Radiotherapy and Oncology 196 (2024) 110277

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

# A joint physics and radiobiology DREAM team vision – Towards better response prediction models to advance radiotherapy

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ARTICLE INFO

*Keywords:*
Models
Prediction
Radiobiology

ABSTRACT

Radiotherapy developed empirically through experience balancing tumour control and normal tissue toxicities. Early simple mathematical models formalized this practical knowledge and enabled effective cancer treatment to date. Remarkable advances in technology, computing, and experimental biology now create opportunities to incorporate this knowledge into enhanced computational models.

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https://doi.org/10.1016/j.radonc.2024.110277
Received 17 January 2024; Received in revised form 21 March 2024; Accepted 11 April 2024
Available online 25 April 2024

Data science
AI

The ESTRO DREAM (Dose Response, Experiment, Analysis, Modelling) workshop brought together experts across disciplines to pursue the vision of personalized radiotherapy for optimal outcomes through advanced modelling. The ultimate vision is leveraging quantitative models dynamically during therapy to ultimately achieve truly adaptive and biologically guided radiotherapy at the population as well as individual patient-based levels. This requires the generation of models that inform response-based adaptations, individually optimized delivery and enable biological monitoring to provide decision support to clinicians. The goal is expanding to models that can drive the realization of personalized therapy for optimal outcomes.

This position paper provides their propositions that describe how innovations in biology, physics, mathematics, and data science including AI could inform models and improve predictions. It consolidates the DREAM team's consensus on scientific priorities and organizational requirements. Scientifically, it stresses the need for rigorous, multifaceted model development, comprehensive validation and clinical applicability and significance. Organizationally, it reinforces the prerequisites of interdisciplinary research and collaboration between physicians, medical physicists, radiobiologists, and computational scientists throughout model development. Solely by a shared understanding of clinical needs, biological mechanisms, and computational methods, more informed models can be created. Future research environment and support must facilitate this integrative method of operation across multiple disciplines.

## Preamble

RT is one of the cornerstones of cancer treatment. However, it comes with inevitable radiation dose to normal tissues. Achieving best possible treatment outcome for individual patients through informed selection of modalities and their careful application requires a quantitative description of their contribution to tumour control and side-effects with the help of models (see Table 1).

RT responses of normal tissues and disease result from tissue- and tumour-specific response mechanisms that are affected by many treatment, patient- and disease-related factors (Fig. 1). This makes the identification of relevant response patterns in data from modern treatments challenging. Conversely, using such data to increase the understanding of mechanisms and responses is equally challenging as the interactions are often missed in the search for parsimonious mathematical formalisms.

Overcoming these challenges requires a collaborative, cross-disciplinary effort to inform such formalisms with biological experimental models. Therefore, medical physicists, radiobiologists, and computational scientists congregated at the DREAM (**D**ose **R**esponse, **E**xperiment, **A**nalysis, **M**odelling) workshop conducted at the 2022 ESTRO physics meeting in Lisbon, Portugal, to discuss their perspectives and challenges in model development. Aiming to bridge gaps between disciplines and to render accurate radiotherapy (RT) response prediction a "dream come true", a shared mission, and joint strategies and positions were formulated.

This paper aims to provide the vision and related positions derived from this ESTRO DREAM workshop. Here we stress the need for rigorous and multifaceted model development, comprehensive validation, and the need for clinical applicability and significance. We argue that the generation of robust and clinically meaningful models in radiation oncology requires the concerted action of all stakeholders with a shared mission to improve such models through incorporating a variety of methodologies and technologies in an integrated way.

**Table 1**
**Model types in radiation oncology** Central to our DREAM propositions are models. However, the term "models" has different meanings for the different disciplines involved. In general, a model is a simplification of reality, which all disciplines use to improve insight into a process that is studied. A first major distinction can be made between 'experimental models', model systems that allow the experimental interrogation of processes, and 'mathematical and computational models' that offer a quantitative description and simulation of these processes. In our fields, the various types of models are defined as depicted in the table.

| Type | Features | Examples |
|---|---|---|
| Models in experimental biology | Biological systems that aim to recapitulate specific biological entities and processes | Cellular 2D and 3D in vitro models, animal models (Fig. 1B) |
| Epidemiological models | Descriptive, extensive statistical framework for development and validation | Multivariable (logistic) regression analyses |
| Biophysical models | Descriptive, but formulation inspired by mechanistic hypotheses | Functional subunits (FSU)-based models, Lyman-Kutcher-Burman model, linear quadratic model |
| Computational models | Detailed simulation of mechanisms / processes, leading to predicted outcome measures | Monte Carlo simulations, multi-scale models |
| AI and ML | Highly flexible, can handle large numbers of variables, unbiased approaches | Neural networks or classifiers for predicting toxicity, and/or tumour response prediction |

## The DREAM vision

The vision of the DREAM team is "optimal RT treatment outcome by quantitative models that support risk prediction and provide actionable input to clinical patient management". The mission is thus to leverage the full breadth of radiation oncology models (Table 1). This would lead to improved prediction based on a more comprehensive understanding than provided by each of the individual models. The process would include enhanced statistical, mathematical, and computational tools in combination with the implementation of radiobiological concepts supported by bidirectional translation between clinic and laboratory. Such models should be complex enough to allow individualised comparative assessment of multiple treatment strategies involving both RT treatment modalities and techniques as well as drug-radiation combinations.

## Radiation response prediction models to date and unmet needs

Clinical risk prediction models are at the core of recommended dose constraints in RT practice guidelines, treatment schedule design, and individual patient treatment optimization [1,2]. Yet, there is an unmet need for more clinically useful models that provide actionable predictors of toxicity or disease control [3]. The organ-by-organ approach *ad modum* QUANTEC may be reaching its limit. [4,5]. Post-QUANTEC normal tissue complication probability (NTCP) models have improved, in part due to increasing study sizes. An ever-increasing study size, on its own, however, will fail at clinical utility if the studied effects are not actionable or capture a sufficient proportion of the cause-effect relationship for clinical outcome. Irrespective of data quantity, more complex predictors of radiation responses require a better integration of radiation oncology models (Table 1).

Data-driven models that define tumour target volumes and doses are important for treatment outcomes but do not satisfactorily meet the needs of modern RT. While potential benefit of sub-volume boosting has

proven effective in some settings [6], individualized risk prediction for patient selection or dose prescription has not reached clinical practice, despite the potential being described by Ling et al more than two decades ago [7]. The difficulties in model development are further exacerbated by interactions with other treatment modalities such as adjuvant immunotherapy [8,9].

To address these issues, there is an eminent need for a unified effort of radiobiology, physics, data science, and clinical oncology to move thoroughly beyond the current state of science.

## Constraints and challenges in model development

Multiple constraints, such as the complexity of biological systems, poor data, and limited outcome assessments, obstruct the development of accurate and clinically useful models for individualized risk prediction or treatment innovations.

The complexity of biological systems and their responses to external factors pose the greatest challenge in accurately determining and predicting the impact of their components on radiation responses [10,11]. Measurable responses are effectively a summation of effects of countless and often unknown biological factors that together constitute a network of interdependent variables. The response of each individual cell, tissue, tumour, or patient is dictated by an epigenetically, genetically, and importantly, also (micro-)environmentally defined unique combination of these parameters, that contributes to the inherently heterogeneous distribution of dynamic radiotherapy responses across individual patients, tissues, and tumours (Fig. 1).

The large number of these potential biological variables restricts an individual assessment of their quantitative relationships for description in mathematical terms. Therefore, while the absorbed radiation dose may be a reliable and standardizable constant across different systems, the important quantitative association with biological response endpoints is often complicated. Such associations are to be carefully evaluated in a context specific and clinically relevant manner. Yet, an increasing number of important biological markers of radiation response are being discovered and validated that demands appropriate integration into current mathematical models (Table 1) and in suitable mathematical terms.

Clinical data are limited in size, highly heterogeneous, and often deprived of detailed data on important clinical and biological factors. This hampers model development and ultimately limits their performance. The diversity of RT protocols, combined with insufficient or discordant reporting of treatment details, outcomes, or follow-up, can further limit the use of larger aggregated data sets [12,13], contribute to noisy data sets and weaken model performance. Similarly, inconsistencies in the generation of experimental data also add to data heterogeneity in the preclinical setting.

In addition to posing constrains in model development, limited and heterogeneous data also complicate statistical valuations [14]. A limit to the number of similarly treated patients, in addition to the inter- and intra-patient response heterogeneity, poses strong numerical constraints for adequate multivariate analysis and opportunities for independent validations. Concurrently, data analysis strategies that aim to test individual hypotheses may use mathematical or computational models that inherently ignore parameters that were not originally defined but could be of potential significance to their performance. Artificial intelligence (AI) and Machine learning (ML) algorithms can offer a solution to some of these challenges and transform data analysis but remain confronted with the problem of insufficient population sizes that require external validation and appropriate methods against overfitting [15,16].

## Model demands for better radiation response predictions

Current mathematical models that calculate probabilities of tumour responses and normal tissue complications are particularly limited in their ability to 1) accurately adjust risks for individual patients according to clinical and biological factors and 2) properly predict biological dose modifications such as caused by combinations with novel molecular agents or innovative radiation treatment modalities.

### *Better models by better model generation strategies*

The clinical purpose of a model must be considered as an integral part of the model generation, model building and performance assessment strategy. This should happen at the design stage, *prior* to tasking a researcher with data collection or analysis. The words of Douglas Altman, *We need less research, better research, and research done for the right reasons,* are still relevant 30 years after the first publication [17]. To enhance the clinical utility of models, a clearly formulated potential addition to our clinical service as a long-term goal of a modeling strategy

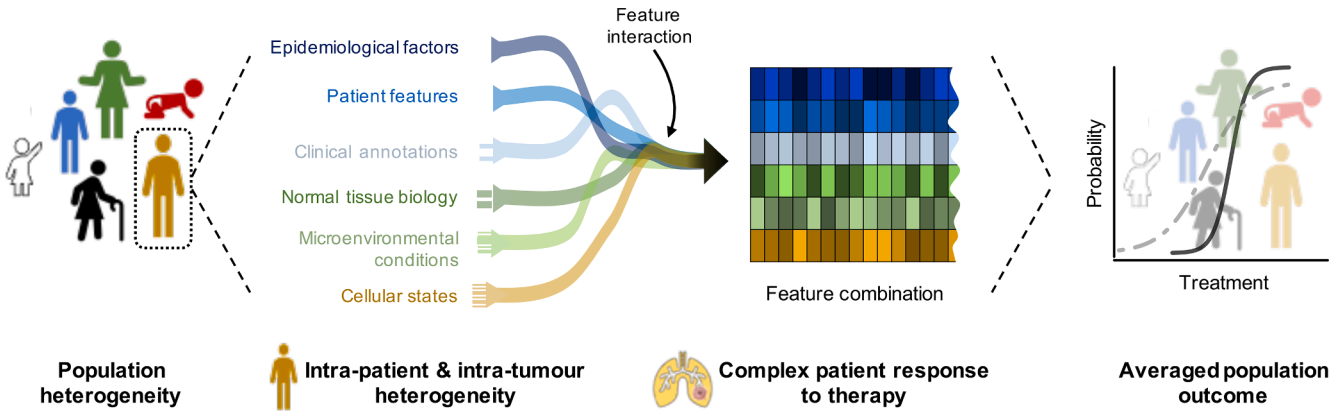


**Fig. 1.** Clinical outcomes are a product of heterogenous and complex biological systems. The high complexity and heterogeneity of biological systems poses challenges in generating treatment outcome prediction models for radiotherapy optimization. Multiple interacting features and states determine the biological effect, giving rise to heterogeneous responses to identical treatments. The variation in outcomes observed between patients (population heterogeneity) results in part from differences in biological (eg. genetic background, age, sex), clinical (eg. comorbidities), and socioeconomic and lifestyle factors (eg. access to healthcare, smoking status). Many additional and patient-specific factors contribute to this heterogeneity. These factors include normal tissue derived, as defined by tumour location, or tumor tissue associated such as microenvironmental (eg. perfusion/oxygenation, immune infiltration, presence of stromal cells) and tumour cell state related that are defined by innumerable molecular and genetic elements and interactions (eg. Mutational profile, differentiation and metabolic status). Together they amount to a unique constellation of response determining features in each individual patient. The probability for different treatment outcome parameters, such as cure or injury from treatment, depends on the combined effect of all these different features and is the root of the highly heterogeneous response to therapy within and between patients.

should be a requirement.

Modeling strategies can be based on clinical data, may involve translations between lab and clinic or follow a testable hypothesis. Model generation strategies should involve independent verifications and model validation steps. There should be a conscious assessment of the avenue forward and destination. Key elements to be considered in model development are dimensionality levels, model quality metrics and validation strategies. Suboptimal performance linked to low dimensionality and overfitting issues associated with high dimensionality require the use of appropriate model quality metrics and can be further optimized with input from experimental models [16]. Recent radiation toxicity prediction studies (QUANTEC and preclinical lung models) exemplify the advances provided by such strategies in model development [18–20]. In the context of Artificial Intelligence (AI) and Machine Learning (ML), methods to ensure transparency and explainability of the models (known as xAI) should also be considered as critical part of the model generation process [21,22].

Clinical outcome models should capture the complexity of the underlying biology, but only to the level where it has a demonstrable impact on outcome. This contrasts with models offering a more comprehensive or detailed description of biology that are more useful for experimental testing, e.g., of mechanistic hypotheses, and that may be informative for subsequent clinical evaluations. Generalizability for any specific clinical scenario is vital. The appropriate reporting of model development design and mathematical algorithms is therefore critical to enable independent validation by other researchers to substantiate its use in the respective specific clinical scenario.

*Prospects using AI*

One of the benefits of AI, and more specifically its algorithmic ML subfield, is its potential to handle large and complex multivariable datasets. AI/ML algorithms are currently transforming the field of radiation oncology with applications spanning its workflow from patient selection and prescription, auto-contouring, treatment planning, to quality assurance prescription from outcome prediction to treatment adaptation [23,24]. The multitude of AI/ML algorithms and training ML methods, such as deep convolutional neural networks (CNNs) facilitate their application for the development of classifiers for improved outcome prediction or the extraction of critical variables and parameters for inclusion in personalized prediction models and treatment planning. For this purpose, larger and more diverse and representative data populations are required, despite the growing opportunities to overcome the performance-limiting effects of small sample sizes on ML models. Federated (distributed) learning is encouraged as a data sharing procedure to increase data quantity [25,26]. In a knowledge-based approach, translational efforts can guide the optimal selection of predictors, either retrospectively or prospectively, based on previously accepted radiobiological and technical knowledge. Given its success and in addition to the anticipated potential of AI in radiation oncology outcome modelling, preclinical radiobiology studies can also strongly benefit from AI/ML applications or increase their clinical relevance.

Reversely, preclinical radiobiology studies offer ample opportunities to test hypotheses on putative causal relationships inferred from clinical data by AI thus addressing some of its current limitations and challenges in advancing radiation oncology [27–29]. Radiobiological studies and models are also well-suited to investigate the potential mechanisms underlying patterns and relationships revealed by AI-supported data analyses.

*Better models by a better understanding of mechanisms and biology*

Data from preclinical studies help generate mechanistic hypotheses for the generation of clinically applicable models. They may also inform models regarding extrapolations or adaptations, for example to address uncertainties in biological effectiveness introduced by technological and pharmaceutical changes to treatment for effect estimates in the clinic [30,31].

Experimental models are crucial to determine dose response patterns and to understand the biological mechanisms underlying radiation responses [32]. They allow an in-depth assessment of individual biological processes and concepts in an isolated manner. A multitude of different preclinical experimental models with varying complexity (Fig. 2) are available to date and support the validation of mechanistic concepts derived from these studies or discovered in clinical data studies. Ultimately tested in the clinical setting, such mechanistic insights can strengthen clinical response predictions and models. A continued effort to optimize these experimental models for this purpose will improve clinical response prediction models [18,33,34]. As the values are not generally transferable to the clinic, radiosensitivity parameters from preclinical experiments or deduced from patient specimen-based analysis are to be optimized for this purpose. While the experimentally established dose–response mechanisms may translate into the clinical setting, the clinical model parameter values are likely different from the experimental ones. Qualitative relationships are however transferable, yet demand better and widely applicable parameterization methods, their development achievable by the concerted interdisciplinary efforts proposed here.

Improved understanding of biology can also help with uncertainties that play an important role when translating findings to and across different clinical settings or when attempting to predict responses by extrapolation from mathematically described response relationships. Different parameterization methods can be helpful in this process. Extrapolations based on mathematical models however show a high parameter sensitivity that contributes to uncertainties; uncertainties that could be reduced by mechanistic assumptions [35,36]. Nevertheless, these extrapolations, when supported by appropriate mathematical models, can be tested in the clinic and in a preclinical setting. ML/AI assisted data mining studies could have an important role in hypothesis generation, by identifying variables that are to be investigated in subsequent systematic experiments [37]. Reversely, clinical investigations and/or biological experiments could improve feature selection also for ML/AI algorithms by identifying or prioritizing which data should be collected and which features should be investigated [38,39].

Next to mechanistic insights, preclinical experimental model studies also provide an important opportunity to assess the impact of novel experimental treatments. To advance radiotherapy, an important mission of many translational radiobiology studies is to investigate novel technologies, modalities, or agents that reduce damage to normal tissues or increase irradiation effects solely in tumours. Within the realms of the workshop objectives, this stresses the need for mathematical or computational models that allow a better comparison of experimentally determined radiation response relationships across different experimental models and studies with the aim to inform clinical trial setting and designs or for better risk assessments.

Experimental models can be used in studies that aim to improve the clinical utility of prediction models [1,40,41]. While individual values, needed to estimate risks in the clinic, cannot be produced or validated in the preclinical setting, radiobiological concepts can be validated. The choice of the experimental model should however be carefully made, providing both a sufficiently high specificity but also sensitivity to test the hypothesis generated from the clinical data. Validation may be obstructed by clinic-specific circumstances or methodologies that could conceal important confounders relevant to the hypotheses (smoking or diabetes are some examples). It is therefore beneficial to make sure to integrate the respective discipline's expertise prior to study design to optimize the legitimacy of such tests as noted earlier.

*Better models by better data and metrics*

Increasing data size and quality is paramount to optimal model development [27,42] and this demands that also GDPR related

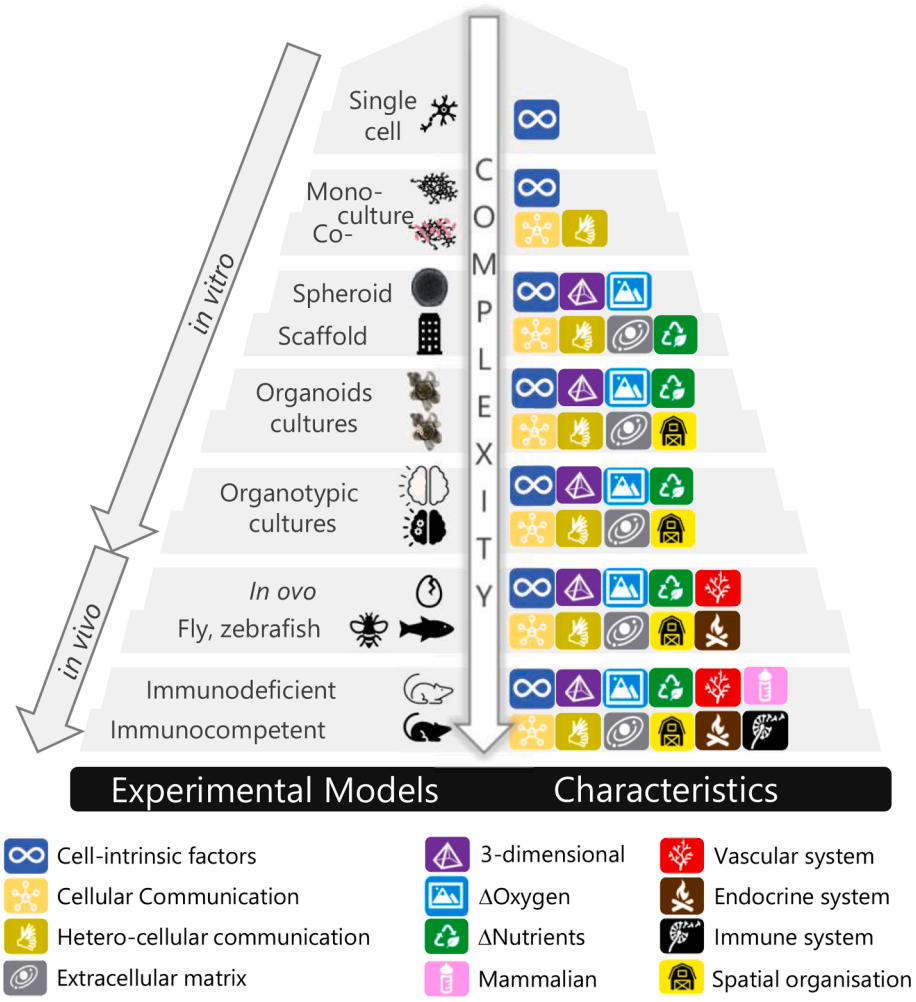


**Fig. 2.** Experimental model complexity Representation of experimental models (Table 1) that are routinely utilised in preclinical radiation biology research and the key characteristics they encompass. The role of certain individual key features (Fig. 1) in radiation response can be interrogated using different experimental models according to the characteristics of the human cancer or healthy tissue constitution that they aim to emulate. Multiple experimental models are being used to understand and evaluate changes in radiation responses, from the most basic using single cells to the most compounded, such as immunodeficient, immunocompetent mammalian models. As depicted in the pyramid, in a progressive comprehension of both normal tissue and cancer response, the ascending complexity of these experimental models results from the increasing number of relevant molecular and biological elements they are composed of (as depicted by symbols). The more complex models provide an opportunity to investigate characteristics absent in the others (such as the role of an intact immune system) and to analyse a potential interplay between the interrogated features. On the other hand, some molecular and cellular mechanisms are most accurately assessed in less complex in vitro models that provide a tractable context.

limitations and real-world data collection challenges are addressed. Improved data collection tools and methods, refined patient related outcome measures and clinician reported measures can contribute to increased data quality, and ultimately clinical utility of such models.

Important to data acquisition and analysis is the appropriate reporting following standards that will need to be defined by interdisciplinary working group efforts. A more conscious effort is required to farm data with common endpoint definitions and accepted reporting variables that are crucial to improved data utility [12,27,43].

Conversions of the absorbed dose to tissue and treatment-specific related quantities are necessary approaches to estimate dose-limiting normal tissue complication probability for treatment plans in clinical practice [44,45]. These conversion methods are to be considered in preclinical experiments and can be questioned in accordingly designed preclinical experiments using different experimental models to account for different levels of complexity (Fig. 1). However, despite having clear utility, translation of such biological effective doses between these systems are non-trivial. Dose response relationships projected from disparate research subjects and differing endpoint measures restrict translation across different systems [11,46,47]. The result is that existing radiation response measures are unlikely to possess sufficient subtlety to capture individualized response and allow biological dose modification. Thus, better measures and computational models will have to be established that enable an aggregation of such values from different experimental results to increase compatibility across clinic and preclinical studies.

### *Better models with improved clinical utility*

Current practice using single dose–response constraints in treatment planning can be improved by the consideration of risk factors such as the clinical factors, patient performance, risk factors of recurrence, and lifestyle. Many options exist for individualized treatment improvement by providing clinical decision-support systems according to the DREAM vision. Success is, however, contingent on the utility of the models in the clinical context.

In this context it will be also important to embrace collaborations with industrial partners. Such collaborations are essential to facilitate

data collection and comparisons across facilities. They also enable the generations of models that are in line with novel radiotherapy technology plans by these industrial partners.

Experimental models and statistical outcome modelling from clinical data are complementary tools that should be considered in conjunction. The clinical utility of a given model or study should however be considered at all stages of the model development, including the translation between laboratory and clinic. In some cases, such as when investigating a mechanistic coupling of organs at risk for cardiotoxicity [18], the experimental models provide critically important insights and lend credibility to the results. The analysis of clinical data, such as the assessment of model performance over a time-varying case-mix in clinical practice, can be an appropriate alternative tool [48].

In addition to clinical credibility, it is necessary to provide quantitative estimates of model performance – relevant for the individual clinical use case – on datasets which are independent in time and place. This also implies a need to publish the models and provide adequate descriptions of the studies' metrics [49]. The external validation of models is important and should be prioritized by using appropriate performance metrics assessed in the external dataset [50].

Neither of these aspects are prohibitive towards high dimensionality or AI models despite the increased complexity. Modern high dimensionality methods are purposely developed to handle the complexity appropriately. However, the more complex the model the greater the consequences of inadequate external validation or inadequate model reporting on model prediction quality [51]. Consequently, in this emerging era of high-dimensionality modelling, the relevance of the translation between experimental models and mathematical models becomes ever more important.

### *Clinical utility of AI-based models*

Radiobiological responses involve complex interactions between patient, treatment, absorbed radiation dose distribution, and tumour microenvironment factors in a multi-omics setting. AI/ML has strengths compared to conventional statistical modelling at identifying non-prespecified and non-linear interactions and should therefore be very well suited for radiobiological applications. Examples of such translational research application opportunities are preclinical studies that make use of AI to develop biomarkers using preclinical models with defined molecular and cellular characteristics in order to test the relevance thereof in clinical outcome studies[52]. or the use of preclinical study data to inform the development of radiomics/imaging-based prediction models using AI [15,53,54]. However, the use in the clinical and preclinical radiobiology scenarios is yet to be fully exploited.

AI-based TCP/NTCP models are multifactorial and susceptible to overfitting and prediction bias risks [55]. Thus, quality assurance of these models should be considered during the development phase and maintained post deployment for as long as the model is clinically used through multidisciplinary collaboration (post-deployment surveillance). A distinction is yet to be made between training/development and deployment in the field [56]. External validation of prediction models is an important step prior to their deployment and clinical use [49,57]. However, legitimate concerns have been raised regarding the risks of overfitting, shortcut learning as well as biases when deploying these techniques [58,59]. Basic independent and external validation requirements are often not met. This can lead to poorly performing models as exemplified in controversial applications during Covid-19 [60–62] and the EPIC sepsis model debacle [49,63]. To overcome this challenge, several societies and journals have been developing guidelines and checklists to ensure rigor and reproducibility of AI/ML methods emphasizing the need for transparency in development and independent validation processes for deployment [49,56]. Known casual relationships should be respected for safe clinical application. The development of a checklist for RT outcome modelling was suggested during the workshop and can be modified for more extensive radiobiological response schemes using not only retrospective but prospective validations as well.

## Interdisciplinary approaches to improved model development

Radiobiology provides the conceptual basis for the description of RT responses by identifying the underlying processes. Most clinical models are, at their core, parsimonious, and phenomenological – attributes that limit the integration of radiobiological findings and biomarker studies. The architecture of current models will have to be revised to enable the integration and adaptation of multiple response defining variables as defined by their relevance in individual radiobiological and clinical studies. This demands both accurate and robust measurements of biological response to radiation using different experimental models or samples analyses, and suitable quantitative descriptions through mathematical models. In support of this process that requires the expertise in biological mechanisms and experimental validation methodologies, as well as clinical model development and medical physics, (Fig. 3) it is crucial to establish close collaboration across all disciplines [64,65] that is fostered by an interdisciplinary research community composed of medical physicists, radiobiologists, radiation oncologists, computational scientists, radiation therapists, radiologists, radiographers, epidemiologists, statisticians and others in the field. Consequently, to improve the utility and relevance of radiation oncology models, the partners in these collaboration are to define the relevant approach together and early during the study-design phase. To further foster such modelling efforts and improvements, interdisciplinary research will also have to be nurtured and facilitated by supporting structures and exchange opportunities to realize truly integrated multidisciplinary approaches [66–68]. Integrally interlinked from the outset, a close partnership between specialities will undoubtedly generate a multitude of opportunities to strengthen clinical model development and to resolve the restricted translation of biological experimental and analytical data into clinical practice.

Well-placed within ESTRO and ESTRO's vision [69], dedicated scientists would be able to combine expertise and data in international and interdisciplinary networks of radiation oncology model developers. However, there is an apparent lack of integrated approaches to establish strong partnerships and joint strategies across disciplines. This is further impeded by a paucity of international collaboration funding opportunities.

## The DREAM team propositions

This position paper highlights the challenges met by physicists, radiobiologists, data scientists and oncologists in advancing dose response, experiment, analysis, and modelling for RT. The DREAM workshop that discussed these produced propositions to address these challenges (Table 2). Propositions were generated that 1) address the scientific needs and requirements to improve radiation oncology models (Table 2A) and that 2) support interdisciplinary partnerships to achieve this remit (Table 2B).

To realize this and enable cross-fertilization, interdisciplinarity will have to be actively pursued when organizing workshops and conferences in this field. Critical in-depth reviews, the development of guidelines and QA/QC recommendations are among the first activities required to address the current challenges. Other imminent plans in this respect encompass the generation of recommendations and tools that address data sharing and data quality issues and improve the validity and utility of models. Radiation oncology model development focused work streams and working groups should be established that leverage and integrate all relevant expertise by actively reaching out to other disciplines. These could provide the framework for the initiation and development of interdisciplinary guidelines, projects and collaborations and consensus on standardization and clinical data quality requirements. ERRS, EFOMP and multi- and interdisciplinary societies

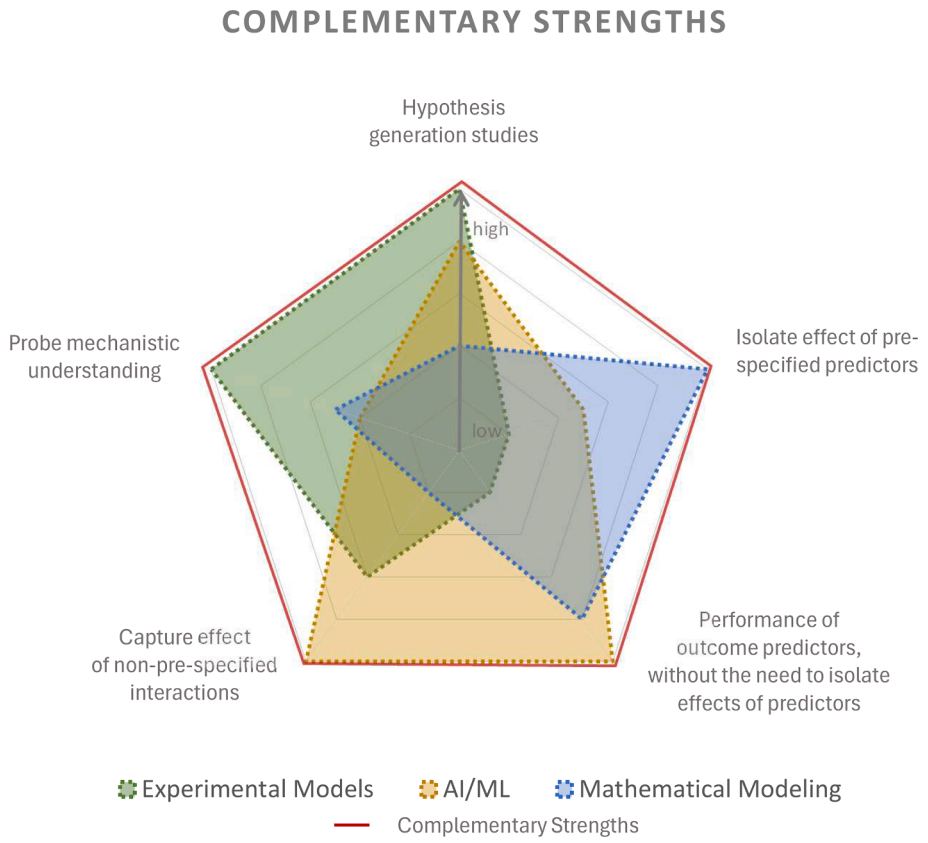


**Fig. 3.** Complementary strengths of disciplines Representation of the complementarity of the respective qualitative strengths and weaknesses of the primary methodology expertise in the different radiation oncology subdisciplines and the synergistic potential of a concerted interdisciplinary approach to radiation oncology model development. The graph depicts the relative strengths of experimental, AI/ML and more conventional mathematical modeling approaches (such as epidemiological, biophysical and computational, Table 1) with respect to key functions required for optimal radiation oncology model development.

such as ESTRO can play a crucial role in facilitating such endeavors. Furthermore, to enable close collaborations, teaching and training opportunities and interdisciplinary research training programs can facilitate communication and knowledge-transfer across disciplines. Training of the interdisciplinary radiation oncology model developer of the future requires the concerted effort of all disciplines involved. Finally, large societies such as ESTRO could play a role in advising funding agencies to address this paucity of the required international and interdisciplinary collaborations in specific calls.

## Conclusions

Better prediction models are needed to advance radiotherapy. This can only be achieved by strongly encouraging interdisciplinary efforts that harness the respective expertise of the involved disciplines. We concluded that enhanced radiobiological and computational technologies enable the generation of clinically relevant and adaptive models for personalized risk prediction in modern RT. An improved mechanistic understanding of radiobiological concepts and novel technologies, such as AI, provide ample opportunities to support model development and the clinical utility that is paramount to radiation oncology prediction models. We recommend that early and close interdisciplinary partnerships are supported to ultimately improve model development, performance, and assessment. These partnerships and joint strategies across disciplines are essential to advance prediction models in radiation oncology.

## CRediT authorship contribution statement

**C. Vens:** Writing – review & editing, Writing – original draft, Conceptualization. **P. van Luijk:** . **R.I. Vogelius:** . **I. El Naqa:** Writing – review & editing, Writing – original draft, Conceptualization. **L. Humbert-Vidan:** Conceptualization, Writing – original draft, Writing – review & editing. **C. von Neubeck:** Writing – review & editing, Writing – original draft, Conceptualization. **N. Gomez-Roman:** Writing – review & editing, Writing – original draft, Conceptualization. **E. Bahn:** Writing – review & editing, Writing – original draft, Conceptualization. **L. Brualla:** Conceptualization, Writing – original draft, Writing – review & editing. **T.T. Böhlen:** Conceptualization, Writing – original draft, Writing – review & editing. **S. Ecker:** Conceptualization, Writing – original draft, Writing – review & editing. **R. Koch:** Writing – review & editing, Writing – original draft, Conceptualization. **A. Handeland:** Writing – review & editing, Writing – original draft, Conceptualization. **S. Pereira:** Conceptualization, Writing – original draft, Writing – review & editing. **L. Possenti:** Conceptualization, Writing – original draft, Writing – review & editing. **T. Rancati:** Conceptualization, Writing – original draft, Writing – review & editing. **D. Todor:** Conceptualization, Writing – original draft, Writing – review & editing. **B. Vanderstraeten:** Conceptualization, Writing – original draft, Writing – review & editing. **M. Van Heerden:** Conceptualization, Writing – original draft, Writing – review & editing. **W. Ullrich:** Conceptualization, Writing – original draft, Writing – review & editing. **M. Jackson:** Conceptualization, Writing – original draft, Writing – review & editing. **M. Alber:** Conceptualization, Writing – original draft, Writing – review & editing. **L. Marignol:** Conceptualization, Writing – original draft.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

**Table 2**
Scientific and structural propositions by the DREAM team vision to enhance the impact of interdisciplinary radiobiology and physics research.

| **Scientific propositions** | | |
|---|---|---|
| Need | Importance | DREAM recommendation |
| Personalized risk prediction by clinically relevant models | Prediction models can inform treatment optimization in clinical practice. | Both experimental and mathematical modelling studies are to be guided by potential clinical relevance and utility from design to implementation. |
| Adaptive models | Evolving oncology treatments and discoveries require adaptive models to enable faster evaluation cycles | Application of modelling techniques / approaches are to be intrinsically capable of updating and learning from new data and insights. This will need to be supported by concerted international clinical data collection. |
| FAIR data | Data access is a prerequisite for reliable and clinically relevant model generation and validation | Adequate reporting and access to data should be enforced. **F**indability, **A**ccessibility, **I**nteroperability, and **R**eusability (FAIR) should be encouraged across experimental and clinical data |
| Generalizable Models | Reliable applicability of prediction models on unseen datasets contributes to their long-term value on real-world scenarios | Validation and external performance measurement is a prerequisite for clinical application. |
| Enhanced radiobiological and computational technologies | Innovative computational technologies and experimental models are crucial to realize clinically useful models. | Technological advances in AI, computer science and experimental models must be supported and applied in an integrated manner in radiation oncology models. |
| **Structural propositions** | | |
| Need | Importance | DREAM recommendation |
| Interdisciplinary consortia and working groups | Clinically relevant model building, and hypothesis testing will greatly benefit from multi- and interdisciplinary expertise and approaches. | We encourage a continued and structured support for interdisciplinary workshops, working groups and consortia. The DREAM workshop and team is one of few such efforts. |
| Clinical trialist and study groups with a multi- and interdisciplinary composition | Multidisciplinary study groups facilitate knowledge transfer and accelerate convergence to improved biology based and clinically useful models | Clinical data, together with mechanistic understanding from experimental models should underlie modelling hypotheses enabled by interdisciplinary study teams. |
| Interdisciplinary data streamlining and scientific dissemination in the interdisciplinary field | Knowledge generation from routine clinical data can be improved by multidisciplinary collaboration on data capture and recording. Reversely, experimental knowledge can improve clinical data analysis for better models. | Policymakers and relevant stakeholders should enable the legal framework for optimal data sharing. Journals should structurally facilitate interdisciplinary studies. Open science platforms and preprint servers can support faster cycles of innovation and encourage the use of open science methodologies. |
| Increased appreciation of validation and confirmatory studies | Validation and confirmation are crucial to clinical use of newly developed models. | Clinical validation studies should be valued higher. Publication of all model details to enable validation should be enforced by reviewers and journals. |
| Funding opportunities for model development at the intersection of biology, physics and computer science | Funding opportunities have a substantial impact on research focus and output. | Funding opportunities often inadvertently reward monodisciplinary excellence over collaborative efforts. Multi- and interdisciplinary efforts with strong clinical perspectives should be prioritized. |

the work reported in this paper.

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