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The Linear Quadratic Model:

Theoretical Overview and Application Examples

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Outline: *Biological Equivalent Dose*

I. Regulatory Framework

II. Mathematical Formulation

III. Examples: Classical Cases

IV. Example: Stereotaxy

Cyril Voyant, Daniel Julian, Rudy Roustit, Katia Biffi, Céline Lantieri. **Biological effects and equivalent doses in radiotherapy: A software solution**. Reports of Practical Oncology & Radiotherapy, Volume 19, Issue 1, 2014, Pages 47-55, ISSN 1507-1367.

http://dx.doi.org/10.1016/j.rpor.2013.08.004

https://cloud.minesparis.psl.eu/index.php/s/dzoXsjaD9MCc5aw/download

https://github.com/cyrilvoyant/LQ-Equiv

Original research article

Biological effects and equivalent doses in radiotherapy: A software solution

Cyril Voyant [a b], Daniel Julian [c], Rudy Roustit [d], Katia Biffi [b], Céline Lantieri [b]

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Abstract

Background

The limits of TDF (time, dose, and fractionation) and linear quadratic models have been known for a long time. Medical physicists and physicians are required to provide fast and reliable interpretations regarding delivered doses or any future prescriptions relating to treatment changes.

Aim

We, therefore, propose a calculation interface under the GNU license to be used for equivalent doses, biological doses, and normal tumor complication probability (Lyman model).

Materials and methods

The methodology used draws from several sources: the linear-quadratic-linear model of Astrahan, the repopulation effects of Dale, and the prediction of multi-fractionated treatments of Thames.

Results and conclusions

The results are obtained from an algorithm that minimizes an ad-hoc cost function, and then compared to an equivalent dose computed using standard calculators in seven French radiotherapy centers.

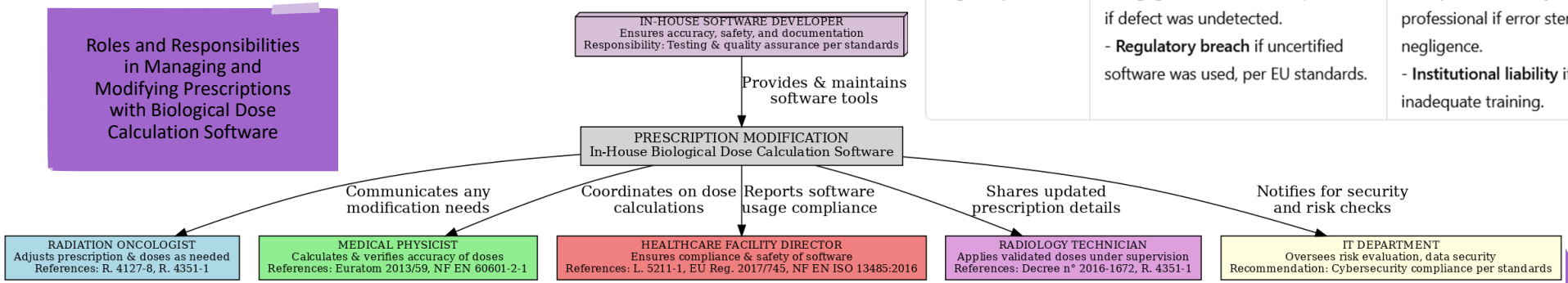
Non-Compliance with Guidelines: Prescription Modification

- **Patient-Specific Response**: Adjust for individual reactions;
- **Dosage Correction**: Fix initial calculation errors;
- **Health Status Changes**: Adapt to evolving patient conditions;
- **Optimize Efficacy**: Update doses per latest guidelines;
- **Reduce Side Effects**: Modify doses to limit adverse effects;
- **Software Updates**: Revise as software methods change;
- **Regulatory Compliance**: Adjust to meet new standards;
- **Data Entry Errors**: Correct to ensure accurate dosing;
- **Treatment Interruption**: Quantify radiobiological impact; adjust; fractionation and schedule if needed. This summary captures essential reasons for modifying a prescription concisely.

Comparison of Responsibilities and Legal Implications in Cases of Software Defect vs. User Error in Medical Dose Calculation

Case Study	Defective Software: Patient dies or suffers irreversible harm due to a software defect causing incorrect dose calculations.	Misuse of Software: Patient dies or suffers irreversible harm due to a user error in dose calculation.
Primary Responsibility	**Developer**: Responsible for testing and safety compliance (e.g., **EU Reg. 2017/745**). Negligence liability if a defect caused harm.	**Physicist/Oncologist**: Responsible for accurate data entry and following protocols. Liability if misuse caused harm.
Secondary Responsibility	**IT Department**: Accountable if risk monitoring was insufficient to catch defects.	**Healthcare Facility Director**: Responsible if training or guidance was inadequate. Liability for insufficient protocols or oversight.
Shared/Indirect Responsibility	**Facility Director**: Liable if the software was uncertified or improperly vetted for clinical use.	**Developer**: Some responsibility if unclear interface contributed to error. Must ensure software is intuitive and provides clear instructions.
Legal Implications	- **Negligence** for the developer or IT if defect was undetected. - **Regulatory breach** if uncertified software was used, per EU standards.	- **Malpractice** liability for the healthcare professional if error stemmed from user negligence. - **Institutional liability** if misuse was due to inadequate training.

Roles and Responsibilities in Managing and Modifying Prescriptions with Biological Dose Calculation Software



Enhanced Timeline of Key Publications in Radiotherapy

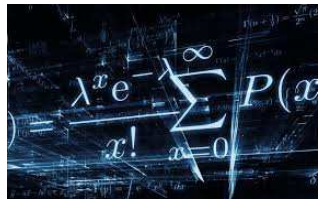
LQ Model

- **Foundation and Early Models:** The LQ model's basis was laid by Lea & Catcheside (1942) with the indirect action of radiation, later expanded by models for dose fractionation (Thames & Bentzen, 1985) and complication probability (Lyman, 1985).

- **Key Concepts Introduced:** BED (Fowler, 1989) and tumor repopulation factors (Dale, 1989) became essential for fractionated treatments.

- **Advanced Modifications:** Extensions for high-dose (Astrahan, 2008) and inhomogeneous dose distributions (EUD by Niemerko, 2000) refined the model.

- **Terminology and Standardization:** Standardized BED terminology was established (Bentzen, 2012), with RBE quantification critical for ion and proton therapy (Elsässer, 2010; Paganetti, 2019).



1942 — The Mechanism of the Indirect Action of Radiation
Lea & Catcheside
Introduced the indirect action of radiation, foundational to the LQ model.

1985 — Fractionation Analysis Using Log Survival
Thames & Bentzen
Explored bifractionation for dose fractionation analysis in radiotherapy.

1985 — Complication Probability from Dose-Volume Histograms
Lyman
Developed NTCP model, a key tool for complication probability prediction.

1989 — The Linear-Quadratic Formula and Progress in Fractionated Radiotherapy
Fowler
Established BED using the LQ model for fractionated radiotherapy.

1989 — Time-Dependent Tumour Repopulation Factors in Linear-Quadratic Equations
Dale
Introduced repopulation factors for time-sensitive treatments.

1996 — Kick-Off Time for Tumor Cell Repopulation: Impact on Treatment Outcome
Van Dyk
Defined 'kick-off' time for tumor repopulation impacting treatment outcomes.

2000 — Equivalent Uniform Dose Formulation Based on the LQ Model
Niemerko
Proposed EUD concept for analyzing inhomogeneous tumor dose distributions.

2008 — Linear-Quadratic Linear Model. Extending the LQ Model for High Doses
Astrahan
Extended LQ model for high-dose treatments with the LQL modification.

2009 — BED Application in Radiohyperthermia
Plataniotis & Dale
BED in radiohyperthermia - Assesses hyperthermia's tumor control contribution.

2010 — Quantif of RBE in Ion Beam Therapy
Elsässer
Quantification of RBE in ion beam therapy - Essential for ion therapy efficacy.

2010 — 21 years of Biologically Effective Dose
Fowler
Comprehensive review of BED applications.

2012 — Standardized BED Terminology in Radiation Oncology
Bentzen
Standardized BED terminology - Sets key units and concepts for radiotherapy.

2019 — Relative Biological Effectiveness of Proton Beams in Radiation Therapy
Paganetti
RBE of proton beams - Foundational report for proton therapy planning.

LQL-Equiv Software

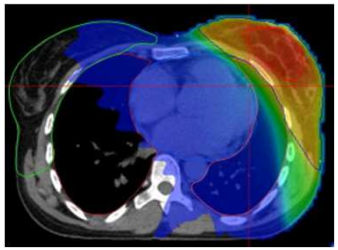
- Purpose and Interface: LQL-Equiv provides a user-friendly calculation interface for medical physicists and radiotherapy doctors to manage equivalent and biological doses and to predict tumor complication probabilities (using the Lyman model).

- Main Features of LQL-Equiv Software:

  - Biological and Equivalent Dose Calculations: Designed to calculate doses based on multiple models, including Astrahan's Linear-Quadratic-Linear (LQL) model and Dale's repopulation effects.
  - Multi-Fraction Effect Prediction: Capable of modeling multi-fraction radiotherapy treatments, accounting for fractionated treatment effects and dose variations.
  - Lyman Model Integration: Incorporates the Lyman model to calculate normal tissue complication probability, enhancing risk assessment for administered doses.

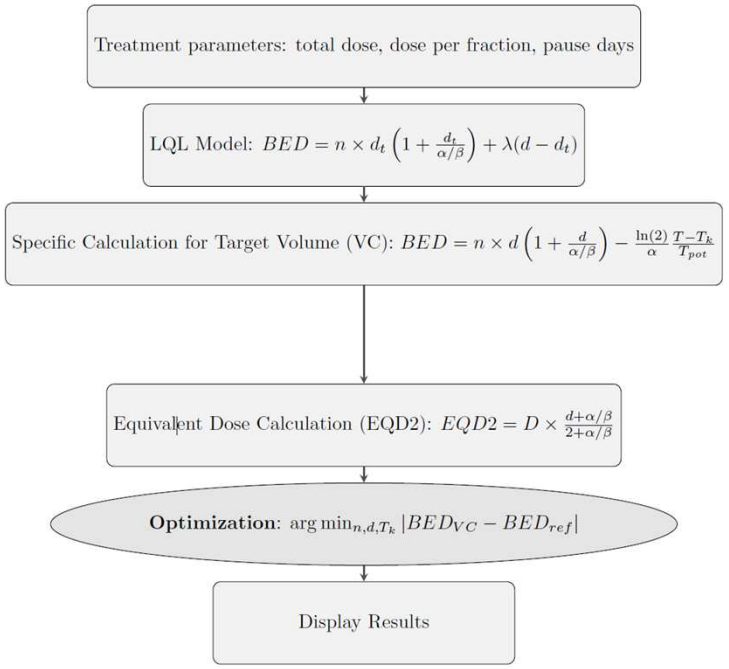
- Use in Radiotherapy Centers:

  - Limited information is available on the extent of LQL-Equiv's adoption in radiotherapy centers. However, due to its advanced calculation capabilities and GNU licensing, it is likely used in research contexts and possibly in some specialized centers.



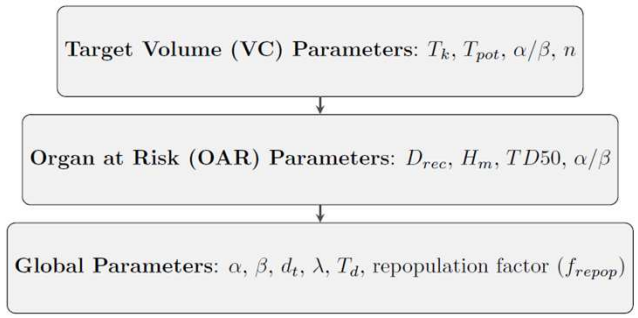
Here are the key points on the **LQL-Equiv Software** as presented in the article *"Biological effects and equivalent doses in radiotherapy: A software solution"* by Cyril Voyant and Daniel Julian, published in *Reports of Practical Oncology and Radiotherapy* in 2014

Calculation Process and Specific Parameter List for Target Volume (TV), Organ at Risk (OAR) and Global Parameters

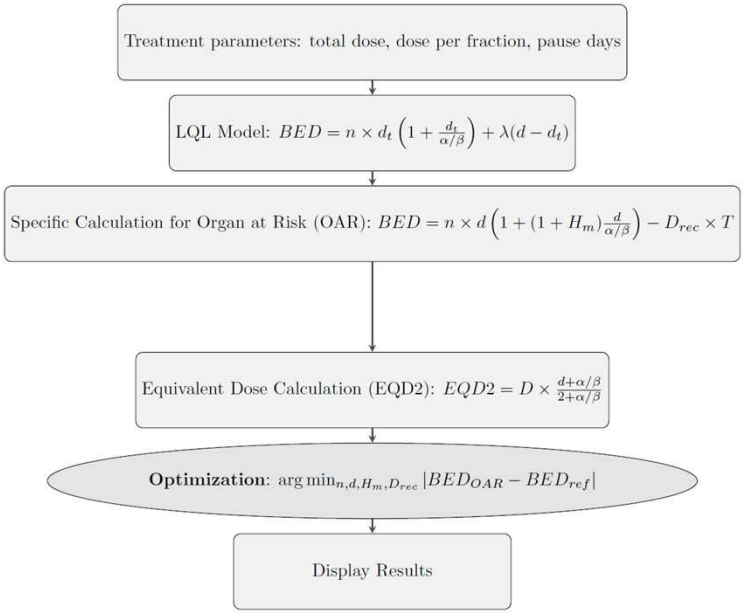


TG

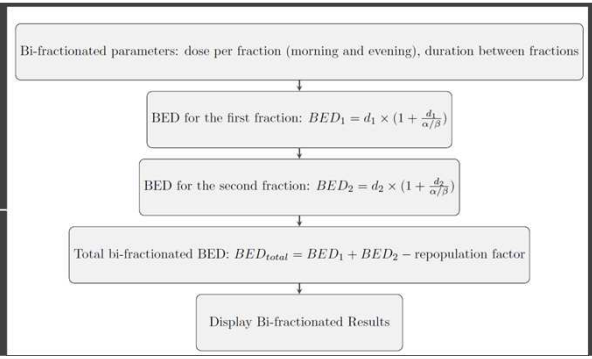
Specific Parameter List for VC, OAR, and Global



OAR



Calculation Process



Optimization and Overall methodology

Current Method: Brute Force Optimization

- A classic brute force approach is currently used to minimize the cost function.
- The cost function evaluates the difference between the predicted BED (Biological Effective Dose) and the target BED.
- This approach tests multiple parameter combinations to find the configuration that minimizes the cost function.
- While effective, brute force is computationally intensive and may not scale well with complex or high-dimensional data.

Future: Machine Learning-Based Optimization

- The goal is to transition to a machine learning approach for optimization.
- Machine learning models, such as neural networks or advanced optimization algorithms, could predict optimal parameters more efficiently.
- A data-driven model would potentially learn patterns from historical cases, allowing for faster and more accurate optimization.

This shift would reduce computational overhead, improve accuracy, and enable adaptive adjustment to new data patterns.

AI Integration to Replace the Numerical Model :This transition aims to enhance the optimization process by leveraging predictive capabilities and reducing reliance on exhaustive search methods.

Clinical Case #1

ORL (oropharynx)
Le schéma SIB est le suivant
33x2,12Gy pour T & N+
33x1,54 pour N-
Dmax_moelle=13Gy au bout de 10 Fractions

Sein
Le schéma est le suivant
25x2Gy pour le Sein
8x2Gy pour SI
EUD_Coeur=2,5Gy au bout de 10 Fractions

Vessie
Le schéma est le suivant
35x2Gy
D10_Grêle=13Gy au bout de 10 Fractions

Contexte
Un patient reçoit un traitement curatif qui doit être interrompu en raison d'une toxicité cutanée radio-induite. Cette interruption dure 1 semaine et survient après 2 semaines de traitement, correspondant à 10 fractions administrées..

Problématique clinique et dosimétrique
Déterminer le schéma thérapeutique optimal pour la poursuite du traitement. Les critères à respecter sont les suivants :

- **Dose maximale au niveau médullaire (PRV) : 45 Gy.**
- **Dose moyenne au niveau cardiaque (EUD) : 7 Gy.**
- **Dose à l'organe maximale au grêle : V50 < 10%.**

Evaluer les effets potentiels du traitement, tant aigus que tardifs, tout en identifiant les facteurs limitants concernant les organes à risque (OAR). Il est impératif de maintenir une toxicité (**NTCP**) inférieure à 5 % et de **conserver** le nombre initial de fractions prévues.

ORL

Inscrire la Dose par Fraction :

Sein

Inscrire la Dose par Fraction :

Vessie

Inscrire la Dose par Fraction :

Clinical Case #2

Options de schémas thérapeutiques proposés pour la surimpression
Plusieurs options de fractionnement ont été envisagées pour répondre à ces objectifs dosimétriques

Approches séquentielles
10 x 3 Gy + 3 x 2 Gy
10 x 3 Gy + 2 x 3 Gy
15 x 2,5 Gy + 1 x 5 Gy

Approches par boost intégré simultané (SIB)
10 x 3 Gy ^ 10 x 3,2 Gy
10 x 3 Gy ^ 10 x 3,5 Gy
10 x 3 Gy ^ 10 x 3,6 Gy

Contexte

Dans le cadre d'un traitement palliatif pour une métastase cérébelleuse d'origine mammaire, une irradiation cérébrale de 30 Gy en 10 fractions est prévue.
Cependant, la métastase au niveau du cervelet, particulièrement symptomatique, nécessite un renforcement de dose ciblé pour améliorer le contrôle tumoral local et soulager les symptômes, tout en respectant les contraintes de dose pour les organes à risque, notamment les structures visuelles et le parenchyme cérébral.

Problématique clinique et dosimétrique

Déterminer le schéma thérapeutique le plus adapté pour délivrer la surimpression au niveau de la métastase tout en respectant les contraintes suivantes :

- **Dose maximale au niveau cérébral** : 55 Gy.
- **Dose minimale au niveau de la métastase** : garantir au moins 40 Gy.
- **Protection des organes à risque liés à la vision** : < 45 Gy pour les OAR « Vue ».
- **Privilégier les traitements courts**

Choix Pour Approche Séquentielle

Inscrire le Nombre de Fractions :

Inscrire la Dose par Fraction :

Choix Pour Approche SIB

Inscrire la Dose par Fraction :

Choix Global

Choix de la méthode :

1. Séquentielle
2. SIB

Clinical Case #3

Calculer l'équivalence en dose biologique pour un traitement de référence de 3Gy
Ou alors faire le calcul pour une référence de 2Gy et faire coïncider les équivalences initiales et proposées

Nbre de Fractions = 5
5x3 (2 semaines) 5x3,1
5x3 (2 semaines) 5x3,5
5x3 (2 semaines) 5x3,8

Nombre de Fractions ≠5
5 x 3 Gy ^ 1 x 8 Gy
5 x 3 Gy ^ 3x 4 Gy
5 x 3 Gy ^ 10 x 2 Gy

Contexte

Un patient atteint d'un cancer pulmonaire métastatique est en traitement de radiothérapie ciblant les vertèbres L2-L3. Le plan de traitement initial prévoit une dose de 30 Gy répartie sur 10 fractions.

Problématique clinique et dosimétrique

Après la première semaine de traitement (5 fractions administrées), le patient est hospitalisé, entraînant une interruption du traitement de 2 semaines. Afin de terminer le traitement en maintenant les mêmes effets biologiques que ceux initialement prévus, proposez un schéma thérapeutique de reprise du traitement :

Dans le cas où le nombre de fractions est conservé (reste à 5 fractions en tout pour la reprise).

Dans le cas où le nombre de fractions est modifié (avec possibilité d'augmenter ou de diminuer le nombre de fractions restantes).

Même Nombre de Fractions

Inscrire la Dose par Fraction :

Nombre de Fractions Différent

Inscrire le Nombre de Fractions :

Inscrire la Dose par Fraction :

Choix Global

Choix de la méthode :

1. Nbre de Fractions = 5
2. Nbre de Fractions ≠ 5

Thank you for your kind attention

I would like to express my sincere gratitude to the organizers of this excellent conference