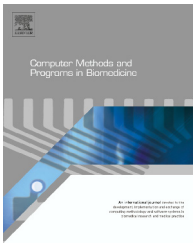
COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 110 (2013) 528–537

journal homepage: www.intl.elsevierhealth.com/journals/cmpb



Software for quantitative analysis of radiotherapy: Overview, requirement analysis and design solutions

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ARTICLE INFO

Article history:
Received 29 November 2011
Received in revised form
26 January 2013
Accepted 4 March 2013

Keywords:
Radiobiological model
TCP
NTCP
Dose comparison
Radiotherapy analysis software

ABSTRACT

Radiotherapy is a fast-developing discipline which plays a major role in cancer care. Quantitative analysis of radiotherapy data can improve the success of the treatment and support the prediction of outcome. In this paper, we first identify functional, conceptional and general requirements on a software system for quantitative analysis of radiotherapy.

Further we present an overview of existing radiotherapy analysis software tools and check them against the stated requirements. As none of them could meet all of the demands presented herein, we analyzed possible conceptional problems and present software design solutions and recommendations to meet the stated requirements (e.g. algorithmic decoupling via dose iterator pattern; analysis database design). As a proof of concept we developed a software library "RTToolbox" following the presented design principles. The RTToolbox is available as open source library and has already been tested in a larger-scale software system for different use cases. These examples demonstrate the benefit of the presented design principles.

1. Introduction

Radiotherapy is a comprehensive and fast-developing discipline which plays a major role in cancer care. More than half of all cancer patients are treated with radiotherapy at some stage. Radiotherapy may be used for adjuvant or curative cancer treatment as the primary therapy. It is also commonly applied in combination with other therapy techniques such as surgery, chemotherapy, hormone therapy or some mixture of these.

The success of radiotherapy critically depends on accurate targeting and delivery of the prescribed radiation dose. Modern imaging technology such as CT and MRI allow obtaining the 3D dose distribution. Based on this 3D information the treatment planning system can design dose distributions that conform the dose closely to the shape of the tumour and spare the adjacent normal tissue. Radiotherapy critically depends on this 3D information; however, gaining maximum benefit from this knowledge still remains a challenge.

The evaluation and comparison of the 3D dose distributions is complex and thus requires a powerful software environment with dedicated analysis tools. Dose–volume-histograms (DVHs) [1–3] together with statistical parameters such as mean dose and minimum/maximum dose, which characterize the dose distribution within an organ at risk,

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http://dx.doi.org/10.1016/j.cmpb.2013.03.002

the tumour or any other volume of interest (VOI), are essential to summarize and analyze the 3D data. Predictors, such as tumour control probabilities (TCP) [4–8] and normal tissue complication probabilities (NTCP) [9–13] are extensively used to predict the radiotherapy outcome based on radiobiological models [14]. Determining the parameters of radiobiological models, such as tumour cell radiosensitivity and clonogenic cell density, still remains a big challenge [15–20]. It requires intensive research based on large scale clinical trials and retrospective analysis of clinical data [21]. This requires powerful software systems for data analysis.

Several software systems for quantitative analysis of radiotherapy have been developed and published [22–28]. To provide a suitable analysis system for our heterogeneous research environment, we have identified and analyzed conceptional and general requirements that are important and therefore should be met by the analysis software. We present herein an overview of available radiotherapy analysis systems and check them against the stated requirements. Because none of the available systems could match all of our requirements, we analyzed the conceptional problems and present software design solutions and recommendations to tackle them. As a proof of concept and core for our own quantitative radiotherapy research, we have implemented a software library, called RTToolbox. It was designed following the presented design principles. In the last section we present different use cases that build upon the RTToolbox and the integration of the RTToolbox in a large scale software platform. These examples demonstrate the benefit of the presented design principles.

2. Background and design considerations

Typical radiotherapy data includes images, dose distributions, structure sets and radiotherapy plans. Radiooncologists and medical physicists usually have to analyze data from different systems and treatment modalities, and compare the analysis results to evaluate the treatment plan either retrospectively or prospectively. Thus the analysis software should facilitate data exchange between different systems, and provide comparability and consistence of the analysis results. The detailed requirements and design considerations are described in Section 2.1. In Section 2.2 we present an overview of existing applications and check them against the requirements.

2.1. Requirements and design considerations

1. Functional requirements
   a. *Dose statistics and DVH calculation*. Maximum, mean and other statistics are standard metrics to evaluate a dose distribution. The DVH is an important method to reduce the complex information contained in a 3D dose distribution to a 2D histogram.
   b. *Comparison of dose distributions*. To compare two dose distributions or plans, indices such as coverage index (CI) and homogeneity index (HI) are very useful.
   c. *Radiobiological analysis*. The tumour control probability (TCP) and normal tissue complication probability (NTCP) play an important role to predict the radiotherapy outcome based on radiobiological models [29].
2. *Versatility and extensibility of the software*. To support data exchange with different software systems and enable reusability and extensibility for different use cases, a clear separation between data, evaluation methods and graphical user interface is essential. If this requirement is not fulfilled, any change in the data format is likely to require changes in the evaluation engine and user interface.
   a. *Versatility of DVH calculation and other dose evaluation methods*. The DVHs of different volumes-of-interest (VOIs) are very essential for treatment planning and also for quantitative evaluation during and after the therapy. The DVH calculation results depend significantly on the applied voxelization method [30]. To provide versatility on one hand but also consistence and comparability of results on the other hand, the system has to meet two requirements: (i) It must allow to select or exchange the voxelization method as well as DVH calculation algorithm (with minimum impact on the system infrastructure); (ii) It must allow the handling of arbitrary data types (e.g. different structure or dose formats, and masked and unmasked dose). If these requirements are not met, production of consistent results and further development of the system is difficult to maintain.
   b. *Extensibility of radiobiological models*. Depending on the tumour or normal tissue type, radiobiological models can be calculated using different algorithms. Because the development of these models is fast-moving, the analysis software should not only support the standard radiobiological algorithms, but also be easily extensible to new methods and algorithms.
3. *Data management using analysis database and database interface*. Analysis of clinical data requires a well-designed analysis database to collect, manage and analyze these data as well as the obtained results. Storing data and analysis results in a common database allows treating complex questions such as that of the location of tumour recurrences in a cohort of patients (inside/outside or on the border of a VOI), the minimum/maximum received by the recurrences, as well as the correlation with model predictions. Furthermore, the database should have an easily extensible structure because of requirement 2. Therefore extending the database by data from new algorithms or models should be possible with no (or only minor) changes to the existing structures.
4. *General requirements on the software*. The programming language and especially the required tools used in the software solution should be *freely available*. The software solution should be as *platform/compiler independent* as possible to be reusable, comparable and consistent for different systems. In addition, it should provide *high-performance* to allow "on-the-fly" computations.

2.2. Existing applications

A number of tools to support radiotherapy evaluations have been published previously (see Table 1). The BIOPLAN [25] was one of the first published software tools published to support the evaluation of treatment plans with respect to the biological responses of the irradiated tissues. The DICOM-RT based toolbox [26] was developed for the evaluation and the verification

Table 1 – Features of existing tools for radiotherapy treatment plan analysis.

Tools	DVH calculator (req. 1a)	Dose comparison (req. 1b)	TCP/NTCP (req. 1c)	Independence from GUI (req. 2)	Analysis database (req. 3)	Technology/realization (req. 4)[a]
BIOPLAN [25]	×	×	√	×	×	Visual Basic
DICOM-RT toolbox [26]	√	×	×	×	×	MATLAB
TCP_NTCP _CALC [28]	×	×	√	×	×	MATLAB
CERR [22]	√	×	×	×	√	MATLAB
DREES [24]	×	×	√	×	×	MATLAB
EUCLID [23]	×	×	√	×	×	Based on DREES
Computational platform from Liu [31]	×	×	√	√	√	C++, OPENGL, MATLAB, JAVA, ASP, HTML, and SQL
BEUDcal [27]	×	×	√	×	×	MATLAB

[a] Most important to meet requirement 4. × = feature not included; √ = feature included.

of radiotherapy treatment plans using Monte Carlo dose calculation and DVH calculation. The software TCP_NTCP_CALC [28] was developed for estimating the TCP or NTCP arising from differential (frequency) DVHs. The software DREES [24] in combination with CERR [22] provided an open source environment for analyzing treatment outcomes, including importing, visualizing, contouring the radiotherapy data and the calculation of DVH and TCP/NTCP. The software EUCLID [23] was based on the DREES software to predict an outcome probability based on a large number of clinical, biological, physiological and dosimetric factors. The computational platform from Liu [31] was presented to facilitate radiotherapy research and outcome studies consisting of an infrastructural database, a data exchange interface tool, a TCP/NTCP calculator and a visualization package for IMRT data. The software BEUDcal [27] was developed for evaluating the effectiveness and for predicting the outcome of treatment plans by calculating the biologically effective uniform dose (BEUD) and complication-free tumour control probability.

As shown in Table 1, none of the above tools can meet all of the presented requirements. There are the following limitations:

- None of the tools support DVH calculation and radiobiological evaluation at the same time (req. 1a & 1c), which means that the users must call a separate DVH calculator or a biological model calculator if the structure set or the dose distribution was changed. If DVHs are calculated using external tools, the voxelization errors by external tools are not controllable by users of the analysis tool (req. 2a); if radiobiological evaluation is performed using external tools, new radiobiological models and algorithms are not easy to be added (req. 2b). Furthermore, the voxelization results of DVH calculation using external tools may be not the same as the voxelization by 3D visualization, which may cause inconsistency problems. For example, the voxel with minimum dose value of a VOI determined using the voxelization of DVH calculation may be located outside of the structure in the 3D visualization, because this visualization uses a different voxelization method than the DVH calculation.
- Almost all tools are tightly bound to a visualization tool. For example, most tools are based on Matlab. So they are not easy to be reused or extended in other applications (req. 2).
- Most tools have no database support to store and manage the calculated results, which is very essential for the further evaluation in large-scale studies (req. 3).
- All except BIOPLAN and the computational platform by Liu require access to the third party software Matlab, which is not freely available (req. 4). BIOPLAN uses Visual Basic which is not platform independent (req. 4).

3. Design pattern and implementation

According to the requirement 4 (freely available, platform independent and high-performance), C++ should be a well-suited choice for the programming language. Based on the requirements 1–3 the radiotherapy analysis software should consist of the following parts:

i. Data abstraction layer to separate data, methods and user interface (requirement 2);
ii. Evaluation engine supporting dosimetric, geometric and biological evaluation, such as DVH calculation, comparison of dose distributions, evaluation of indices and TCP/NTCP-results (requirement 1);
iii. And analysis database (requirement 3).

To visualize 2D/3D radiotherapy data and analysis results and to support the analysis by user-friendly interfaces, a visualization wrapper upon an independent visualization tool is required. These components are described in the following.

3.1. *Data abstraction layer*

To separate data and methods (requirement 2) a data abstraction layer should be used. A data abstraction layer hides the complexity of data and resolves dependencies. In this data abstraction layer radiotherapy data of different data formats should be transformed to a well-organized logical format that is used for the evaluation algorithms as well as for the visualization wrapper.

The most important data for radiotherapy analysis is the dose distribution which may be represented in different data formats as well as be masked by structures (e.g. target volume and organ at risk). Dose distributions or masked dose distributions are considered as containers storing the dose values following specific access rules. These should not be changed during the evaluation process. Either by dose statistics calculation or DVH calculation, the important information of dose distributions needed for the evaluation are:

1) If the current voxel position is valid;
2) If yes, the received dose of the current voxel;
3) The geometric information (transformation matrix, spacing, etc.) of the current voxel.

Therefore the iterator pattern is well-suited to decouple algorithms and dose distributions (container), similar to the Standard Template Library (STL) [32] iterator of different STL containers. The dose iterator hides the complexity of physical dose distribution and structure set, and enables a better organization of the data for dose distributions (masked or unmasked). Necessary information for the evaluation engine can be accessed by the dose iterator (see Fig. 1), without any knowledge about the physical dose distribution and the structure set or their concrete implementation.

By implementing the access to the dose value for each voxel position as well as the transformation from voxel positions to world coordinates, the set of dose iterators can easily be extended to support new data formats for dose distributions and masks. Using the presented design concepts, different data types can be evaluated by the evaluation engine, thus the requirement 2a is fulfilled. For example, the dose statistics can be calculated on a planning dose distribution or on a masked dose distribution by a planning target volume (PTV), if instances of different derived classes (e.g. rttb::core::GenericDoseIterator and rttb::core::GenericMaskedIterator) are used.

Using this concept, the developed RTToolbox can currently handle masked and unmasked radiotherapy data from DICOM-RT compatible planning systems as well as from Virtuos, our in-house developed planning system [33,34]. The open source library DCMTK from OFFIS [35] is used in the RTToolbox to parse and to generate the DICOM data.

3.2. *Evaluation engine (EE): dosimetric, geometric and radiobiological evaluation*

The evaluation engine receives the input data from the data abstraction layer, thus all evaluation methods could be developed independent of the original data format. Based on requirement 1, the evaluation engine should consist of the following functional components for different evaluation purpose:

- Arithmetic operations on dose distributions and structure relationship analysis (e.g. fully contained, partially contained) to perform basis evaluations;
- Dose statistics computation to analyze dose distributions using minimum maximum, etc.;
- DVH calculation;
- Different dose/plan comparison indices to compare or score dose distributions and plans;
- Radiobiological evaluation based on biological models including TCP, NTCP, equivalent uniform dose (EUD) and biological effective/equivalent dose (BED).

According to the iterator concept described in Section 3.1 DVH and dose statistics are calculated similarly using masked or unmasked dose iterators. Using the calculated DVHs and statistics, dose/plan comparison and radiobiological analysis can be performed.

Although different algorithms of biological models use different formulas and different parameters, they have common properties, e.g. each biological model is a function of the reference dose value and some parameters. Therefore, the radiobiological modelling should be developed using abstraction and encapsulation principles, which enable the independent development of the general analysis as well as the extension by new models (requirement 2b). Fig. 2 shows the class diagram of an example implementation in the RTToolbox using object-oriented programming. An abstract class rttb::models::BioModel is developed to encapsulate the generalized properties of a radiobiological model. The curve of radiobiological response vs. prescribed dose is supported (rttb::models::getCurveDoseVSBioModel()), and the analysis of the parameter uncertainty of the models as well (rttb::models::getScatterPlot()). By use of polymorphism the abstract interface of rttb::models::BioModel enables easy extension to new biological models.

3.3. *Analysis database*

The analysis database plays an important role in the analysis software to store and manage the study information and analysis results (requirement 3). The study information should be collected and stored in the database tables, including patient, therapy and follow-up information, the images before, during

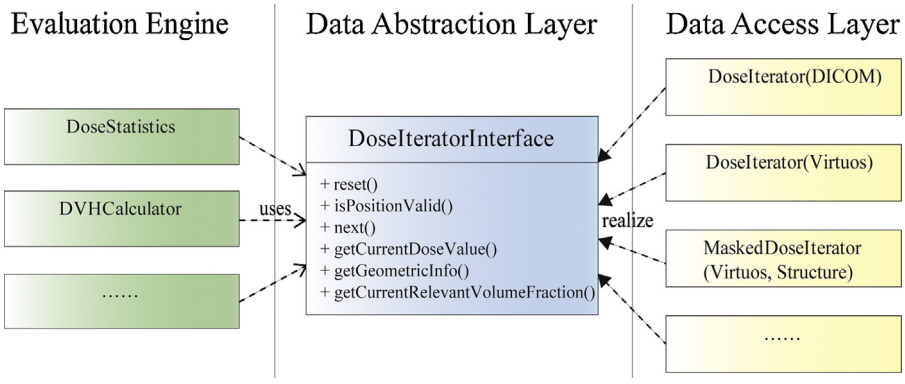

Fig. 1 – The dose iterator and the interaction with evaluation engine.

and after the therapy, the structure sets and dose distribution, and the analysis results such as DVHs and TCP/NTCP. In the design of the relational analysis database the database tables should be normalized using the Third Normal Form (3NF) [36] to produce well-structured relations and minimize the redundancies and inconsistencies.

Since the dose distribution could be imported as plan dose, fraction dose or may be calculated by dose operations, separate tables are generated to store different types of dose distribution. A general table for dose distribution called DoseType is structured to store the references of different dose types. It is used to define the relationships which are independent from the dose types, such as dose statistics and DVH calculation. If the database is to be extended to allow the handling of new dose types, the pre-existing independent database structure such as DoseStatistics and DVHSet can remain largely or entirely unchanged. Similarly the algorithms, parameter names, parameter values and model values of radiobiological models are stored separately in the different tables. When extending the database to new biological models, the users only need to add a new algorithm name and reference in the BioModelAlgorithm table and new parameter names in the BioModelParameterSet tables; no further changes in other tables are required. All these design considerations enable flexible extension of further models and parameters, and minimize the redesign of the database and the effects of applications interacting with the database.

Currently a PostgreSQL database is supported in the developed RTToolbox to collect and manage study information and analysis results. All the database tables are generated according to the presented entity relationship diagram. In summary, the RTToolbox was developed according to all of the above design and implementation considerations. The cooperation of all components is displayed in Fig. 3.

4. Use cases

4.1. *The usage of arbitrary data on an open array of evaluation algorithms*

In context of our own research work, we have incorporated different evaluation algorithms. Except for the standard maximum, minimum, standard derivation and variance, all quantities that can be calculated by RTToolbox as part of

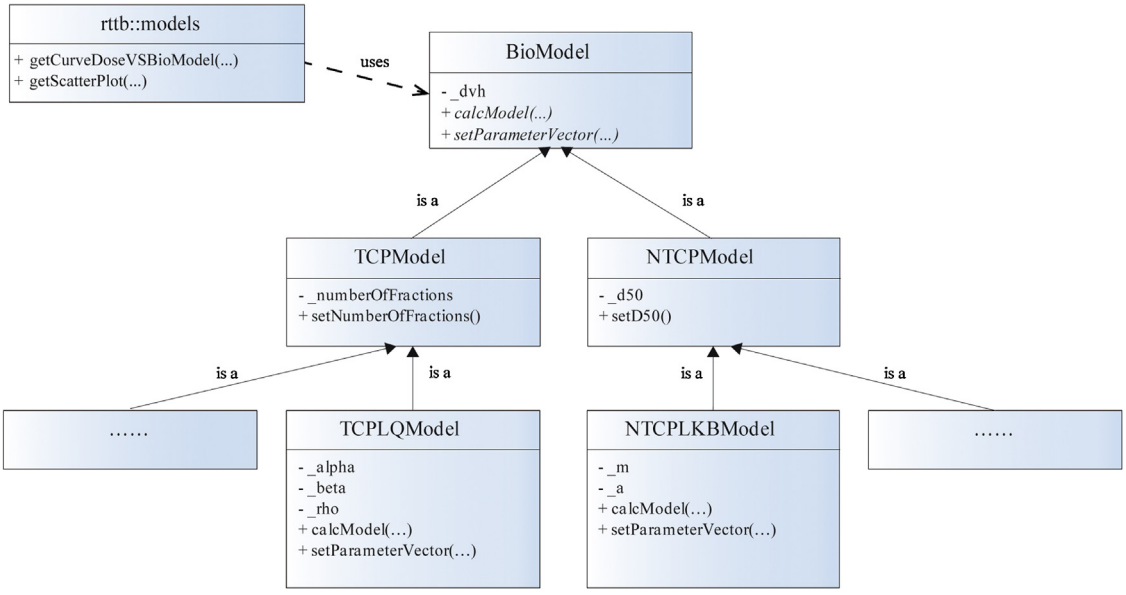

Fig. 2 – The class diagram of an example implementation of biological models.

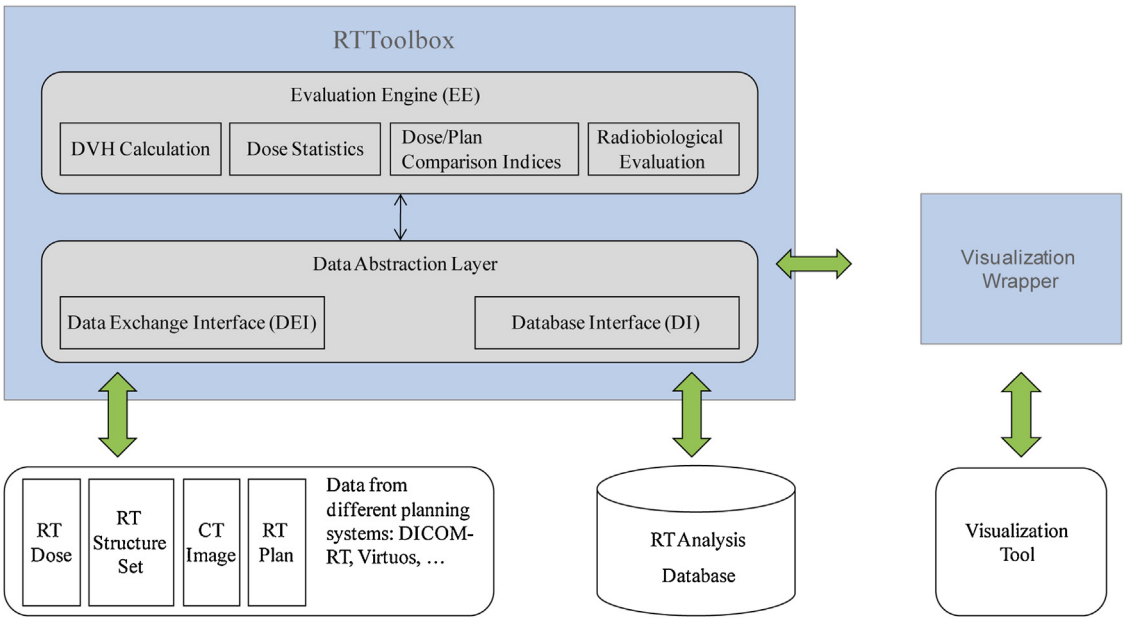

Fig. 3 – General architecture of the RTToolbox.

the dose statistics are described in Table 2. The last four metrics MOH_x, MOC_x, $MaxOH_x$, $MinOH_x$ are calculated to determine the effect of hot spots and cold spots on the dose statistics. They are useful supplements to the standard statistics.

DVH calculation is supported using the presented iterator pattern (see Section 3.1). Furthermore, several dose/plan comparison indices have been realized by utilizing these design concepts to compare dose distributions and to score plans. The indices are calculated based on the DVH of the corresponding VOI, e.g. planning target volume (PTV). For a detailed description and reference of each of the indices see Table 3.

Radiobiological models are also covered. Table 4 lists the models currently implemented in the RTToolbox by using the pattern. The multitude of already implemented analysis schemes is a sound verification of the suitability of the data abstraction layer and evaluation engine concepts.

Table 2 – Dose statistics and its description.

Dose statistics	Description
Mean dose	The sum of the doses assigned to each voxel divided by the total number of voxels
Median dose	The dose level where the same number of voxels are found at higher and lower doses
V_x	The volume irradiated to ≥x% of prescribed dose (or absolute dose)
D_x	The minimum dose delivered to x% of VOI (or absolute volume)
MOH_x	The mean dose to the hottest x% (or absolute) volume
MOC_x	The mean dose to the coldest x% (or absolute) volume
$MaxOH_x$	The maximum outside of the hottest x% (or absolute) volume
$MinOH_x$	The minimum outside of the coldest x% (or absolute) volume

Table 3 – Dose/plan comparison indices.

Dose metrics	Description	References
Homogeneity index (HI)	$HI = \frac{D_{max(PTV)}}{D_{min(PTV)}}$ or $HI = \frac{D_{max(PTV)} - D_{min(PTV)}}{D_{ref}}$	[38]
Coverage index	Fraction of the target volume receiving a dose ≥ the reference dose	[38]
Conformity index (CI)	$CI(D) = IF_{PTV}(D) \times (1 - IF_{HT}(D))$, D, the dose used to define the treated volume; IF_{PTV} (D), the irradiation factor of the PTV, defined as the fraction of the PTV receiving a dose higher than D, IF_{HT} (D), the irradiation factor of healthy tissue, defined as the radio of the volume of tissue outside the PTV receiving a dose greater than D to the volume of isodose D	[39]
Conformation number (CN)	$CN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}}$, TV, target volume; TV_{RI}, target volume covered by the reference isodose, V_{RI}, volume of the reference isodose	[40]
Conformal index (COIN)	$COIN = CN \times \prod_{i}^{N_{CO}} (1 - V_{ref,i}/V_{co,i})$, N_{co}, number of critical organs (CO), $N_{ref,i}$, ith critical organ volume receiving at least the reference dose, $V_{co,i}$, ith critical organ volume	[41]

Table 4 – Radiobiological models.

Models	Description	References
Biological effective/equivalent dose (BED)	$\mathrm{BED} = nd\left(1+\frac{d}{\alpha/\beta}\right) - \frac{\ln 2}{\alpha T_d}(T-T_k)$, n is the number of fractions, d is the dose per fraction, α and β are parameter characteristics of the population of cells.	[42,43]
Linear equivalent dose for 2 Gy	$\mathrm{LQED}_2 = nd\frac{\alpha/\beta+d}{\alpha/\beta+2}$, n, d, α and β are same as above	[42]
Generalized equivalent uniform dose (gEUD)	$\mathrm{EUD} = \left(\frac{1}{N}\sum_i D_i^a\right)^{1/a}$, N is the number of voxels in the anatomic structure of interest, D_i is the dose in the ith voxel, and a is the tumour or normal tissue-specific parameter that describes the dose–volume effect, e.g. −10 for prostate.	[44]
TCP of an individual patient	$\mathrm{TCP}(\alpha,\alpha/\beta,\rho_c) = \prod_j \exp\left\{-\rho_c v_j \exp\left[-\alpha D_j\left(1+\frac{\beta}{\alpha}d_j\right)\right]\right\} = \prod_j \exp\left\{-\rho_c v_j \exp\left[-\alpha \mathrm{BED}_j\right]\right\}$	[7]
TCP of a patient population	$\overline{\mathrm{TCP}} = \sum_i g_i TCP(\alpha_i,\alpha/\beta,\rho_c)$, where a fraction g_i is the probability of patients which have $\alpha=\alpha_i$, and $g_i \propto \exp\left[-(\alpha_i-\bar{\alpha})/2\sigma_\alpha^2\right]$.	[7]
Lyman–Kutcher–Burman model for NTCP	$\mathrm{NTCP}(\mathrm{EUD}_a,\mathrm{TD}_{50},m) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-t^2/2}$, where $t = \frac{\mathrm{EUD}_a-\mathrm{TD}_{50}}{m\mathrm{TD}_{50}}$;	[11]
Relative seriality model for NTCP	$\mathrm{NTCP} = \left[1-\prod_{i=1}^{M}\left(1-P(D_i)^s\right)^{\Delta v_i}\right]^{1/s}$, where $P(D)$ is the Poisson model.	[29]

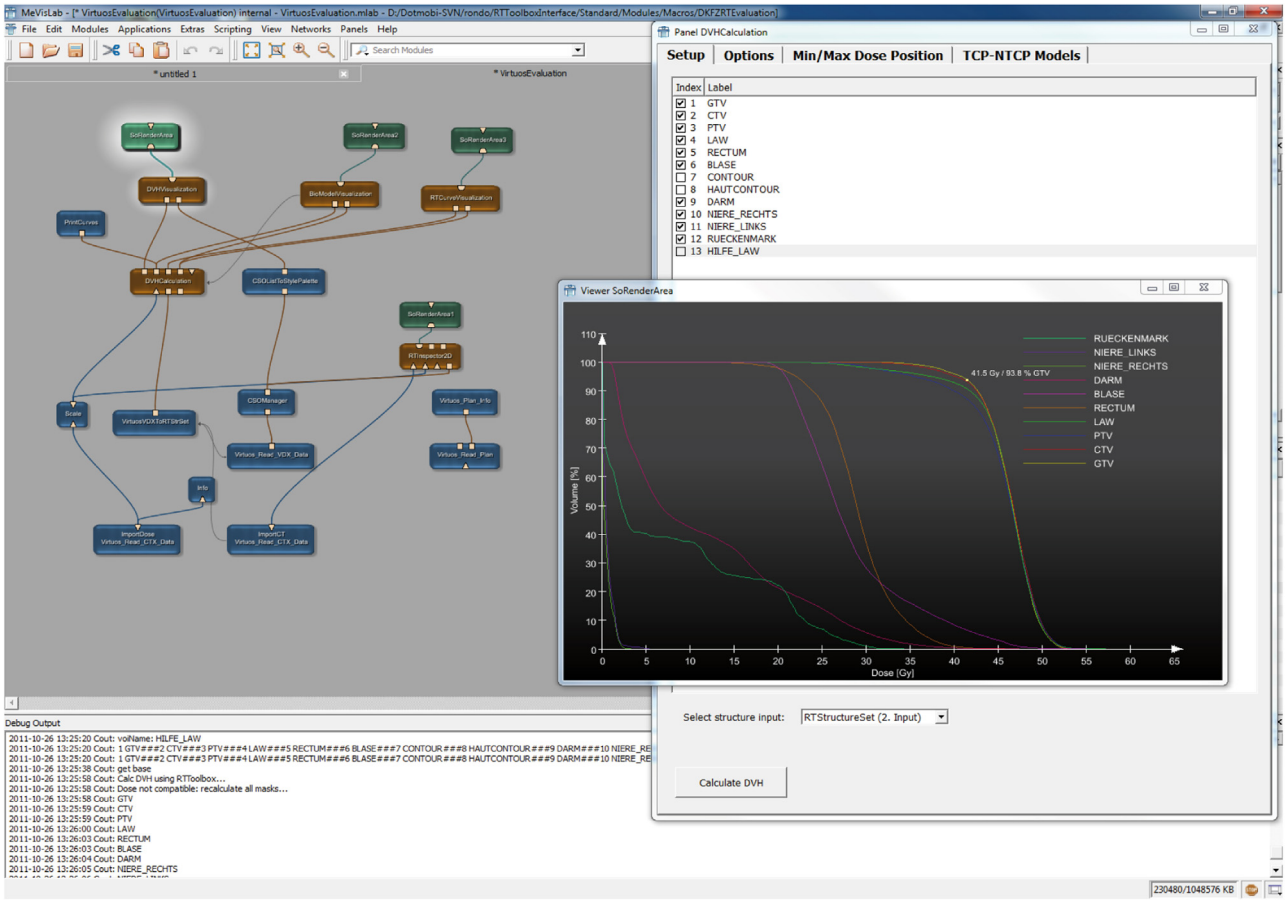

Fig. 4 – A MeVisLab network to visualize DVH calculation settings and DVH curves for radiotherapy data in Virtuos formats.

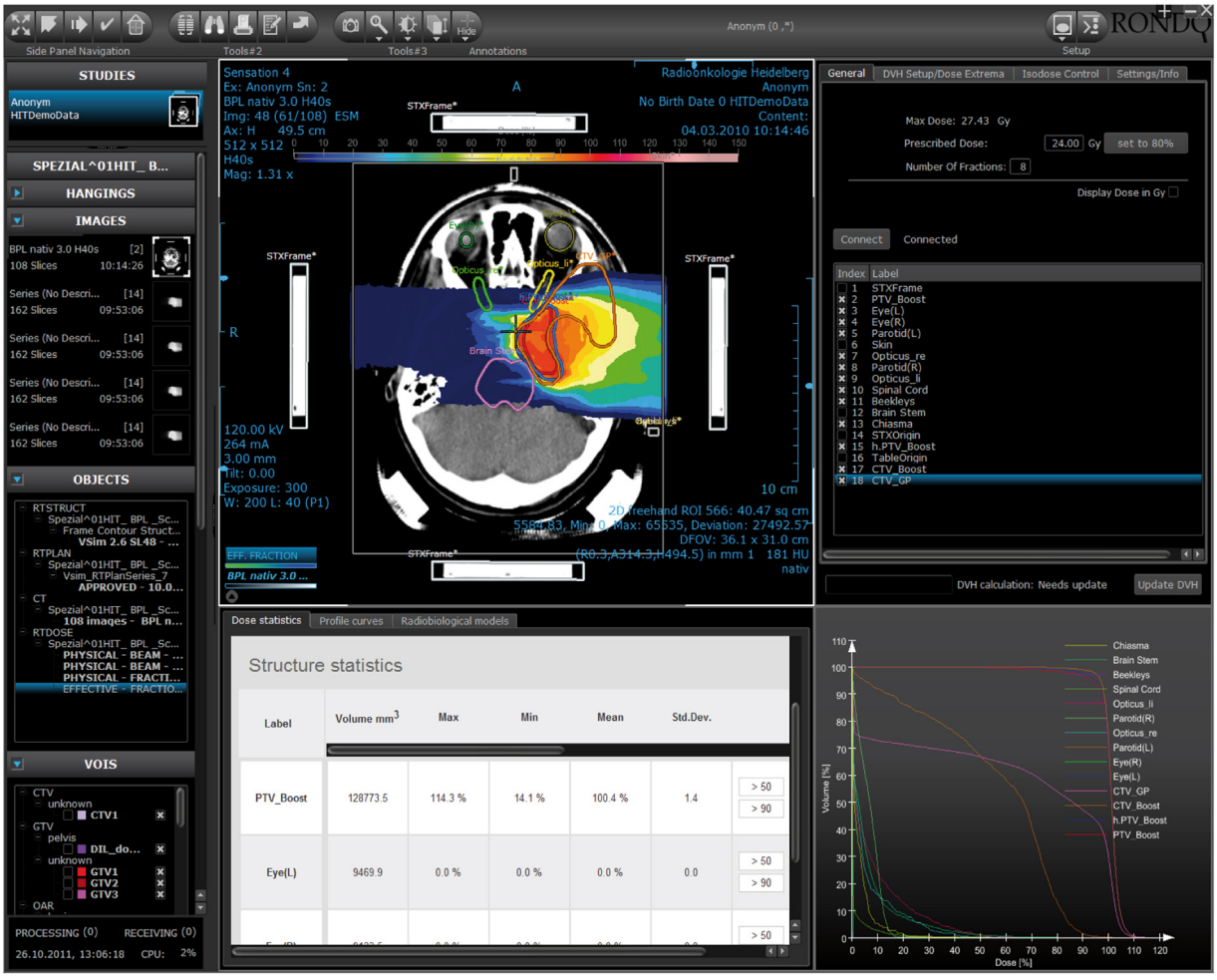

Fig. 5 – RONDO radiotherapy plan review.

4.2. *Flexible visualization and usage*

The separation between data, models and visualization enables flexible visualization and usage of the evaluation software. A wrapper between the evaluation software and a visualization software should be developed. Due to the data abstraction layer only the conversion between the output of the data abstraction layer and the data formats of the visualization software should be implemented to enable the visualization of the data.

As an example visualization tool for the RTToolbox, we decided to use MeVisLab, as it provides fast development of application prototypes. MeVisLab is a platform for image processing research and development with a focus on medical imaging. It was developed by our cooperation partners Fraunhofer MEVIS and MeVis Medical Solutions. Some wrapper modules were developed to provide most functionalities of RTToolbox in MeVisLab and support a user interface (see Fig. 4). The outputs from the data abstraction layer were converted to the MeVisLab data formats to enable 2D and 3D visualization for the important radiotherapy data such as dose distribution, structure set and DVHs. Important components of the evaluation engine were integrated in the wrapper models to support the selection of algorithms and parameters, the calculation of models and so on. The MeVisLab wrapper modules for the RTToolbox were implemented using C++ and Python.

4.3. *Integration in a workflow oriented system: RONDO RT plan review*

Thanks to presented design concepts, the RTToolbox has now been integrated into the RONDO platform [37] developed within the DOT-MOBI project (http://www.projekt-dot-mobi.de) to support plan review and comparison for radiotherapy (see Fig. 5). The user can select a dose distribution and drag it to the inspector-window. The corresponding plan, structure set and CT information are gathered and visualized automatically. Then the DVHs are calculated for the selected VOIs and the DVH curves are shown in the curve-window. The dose statistics and coverage/homogeneity index are computed to compare or rank the plans. The maximum/minimum dose of selected VOIs and the corresponding voxel positions can be displayed in the CT image. It provides also radiobiological evaluation using EUD, BED and TCP/NTCP curves.

5. Conclusions

A software solution that not only supports comprehensive plan review and model calculations, but also facilitates easy data exchange between different systems and enables flexible model extension is essential to support large-scale quantitative evaluation, comparison and therefore optimization of radiotherapy. There are a number of tools published in this context. However, none of them could meet all of our demands. Here, we presented important requirements and design considerations for such a software solution. Using a well-designed data abstraction layer, the developed software can be integrated easily in different radiotherapy evaluation applications. As a proof of concept we have developed an object oriented C++ library, the RTToolbox, to support the full range of radiotherapy evaluation for different use cases. The flexibility of the RTToolbox has already been tested in larger-scale software systems such as the RONDO platform. Future work will focus on extension of the analysis tool for the parameter uncertainty analysis of radiobiological models based on patient data.

The current version of RTToolbox (v 2.0 rc) is released as open source code under the GPL v3.0. Interested researchers are invited to contact the authors or go to project website (http://sourceforge.net/projects/rttb or http://www.dkfz.de/en/sidt/projects/rttb/info.html).

Acknowledgements

Parts of this work were supported by the Federal Ministry of Education and Research (BMBF) Germany, grant number 01IB08002 (DOT-MOBI). We wish to thank OFFIS e.V., Fraunhofer MEVIS and MeVis Medical Solutions AG for ongoing support. We would especially like to thank Alexander Köhn and Christoph Brachmann from Fraunhofer MEVIS as well as Daniel Unholtz from the Heidelberg Ion-Beam Therapy Centre for their work and support in several of the use cases.

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