also provide the necessary framework for the associated situational awareness and decision support that will be required for the performance of MGT, as well as the generation and validation of Model-Based Medical Evidence (MBME) when generated through MGT.

Structurally, MEBN logic expresses probabilistic knowledge as a collection of MEBN fragments (MFrags) organized into MEBN Theories (MTheories) [3]. An MFragment represents a conditional probability distribution of the instances of its resident random variables, given the values of instances of their parents in the Fragment graphs and given the context constraints. An example of an MFragment that might be used in conjunction with other MFrags to predict the outcome of an ablation treatment of HCC is presented in Fig. 2.4. There is no theoretical limit to the number of MFrags that may be used in an MEBN.

A collection of MFrags represents a joint probability distribution over an unbounded, possibly infinite number of instances of its random variables. The joint distribution is specified by means of the local distributions together with the conditional independence relationships implied by the fragment graphs. Context terms are used to specify constraints under which the local distributions apply [3].

A collection of MFrags that satisfies consistency constraints, ensuring the existence of a unique joint probability distribution over its random variables, is called an MTheory. MTheories can express probability distributions over truth values of arbitrary First Order Logic sequences and can be used to express domain-specific ontologies that capture statistical regularities in a particular domain of application [3].

In addition, MTheories can represent particular facts relevant to a given reasoning problem. Conditioning a prior distribution represented by an MTheory on its findings is the basis of probabilistic inference with MEBN logic [3].

The MFragments may be assembled to form graphs, e.g. Situation Specific Bayesian Networks (SSBN), for evaluating hypothetical conditions [3]. Support for decision constructs in MEBN is provided via Multi-Entity Decision Graphs (MEDG) that are related to MEBN the same way influence diagrams are related to Bayesian Networks [3]. An MEDG can be applied in any application that requires optimizing a set of alternatives (i.e.—an MEDG policy) over the given constraints of a specific situation. MEBN logic also provides a means of learning the structure of a MEBN Theory on the basis of data (i.e. Bayesian learning), while parameter learning can be expressed as inference in MEBN theories that contain parameter random variables. Thus, the MEBN provides comprehensive methodology for DPM description, as well as tools for decision support.

2.1.4 *UnBBayes*

The design of a MEBN is facilitated through the open source software called UnBBayes [4, 5]. This is a probabilistic network framework with a graphical user interface (GUI) and an application programming interface (API) supporting applications for inference, sampling, learning, evaluation, and other functions.

To create a MEBN in UnBBayes, for a generic PSM relating to HCC, it is important to identify and define the domain of discourse of interest and then to select the relevant IEs for this domain. IEs may be derived from the information accumulated in a clinical cancer center—medical examination, medical imaging, endogenous human characteristics (e.g. age, gender, and genetics), and exogenous factors (e.g. alcohol consumption and pathogens such as hepatitis exposure). Criteria need to be established that enable classification and organization of the identified IEs.

This activity will be accomplished through the extraction of IEs (which will be identified in the following Chapters), and the establishment of adequate probabilities for the criteria and importance ratings (weights) for the IEs (which will be addressed in future work). After this information is accumulated, sets of IEs will be formed that can be regarded to be logically connected. Subsequently, independent IEs will be assigned as Resident Nodes with their own MFragments.

After finalizing an MTheory with a complete set of MFragments, a generalized patient entity will be created. From this generic entity, instances for every real patient may be created. Finally, findings for a specific patient may be assigned to a particular instance and the corresponding MTheory may then be visualized as a graph with the given IEs, probabilities, and findings. It is important to keep in mind that the relationship between IEs (or, random variables) in the MEBN can be updated as more experience and evidence are added to the system, according to Pearl's Bi-directional Belief Updating Algorithm [6, 7]. Therefore, in the initial development of the MFragments and MTheories, close approximations of probabilities as established

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