Bayesian Decision Support for Adaptive Lung Treatments

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Abstract. Purpose: A Bayesian Decision Network will be demonstrated to provide clinical decision support for adaptive lung response-driven treatment management based on evidence that physiologic metrics may correlate better with individual patient response than traditional (population-based) dose and volume-based metrics. Further, there is evidence that information obtained during the course of radiation therapy may further improve response predictions.

Methods: Clinical factors were gathered for 58 patients including planned mean lung dose, and the bio-markers IL-8 and TGF-β obtained prior to treatment and two weeks into treatment along with complication outcomes for these patients. A Bayesian Decision Network was constructed using Netica 5.0.2 from Norsys linking these clinical factors to obtain a prediction of radiation induced lung disease (RILD) complication. A decision node was added to the network to provide a plan adaption recommendation based on the trade-off between the RILD prediction and complexity of replanning. A utility node provides the weighting cost between the competing factors.

Results: The decision node predictions were optimized against the data for the 58 cases. With this decision network solution, one can consider the decision result for a new patient with specific findings to obtain a recommendation to adaptively modify the originally planned treatment course.

Conclusions: A Bayesian approach allows handling and propagating probabilistic data in a logical and principled manner. Decision networks provide the further ability to provide utility-based trade-offs, reflecting non-medical but practical cost/benefit analysis. The network demonstrated illustrates the basic concept, but many other factors may affect these decisions and work on building better models are being designed and tested.

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1. Introduction
Adaptive radiation therapy is an approach to improve treatment outcome by refining treatment techniques based on patient specific clinical findings prior to and during treatment. An increasing number of indicators are now available that can be correlated with the effectiveness of treatment. However this increase means that clinical decisions that utilize these factors become increasingly difficult. Further complicating decision making, these indicators are statistically uncertain in terms of their measurements and predictive value. The Bayesian decision support approach described in this paper provides a principled way to deal with statistical uncertainties and to combine them in order to provide clinicians with a better appreciation of the key factors and of their potential impact on treatment outcome.

This paper will discuss the role of the clinical indicators being used for adaptive decisions. In addition a brief overview of Bayesian statistics and how these statistics with graphical modelling and decision support networks can be used in clinical decision support. Examples will focus on treatment of lung cancer and in particular on predictions of radiation toxicity which limits the effectiveness of radiation treatments.

2. Clinical evidence for individualized radio-biology based adaptive corrections
The most common radiation toxicity in the treatment of lung cancer is radiation pneumonitis, which comes from the irradiation of an excessive lung volume. This is a particularly acute issue because
patients are receiving chemotherapy with radiation, which dramatically increases the risk of radiation pneumonitis. To aid in our ability to predict lung injury before it occurs, we have determined if plasma cytokine measurements during treatment can improve our radiation induced lung toxicity (RILT) model over the physical DVH alone. In initial studies, we found that radiation-induced elevation in plasma TGF-ß1 (transforming growth factor beta 1) during-RT was significantly correlated with RILT. The increase in the ratio of TGF-ß1 at 4-weeks during-RT compared to pre-treatment was also associated with worse diffusing capacity of the lung for carbon monoxide (DLCO) 3 months post-RT (p=0.05). The significance of the TGF-ß1 ratio was supported through a multicenter analysis of Duke University, Peking Union Medical College, and University of Michigan. Combining TGF-ß1 ratio with mean lung dose had a better predictive accuracy than models using TGF-ß1 ratio or mean lung dose alone.

To attempt to build a more comprehensive model, the correlation with the levels of a second plasma cytokine Interleukin 8 (IL-8) and RILT has been assessed. Lower pre-treatment IL-8 levels were significantly correlated with the development of RILT. CT lung dosimetric parameters were borderline significant for its association with RILT. Using receiver operator characteristic curves for predictive risk assessment modelling, the combination of IL-8, TGF-ß1, and mean lung dose into a single model yielded an improved predictive ability (AUC 0.80, 95% CI 0.66-0.94, p <0.001) compared to our original model using mean lung dose alone.

While logistic regression models and Cox proportional hazards models are commonly used methodology for these assessments, we propose instead to use a Bayesian Network approach which has some advantages for uncertain (probabilistic) data, smaller data sets, for handling missing data, and to include more “speculative or knowledge-based” belief information into a decision making strategies.

3. Data management
Adaptive decisions require data management beyond current usage. Clinical observations need to be gathered along with derived information (ex: ratios) along with relevant treatment planning results (ex: mean lung dose). The timing of these observations with respect to decision points is also critical to capture. The data needed is generally simple measurements but can also be more extensive in particular functional imaging studies and correlations to radiation plan dose distributions. With the variety of data required for adaptive decision making and the goal of incorporating new and different finding that have a correlation with outcomes, we are developing an ontology (semantic knowledge driven) approach using standard terminologies and coding when available.

4. Bayesian statistics
Bayesian statistics began with a posthumous publication in 1763 by Thomas Bayes. In essence Bayes described a subjective way to infer the likelihood (probability or belief) of a particular hypothesis given an initial estimate of that likelihood (prior to new evidence being added) (i.e. the prior likelihood) times the likelihood of changes to the likelihood of that hypothesis based on new evidence. I.E.

\[ \text{Posterior likelihood} = \text{Prior likelihood} \times \text{Likelihood of change based on evidence} \]

This Bayesian inference provides a principled way of combining new evidence with prior beliefs. This statistical approach is contrasted with those based solely on the evidence as a whole, with no reference to prior beliefs. Bayesian inference has many applications in science, engineering, medicine, and law.

Bayes' statistics can be applied iteratively. That is, after observing some evidence, the resulting posterior probability can then be treated as a prior probability, and a new posterior probability computed from new evidence. This allows for Bayesian principles to be applied to various kinds of evidence, whether viewed all at once or over time. This procedure is termed Bayesian updating.
5. **Bayesian belief networks**

In describing a complex system with multiple variables (observations or indicators), a useful approach is to build a graphical model. Using the lung toxicity example introduced earlier, Figure 1 shows “nodes” (boxes) for mean lung dose (MLD), IL-8 at week 2 (il8_wk2), and TGF-β1 at week 2 ratio (compared to pre-treatment value) (tgfbeta_wk2_ratio). These nodes are connected (directed lines) to a lung complication probability node. Although this example is simple, Bayesian networks can become extremely complex with hundreds of nodes and connecting relationships.

6. **Bayesian decision support**

Finally we come to Bayesian decision support. What we really want for adaptive therapy decisions are not just a prediction of probabilities but a way to assess the “utility” between no change or making a change (adapting). Clinically, the expected utility would increase with an improvement of tumor control and with a decrease in normal tissue complications. In addition to clinical utility, a decision to make a change in the course of treatment is often tempered by practical factors. Making a change in a course of therapy is generally fairly costly in terms of the need for new treatment planning and evaluation, the need for additional quality assurance checks on a revised approach, the addition of changes in delivery procedures, and the potential of associated hazards. Therefore, there is need to assess the trade-offs between potential therapeutic improvement versus cost and risk assessments.

Within a Bayesian network, decision support nodes are added to the network along with utility nodes which link to other parts of the network. In a Bayesian decision network, the decision node outcome values are optimized to maximize the utility function(s).

In Figure 2, we look at the decision network again, this time entering a finding for a single patient who has a predicted mean lung dose of 17.5, IL-8 value of 7.5 at week 2, and a TGF-β1 ratio of 2.75 at week 2. The utility node “U” provides relative weights for the lung complication probabilities and for a new node called “Complexity” which is used in this example as an additional factor that would affect the “utility” of making a decision to adapt the treatment. In Figure 2a), the complexity is selected as “Low” and the decision node “Adapt?” indicates a preference to make a change in treatment. However, in Figure 2 b), the complexity is selected as “High” and this changes the decision node towards the preference of not making a treatment change.

This decision network is, of course, overly simple in that there will be other clinical factors that affect lung complication predictions and there are other organs such as the heart and oesophagus that may also affect a decision to adaptively change the treatment. Furthermore, there are other factors that would affect the utility of making a change in treatment.
7. Discussion
Computerized clinical decision support has found acceptance in a large number of areas in medicine such as for clinical practice skill improvements, in guideline recommendations, and for checks to reduce preventable medical errors. In general, we are using a computer program to sort through all of the pertinent findings to date to aid the clinician in making the most appropriate decision regarding the ongoing management of a patient’s treatment based on expert knowledge and prior experience. Few of these programs are used in a fully autonomous manner and instead provide decision recommendations along with feedback of the data and the knowledge base factors on which a particular decision recommendation is based.

8. Conclusion
This paper introduced the concepts of Bayesian Decision Networks to provide clinical decision support for adaptive (individualized) radiation therapy. The issues affecting the ability of radiation to be used as an effective treatment are complex and require an understanding of biological processes involved in cancer growth and in cellular repair mechanisms. Utilizing this knowledge and associated clinical tests along with techniques for adjusting the radiation delivery provides radiation oncology with a unique ability to improve treatments over what would be given using a conventional population–based approach.

9. References

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