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A Bayesian Approach for Sequential Updating of Dose-Response Relations in Radiation Therapy

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Sammanfattning

In radiation therapy, the analysis of historical data gives population estimates on various parameters which are useful when designing treatments for future patients. However, if the time lag between the treatment of historical patients and the treatment of new patients is long this information is not up to date and might even be outdated. It is therefore more important to continuously integrate treatment outcome data by sequential updated feedback to more accurately taylor the treatment of each new patient. Brief descriptions of the radiobiological background and of the statistical tools needed for clinical implementation of such a feedback system are given.

The feedback system is implemented by developing a Bayesian approach for sequentially updating radiobiological parameters of dose-response relations which then can be used for calculating optimal curative treatment doses for cancer patients recieving radiation therapy. The model is quantified in terms of the probability of achieving tumor control and the risk of inducing severe injury. Formally the statistical model is specified as a generalized linear model with a log-log link. The underlying model and computational algorithms as well as simulation results from a four parameter radiobiological model showing the effect of sequentially updating the radiation treatment are presented.

KEY WORDS: Radiation therapy optimization; Generalized Linear Model; Bayesian inference; Markov chain Monte Carlo.

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Marianne Mæhle Schmidt.

Abstract

In radiation therapy, the analysis of historical data gives population estimates on various parameters which are useful when designing treatments for future patients. However, if the time lag between the treatment of historical patients and the treatment of new patients is long this information is not up to date and might even be outdated. It is therefore more important to continuously integrate treatment outcome data by sequential updated feedback to more accurately taylor the treatment of each new patient. Brief descriptions of the radiobiological background and of the statistical tools needed for clinical implementation of such a feedback system are given.

The feedback system is implemented by developing a Bayesian approach for sequentially updating radiobiological parameters of dose-response relations which then can be used for calculating optimal curative treatment doses for cancer patients recieving radiation therapy. The model is quantified in terms of the probability of achieving tumor control and the risk of inducing severe injury. Formally the statistical model is specified as a generalized linear model with a log-log link. The underlying model and computational algorithms as well as simulation results from a four parameter radiobiological model showing the effect of sequentially updating the radiation treatment are presented.

Keywords: Radiation therapy optimization; Generalized Linear Model; Bayesian inference; Markov chain Monte Carlo.

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1 Aims

The work presented in this licentiate thesis is the result of a cooperation between Mathematical Statistics at Stockholm University and Medical Radiation Physics at Karolinska Institutet. At the beginning of this cooperation the aim of the work was set to 1) understand the radiobiological problem of achieving complication free tumor control in a radiotherapeutic setting, 2) to learn about Bayesian inference and build up a Bayesian model for the problem, 3) to check out software and check the properties of the model, 4) and to build up a model for implementation into the clinic. Items 1), 2) and 3) are the basis for this licentiate thesis. The result of 1) is shown in sections 3 and 4, the result of 2) is shown in sections 5, 6 and 7, and the result of 3) is shown in sections 8 and 9. Appendices A, B and C contains statistical background, appendix D contains information on software and programs. In section 10 considerations for carrying on with 4) are drawn.

2 Introduction

In current clinical radiation therapy practice the tumor stage and spread are the main determinants for radiation modality and target dose while individual characteristics such as sensitivity to radiation are not accounted for. The radiobiological model presented here takes radiobiological parameters of the patients into account during treatment planning. A characteristic distribution for the radiobiological parameters in the group of patients under study is assumed. The variance of this distribution reflects unknown patient heterogeneities as well as other sources of uncertainty. In the literature the concentration is often on either tumor control or on normal tissue injury. However, since the clinical aim when treating a cancer patient with radiation therapy is to achieve complication free tumor control by eradicating all the tumor cells without severely injuring the surrounding normal tissues, cf. [Brahme (1994)], a criteria function representing this trade-off is used for finding the optimal treatment dose in the model presented here. In order to include the newest information into the model it is updated after each treated patient. A Bayesian approach is taken, assuming a prior distribution on a historical set of radiobiological parameters, using a corresponding historical treatment dose and the observed outcomes and the criteria function to calculate the posterior distribution for the radiobiological parameters and the optimal treatment dose for the next incoming patient. Using the posterior distribution of the radiobiological parameters as the new prior this process is then iterated after each treated patient. Together with inclusion of more individual information into the model, such as molecular markers on sensitivity to radiation, cf [Haghdoost et al. (2001), Friesland et al. (2002)], this feedback model can be used to get the subgroups in the population under study more homogeneous, hereby allowing for more individualized treatment schedules.

3 Radiobiological background

Radiobiology is the study of the action of ionizing radiation on living targets, cf [Hall (1994)]. The important characteristic of ionizing radiation is the release of large amounts of energy in local areas. Depending on the type of particles (electrons, protons, α-particles, neutrons, light or heavy ions) used for irradiating, the particles interact with tissues, they spread and

deposit the released energy at different tissue levels. Absorbed radiation dose is measured in Gray, Gy, defined as 1 joule per kg irradiated target.

DNA is the principal target for the biological effects of radiation, including cell killing, mutation and carcinogenesis. The genetic coding of an individual is given in the DNA. The DNA is built up of many substances, but to simplify, it consists of two strands that form a double helix. If a single strand break occurs the strand is quite easily repaired by the DNA itself copying from the non-damaged strand. A repair might be incorrect, though, resulting in a mutation. A double strand break, occuring if both strands are broken opposite or close opposite to each other, is believed to be the most important radiation damage. It can lead to chromosome aberrations both for the irradiated person and for following generations.

Mammalian cells propagate and proliferate by mitosis, a type of cell division. Cell division is a cyclic phenomenon. Following the cell division phase, the mitotic or M phase, is the G_1 phase (G for gap, a resting phase). At the end of this phase there is a molecular checkpoint at which the cell decides whether to commit itself to the complete cycle. If it does, then comes the S phase (synthethic) where the cell replicates its DNA. Then again there is a resting phase, the G_2 phase, where the cell prepares to divide and after that another mitosis occurs. The length of the various phases as well as of the whole cell cycle varies with the type of cells studied. In general, G_1 is the most variable phase with respect to length, the M and G_2 phases are the most radiosensitive phases and the S phase is the most radioresistant phase. At a certain point in time cells are in different phases. Cells can die a mitotic death, that is they die in attempting the next or later mitosis, or they can die an apoptotic death, which is a 'programmed' cell death. There are a large number of control genes and processes that control the cell division system. For a tumor to start developing one or more of these mechanisms fail. Year 2001 the Nobel prize in Medicine, was given to 3 researchers, LH Hartwell, RT Hunt and PM Nurse, who discovered molecules that control and coordinate cell division, cf. section 10. Controlling these molecules and then forcing cancer cells to be 'arrested' resulting in apoptosis as well as developing methods to force the cells into the radiosensitive parts of the cell cycle are important goals for the cancer research.

A cell that has retained its reproductive integrity and is able to proliferate indefintely to produce a large clone or colony is said to be *clonogenic*. For a tumor to be eradicated it is only necessary that the tumor cells be killed in the sense that they are unable to divide and cause further growth and spread of the malignancy. For the normal tissue cells the tolerance to radiation depends on the ability of the clonogenic cells to maintain a sufficient number of mature cells suitably structured to maintain organ function.

Radiation therapy of cancer patients can be split into a number of partial treatments called fractions. This way the same total dose can be given via different combinations of number of fractions and fractionation doses. For a specific tumor the total dose must be increased to achieve a specific effect if the treatment is prolonged. For the normal tissues this break between fractions can be used for sublethal damage repairing of DNA strand breaks before they can interact to form chromosomal aberrations. Thus a prolongation of the treatment spares the normal tissues. For the tumor tissue there will first be a prompt (tissue-depending) repair of sublethal radiation damage, then reassortment meaning progression of cells through the cell cycle and then repopulation due to cell division resulting in a higher surviving cell fraction. However, the reoxygenation process described below might make the cells easier to eradicate. The question on whether or not to split up the treatment depends on the type of cells involved and especially on the timing of the above processes. A typical fractionation

radiotherapy schedule is to treat 5 times a week for 6 weeks with dose equal to 2 Gy. The BIR1 and BIR2 studies referenced in section 4 are studies on fractionation schedules.

The flow of oxygen has been shown to be an important factor in the cell killing process in transplantable tumors in animals. If cells are hypoxic (little flow of oxygen) cells are also resistant to radiation. Hypoxia can be chronic or acute, the latter being due to temporary closing of tumor vessels. Tumor cells might therefore be reoxygenated between fractions and then easier to kill. Reoxygenation cannot be measured in human tumors, but there are indications that reoxygenation occurs in tumors controlled by conventional fractionated radiation therapy.

The probability of tumor control can be increased by escalating the radiation dose to the tumor, cf. [Zelefsky et al. (1998), Zelefsky et al. (2001)]. If the tumor cells are resistant to radiation the dose need to be escalated to the whole tumor or part of the tumor, cf. [Kutcher (1998)]. Normal tissue will always get irradiated during a radiation treatment, since the particles used for irradiating are passing normal tissues on the way to the tumor site and since there need to be a margin in order to ensure that the whole tumor gets irradiated. Even though several methods exist for delievering a non-uniform radiation dose and even though there are ways to shield and protect the normal tissues from getting irradiated during a treatment, cf. [Brahme (1995)], an increase in the tumor dose will most often result in an increase in the dose to the normal tissues, and hereby an increase in the probability of inducing injury to the normal tissues. The increase in injury depends on the location of the tumor and the possibility to protect the normal tissues. Therefore, when prescribing a treatment dose, information on both the tumor and the normal tissues as well as a procedure for weighting the benefit of the treatment against the risk for injury are needed.

4 A clinical dataset - the BIR studies

For a single patient with a specific type of cancer the clinically observed response to radiation treatment are two binary variables indicating whether or not tumor control and normal tissue injury, respectively, have been observed at a given timepoint. Information about the duration of the radiation treatment from first to last treatment fraction, the number of fractions as well as the fractionation dose can be used to calculate the total dose delievered to the patient. As described in section 3 the same total dose can be given by following different fractionation schedules. Besides tumor specific characteristics person specific covariates such as age and sex can be built into the model.

Data sets on radiation treatments are hard to assembly. Person specific covariates as well as follow-up status on tumor eradication/recurrence and normal tissue injury are readily available in clinical databases in Sweden, whereas the routines for storing the complex dose information are only in the planning stage. In order to implement the dynamic dose optimization procedure into a clinical setting in Sweden, routines are needed for storing dose information as well as information on old and new tumor molecular markers. Information could perhaps be retrieved retrospectively from patient journals and biological specimens, in order to set up and test reasonable models for different tumor types. However, this would be very time consuming and expensive.

In order to motivate the radiobiological model used here we present some radiobiological results on a British data set: During 1965 and 1989 the British Institute of Radiology carried

out two multicenter randomized clinical trials of fractionated radiotherapy for squamous cell carcinoma of the larynx and pharynx involving 1345 patients, cf. [Wiernik et al. (1990), Wiernik et al. (1991)]. We will refer to these studies as BIR1 and BIR2. In both trials patients were randomized to two different fractionation schedules in order to study effects of fractionation.

The BIR data are special because they include many patients and because the patients were followed for a long time. The BIR1 study only included information on tumor eradication/recurrence while the BIR2 study also included information on normal tissue injury. The BIR data (and subsets of the data) have been analyzed by many people, e.g. [Chappell et al. (1995a), Chappell et al. (1995b), Slevin et al. (1992)]. In these papers generalised linear models, cf. appendix A, have been used to model some link function of the probability of tumor control as

$$\ln K + \alpha D + \beta d D + \gamma T + l\mathrm{St} \tag{1}$$

where St is the stage of the tumor ($T1 - T3$) reflecting the extent of the tumors invasion, T is the overall treatment time from first to last treatment fractionation, d is the fractionation dose, D is the total treatment dose given to the patient, and $\ln K, \alpha, \beta$, γ and l are fitted parameters.

This model is an example of the linear quadratic model, cf. [Fowler (1989)]. The quadratic dose term indicates that in order to increase the probability of tumor control by killing more tumor cells which can be achieved by dose escalation, the effect gets bigger the more the dose is escalated. Different types of tissue react differently to radiation, reflecting that the different mechanisms described in section 3 take unequally long time. If the tissue repairs fast the effect of the quadratic term is less than if the tissue repairs slowly. So if α/β is high (β is low compared to α) the tissue is early-responding (with respect to tissue repair), reflecting prompt tissue repair. If α/β is low (β is high compared to α) the tissue is late-responding, reflecting that it takes long for the tissue to repair itself. Examples of early-responding tissues are the skin and the colon, whereas examples of late-responding tissues are the lung and the spinal cord, cf. [Hall (1994)]. Typical values for α/β are 3 Gy for late-responding tissues and 10 Gy for early-responding tissues.

In table 1 selected results for fitting model (1) from the above mentioned papers are given. In the first two the traditional logit link is used to model the probability of tumor control. In the last the more biologically motivated complementary log-log link is used, cf. section 5. Note that at least for the first 2 studies planned treatment time, dose and number of fractions are used in order to minimize bias. Bias could arise if one of the groups is treated systematically different from the planned (randomized) treatment schedule.

All analyses showed that higher doses increase tumor control rates, longer treatment periods decrease tumor control rates, and the interaction effect of total dose and fractionation dose is very small and not significantly different from zero. Since β is low compared to α it follows that the tumor tissue is early-responding.

[Chappell et al. (1995a)] also modelled normal tissue damage after 5 years among 479 laryngeal carcinoma patients from BIR2 using logistic regression and a formula similar to (1). They found that higher doses increase normal tissue injury rates (α=.116/Gy, se=[.029]), longer treatment periods decrease normal tissue injury rates (γ=-.0954/day, se=[.0212]), the interaction effect of total dose and fractionation dose is very small (β=-.00808/Gy^2, se=[.00375]), and tumor stage does not seem to influence normal tissue damage.

Reference and study population	**Link function**	**parameter estimates [SE] or (95% CI)**
[Chappell et al. (1995a)] 858 subjets from BIR1 and BIR2 diagnosed with laryngeal carcinoma	logit	constant=-.937 [.979] α=.0591/Gy [.0186] β=.00221/Gy^2 [.00285] γ=-.0419/day [.0124] T2 vs. T1 =-.71 [.188] T3 vs. T1=-1.044 [.187]
[Chappell et al. (1995b)] 766 larynx patients from BIR1 and BIR2 with no neck nodes	logit	constant=-1.042 [1.036] α=.0701/Gy [.020] β=.00312/Gy^2 [.003] γ=-.0536/day [.0135] T2 vs. T1 =-.716 [.194] T3 vs. T1=-1.235 [.198]
[Slevin et al. (1992)] 496 patients with pharynx/larynx cancer from one of the BIR hospitals * Only stage 2 and stage 3 tumors are considered, in the analysis they are combined in one group.	cloglog	constant=4.47 (.04-8.81) α=.22/Gy (.108-.332) β=.-.0149/Gy^2 (-.0326-.0029) γ=-.167/day (.078-.255) * *

Table 1: Selected results of analyses of BIR studies

Other and more flexible link functions than the logistic and cloglog are considered in [Chappell et al. (1995a), Newton et al. (1996)] for analyzing the BIR data, also showing results of β being very small.

Homogenizing the patient group considered with respect to tumor stage and treatment time, and deleting β from the model reduces the model from (1) to include only the parameters $\ln K$ and α, focusing on the effect of total dose on tumor control and injury to the normal tissues. This is the model we use to build a feedback system that includes historical information from previous treated patients to taylor the radiation treatment for new incoming patients. Tumor control and normal tissue effects are modelled jointly, an attempt which is not seen in any of the other studies.

5 The radiobiological model

A radiobiological model with four unobserable radiobiological parameters, following the structure in the paper by [Ågren et al. (1990)] is presented. Throughout the paper the tumor part of the model is indexed by B (for Benefit) and the injury part of the model is indexed by I (for Injury).

Two of the parameters are used to describe the tumor tissue: the radioresistance of the tumor, $D_{0\mathrm{B}}$, and the initial number of clonogenic tumor cells, $N_{0\mathrm{B}}$. The other two parameters describe the normal tissues: the radioresistance of the normal tissues, $D_{0\mathrm{I}}$, and the number of 'functional subunits' building up and assuring organ function of the surrounding normal tissues, $N_{0\mathrm{I}}$, cf. [Hall (1994), Withers et al. (1988)]. For a given type of tumor and subgroup of patients the radiobiological parameters, $N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$, $N_{0\mathrm{I}}$, $D_{0\mathrm{I}}$, may vary from one patient to another, and this unobserved heterogeneity is captured in a distribution for these parameters. Homogeneity of tissues is assumed in the sense that within one patient the radioresistance of every tumor cell is the same, and similarly for the radioresistance of every functional subunit. The probabilities of tumor control and normal tissue injury are functions of the dose distribution, which is included in the model as the total dose, D. We assume a homogeneous dose given to both the tumor and the normal tissues in question.

Tumor control occurs when all clonogenic tumor cells are eradicated. Radiobiological theory suggests a binomial model for this outcome with a log-log link for the probability of achieving tumor control, cf. [Munro & Gilbert (1961)]. We present this model as follows: Define by P_{B} the probability of achieving tumor control conditional on the set of radiobiological parameters, $N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$ and the delivered dose, D. Given $N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$ and D, we assume that for a specific individual the number of surviving tumor cells, $S_{\mathrm{B}}|(N_{0\mathrm{B}}, D_{0\mathrm{B}}, D)$, is Poisson distributed with mean $N_{0\mathrm{B}} \cdot \exp(-D/D_{0\mathrm{B}})$, so P_{B} is the probability of no surviving tumor cells. An increase in the radioresistance of the clonogenic tumor cells, $D_{0\mathrm{B}}$, increases the mean number of surviving tumor cells for given $N_{0\mathrm{B}}$ and D, while an increase in the mean number of surviving tumor cells, $N_{0\mathrm{B}}$, lowers P_{B}:

$$P_{\mathrm{B}} := P(S_{\mathrm{B}} = 0 | N_{0\mathrm{B}}, D_{0\mathrm{B}}, D) = e^{-N_{0\mathrm{B}} \cdot e^{\frac{-D}{D_{0\mathrm{B}}}}}. \tag{2}$$

By considering the log-log link, i.e. log(-log(P_{B}))=log($N_{0\mathrm{B}}$)-$\frac{-D}{D_{0\mathrm{B}}}$, then $N_{0\mathrm{B}}$ corresponds to K, and $-1/D_{0\mathrm{B}}$ to α in (1). An increase in dose increases P_{B} for given $N_{0\mathrm{B}}$ and $D_{0\mathrm{B}}$.

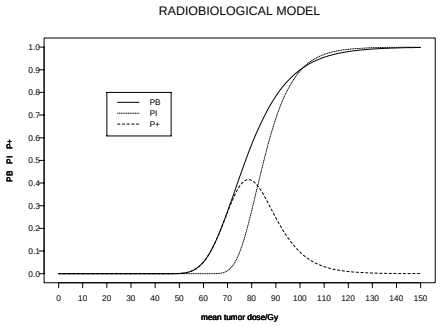

Figure 1: Illustrating probability curves for tumor control, normal tissue injury and complication free tumor control for the true model.

Similarly, for the injury side we define P_{I} to be the probability of inducing severe damage to the normal tissues in the patient given $N_{0\mathrm{I}}$, $D_{0\mathrm{I}}$ and D, and we assume that the conditional number of surviving functional subunits in the irradiated organ, $S_{\mathrm{I}}|(N_{0\mathrm{I}}, D_{0\mathrm{I}}, D)$, is Poisson distributed with mean $N_{0\mathrm{I}} \cdot \exp(-D/D_{0\mathrm{I}})$. P_{I} is then the probability of no surviving functional subunits:

$$P_{\mathrm{I}} := P(S_{\mathrm{I}} = 0|N_{0\mathrm{I}}, D_{0\mathrm{I}}, D) = e^{-N_{0\mathrm{I}} \cdot e^{\frac{-D}{D_{0\mathrm{I}}}}}. \tag{3}$$

A decrease in dose, lowers the probability of eradicating the functional subunits for given $N_{0\mathrm{I}}$ and $D_{0\mathrm{I}}$, while an increase in the radioresistance of the functional subunits given $N_{0\mathrm{I}}$ and D increases P_{I}.

From (2) and (3) it is seen that $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ are the radiation doses (in Gy) at which a fraction of e^{-1} of the initial clonogenic tumor cells respectively the normal tissue rescuing units are killed.

We weight the benefit and the injury by defining the probability of achieving complication free tumor control, P_+, as the probability of eradicating all tumor cells while keeping functional subunits to maintain organ function in the normal tissues:

$$P_+ = P(S_{\mathrm{B}} = 0, S_{\mathrm{I}} > 0|N_{0\mathrm{B}}, D_{0\mathrm{B}}, N_{0\mathrm{I}}, D_{0\mathrm{I}}, D). \tag{4}$$

Assuming conditional independence between the tumor and the normal tissues *given* the radiobiological parameters and the dose, reduces (4) to:

$$P_+ = P_{\mathrm{B}}(1 - P_{\mathrm{I}}) \tag{5}$$

used by [Ågren et al. (1990)].

To illustrate the trade off between tumor control and normal tissue injury we show in figure 1 the probability curves P_{B}, P_{I} and P_+ for a set of radiobiological parameters as functions of the dose. The S-curve to the left is the probability of achieving tumor control, the S-curve to the right is the probability of inducing injury, and the last curve is the probability of achieving complication free tumor control. The optimal dose is achieved at the peak of the P_+ curve.

Note that while the assumption of conditional independence is plausible for an individual, the radiobiological parameters, $N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$, $N_{0\mathrm{I}}$, $D_{0\mathrm{I}}$, are unknowns in the model, and not

measurable on the individual level. We assume unobserved heterogeneity captured by a four-dimensional normal prior distribution for the radiobiological parameters with mean value ξ and covariance matrix Σ given by:

$$\Sigma = \begin{bmatrix} \Sigma_{\mathrm{B}} & \Sigma_{\mathrm{BI}} \\ \Sigma_{\mathrm{BI}}^{t} & \Sigma_{\mathrm{I}} \end{bmatrix}, \tag{6}$$

where each element is a 2×2 matrix. Σ_{B} contains the variances and the covariance between the two tumor parameters, $N_{0\mathrm{B}}$ and $D_{0\mathrm{B}}$, Σ_{I} the variances and the covariance between the corresponding injury parameters, $N_{0\mathrm{I}}$ and $D_{0\mathrm{I}}$, and Σ_{BI} the covariances between the tumor and the injury parameters.

We determine an optimal dose $\widehat{D}$ by maximizing with respect to D an approximation of the expected value of P_+, with expectations taken with respect to the prior distribution.

$$\widehat{D} = \max_{D} \mathrm{E}P_+ \approx \max_{D} \left\{ P_{\mathrm{B}}(D|\mathrm{E}N_{0\mathrm{B}}, \mathrm{E}D_{0\mathrm{B}}) \left[1 - P_{\mathrm{I}}(D|\mathrm{E}N_{0\mathrm{I}}, \mathrm{E}D_{0\mathrm{I}}) \right] \right\}. \tag{7}$$

The approximation on the rigth hand side in (7) neglects the covariances in Σ_{BI} when factorizing $\mathrm{E}P_+$ by $\mathrm{E}P_{\mathrm{B}}\mathrm{E}(1 - P_{\mathrm{I}})$, and a first order Taylor argument is used when replacing $\mathrm{E}(P_{\mathrm{B}}(\cdot))$ and $\mathrm{E}(P_{\mathrm{I}}(\cdot))$ into $P_{\mathrm{B}}(\mathrm{E}(\cdot))$ and $P_{\mathrm{I}}(\mathrm{E}(\cdot))$. While a connection in radioresistance is expected between tumor and normal tissues, i.e. non-zero elements in Σ_{BI}, the simplification in (7) simplifies computations and are not expected grossly to affect the dose determination, see section 8 for more details.

The optimization criteria imply optimization of dose on the group level, i.e. for the subgroups of patients under study. Note that with added measured data on biological markers, the subgrouping will change and $N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$, $N_{0\mathrm{I}}$, $D_{0\mathrm{I}}$ are calculated for new subgroups within the initial group, hereby targetting the dose optimization to these new subgroups.

6 Sequential improvement and the Bayesian approach

The sequential model is illustrated in figure 2. We assume historical estimates of the radiobiological parameters as the only information source when starting the feedback system. The historical information might come from a previous more coarse subgrouping of the patient population. From the historical estimates the optimal dose is calculated according to the criterion in (7). The next group of new incoming patients, will then be treated according to this optimal dose. For the given treatment dose and the observed outcomes on tumor control and normal tissue injury from these new patients the radiobiological parameters are updated and these updated parameters are used for finding an updated optimal dose for the next group of patients. We assume that all patients within and between sequences act independent of each other, implying that no patients are treated more than once.

Inference about the parameters in the radiobiological model, denoted π=($N_{0\mathrm{B}}$, $D_{0\mathrm{B}}$, $N_{0\mathrm{I}}$, $D_{0\mathrm{I}}$), is drawn from the posterior distributions, cf. appendix B. It follows from Bayes rule, $p(\pi|Y) = \frac{p(\pi)p(Y|\pi)}{p(Y)}$, where Y=(S_{B}, S_{I}), is observed data treated as stochastic with distribution indexed by the parameter π, that the joint posterior distribution of the radiobiological parameters given the observed data is proportional to the product of the prior distribution and the likelihood function. If we assume a multivariate normal 'working model' for the prior

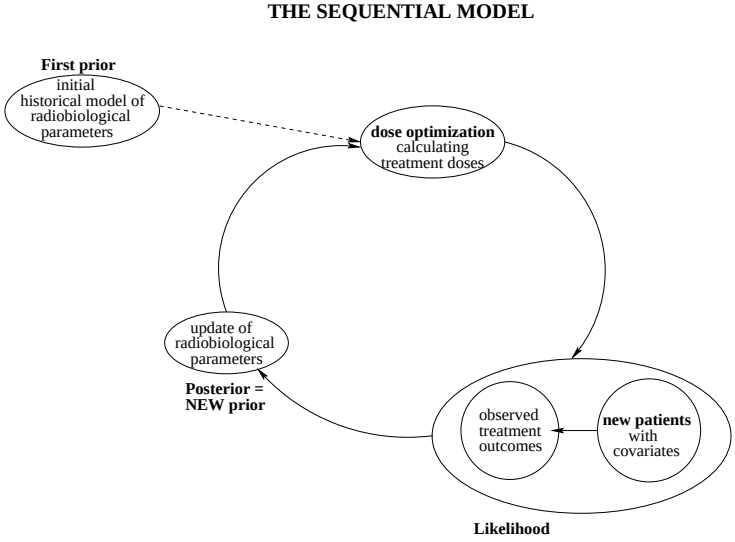

Figure 2: The sequential model built into a Bayesian framework.

of π, where the elements in Σ_{BI} of (6) are set equal to 0, hereby assuming prior independence between the tumor and the normal tissues, the prior factorizes into one part for tumor control and one part for normal tissue injury. Together with the factorization of the likelihood in (4) and (5) this grossly simplifies computation, but is not expected to dramatically affect the dose determination in the respective sequencies. The likelihood in (4) and (5) together with the multinormal prior results in the joint posterior:

$$
\begin{aligned}
& p(N_{0\mathrm{B}}, D_{0\mathrm{B}}, N_{0\mathrm{I}}, D_{0\mathrm{I}} | \{S_{\mathrm{B}}\}_{\mathrm{seqk}}, \{S_{\mathrm{I}}\}_{\mathrm{seqk}}, \{D\}_{\mathrm{seqk}}) \\
& \quad \propto p(N_{0\mathrm{B}}, D_{0\mathrm{B}}, N_{0\mathrm{I}}, D_{0\mathrm{I}}) \prod_{\text{patients in seq k}} p(S_{\mathrm{B}}, S_{\mathrm{I}} | N_{0\mathrm{B}}, D_{0\mathrm{B}}, N_{0\mathrm{I}}, D_{0\mathrm{I}}, D) \\
& \quad = p(N_{0\mathrm{B}}, D_{0\mathrm{B}}) p(N_{0\mathrm{I}}, D_{0\mathrm{I}}) \prod_{\text{patients in seq k}} p(S_{\mathrm{B}} | N_{0\mathrm{B}}, D_{0\mathrm{B}}, D) p(S_{\mathrm{I}} | N_{0\mathrm{I}}, D_{0\mathrm{I}}, D) \\
& \quad \propto (\Sigma_{\mathrm{B}})^{-\frac{1}{2}} (\Sigma_{\mathrm{I}})^{-\frac{1}{2}} e^{-\left[((N_{0\mathrm{B}}, D_{0\mathrm{B}}) - (\mu_{N_{0\mathrm{B}}}, \mu_{D_{0\mathrm{B}}})) \Sigma_{\mathrm{B}} ((N_{0\mathrm{B}}, D_{0\mathrm{B}}) - (\mu_{N_{0\mathrm{B}}}, \mu_{D_{0\mathrm{B}}}))^t\right]} \\
& \qquad \times e^{-\left[((N_{0\mathrm{I}}, D_{0\mathrm{I}}) - (\mu_{N_{0\mathrm{I}}}, \mu_{D_{0\mathrm{I}}})) \Sigma_{\mathrm{I}} ((N_{0\mathrm{I}}, D_{0\mathrm{I}}) - (\mu_{N_{0\mathrm{I}}}, \mu_{D_{0\mathrm{I}}}))^t\right]} \\
& \qquad\quad \times \prod_{\text{patients in seq k}} P_{\mathrm{B}}^{1_{\{S_{\mathrm{B}}=0\}}} (1 - P_{\mathrm{B}})^{(1 - 1_{\{S_{\mathrm{B}}=0\}})} P_{\mathrm{I}}^{1_{\{S_{\mathrm{I}}=0\}}} (1 - P_{\mathrm{I}})^{(1 - 1_{\{S_{\mathrm{I}}=0\}})}.
\end{aligned}
\tag{8}
$$

Here $\{S_{\mathrm{B}}\}_{\mathrm{seqk}}$ and $\{S_{\mathrm{I}}\}_{\mathrm{seqk}}$ are the vectors of the individual treatment outcomes of the n_k patients treated in sequence k, denoting for each individual whether or not tumor control, $\{S_{\mathrm{B}} = 0\}$ vs. $\{S_{\mathrm{B}} > 0\}$, and normal tissue injury, $\{S_{\mathrm{I}} = 0\}$ vs. $\{S_{\mathrm{I}} > 0\}$, occured. The $1_{\{S_{\mathrm{B}}=0\}}$ and $1_{\{S_{\mathrm{I}}=0\}}$ are indicator functions, and $\{D\}_{\mathrm{seqk}}$ is the vector of individual treatment

doses. Since the treatment group is homogeneous the doses are equal for all patients. The priors $p(N_{0\mathrm{B}}, D_{0\mathrm{B}})$ and $p(N_{0\mathrm{I}}, D_{0\mathrm{I}})$ are two-dimensional normal distributions.

Given updated posterior values on means, variances and covariances for the radiobiological parameters and given new data on tumor and injury responses the new optimal dose is found from (7).

7 The updating procedure

A full Bayesian model assumes hyperpriors to be specified for the mean values and the variances of the radiobiological parameters in (6), cf. appendix D. However, in the simulation studies a simplified form of the radiobiological model is tested. Instead of specifying hyperpriors, we provide the prior means and variances of the radiobiological parameters to the program calculating posteriors. To reduce complexity the number of surviving tumor cells, $N_{0\mathrm{B}}$, and the number of functional subunits in the normal tissues, $N_{0\mathrm{I}}$, are treated as known and fixed constants while $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ are treated as random. The software we use assumes independence and normality of the coefficients in the linear predictor in (2) and (3), cf. appendix D. Thus for computationel reasons we assume independence between $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ as discussed in section 5. As another consequence of the program restrictions the normality assmption is made on $(-1/D_{0\mathrm{B}})$ and not on $D_{0\mathrm{B}}$, and similarly for $D_{0\mathrm{I}}$. We have assumed that $D_{0\mathrm{B}} > 0$, that $D_{0\mathrm{B}}$ is concentrated to a small part of the positive axis, and that the expected value of $-1/D_{0\mathrm{B}}$ is well approximated by

$$\mathrm{E}\left(\frac{-1}{D_{0\mathrm{B}}}\right) \approx \frac{-1}{\mathrm{E}D_{0\mathrm{B}}}. \tag{9}$$

From the mean values of the historical radiobiological parameters the approximate optimal dose is calculated from the right-hand side of (7). The approximated optimal dose is used as the treatment dose for the first incoming patient. Only one patient is treated before updating.

The outcomes on tumor control and induced injury for the patients are now generated from the underlying true model in the following way: Patient specific values of $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ are sampled from the true distributions. For the treated patient the value of the true (sampled) $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$, the treatment dose and the fixed values of $N_{0\mathrm{B}}$ and $N_{0\mathrm{I}}$ are inserted into (2) and (3), and outcomes on tumor control and normal tissue injury are sampled from the Bernoulli distribution.

Information on the historical estimates of the radiobiological parameters and their standard deviations, together with the treatment dose and the sampled outcomes are then read into Bugs [Spiegelhalter et al. (1995)], a program for calculating posteriors using Gibbs sampling, cf. appendices C and D. Posterior means and variances of the radiobiological parameters are calculated. For a series of dose values posterior means and standard deviations over the sampled radiobiological parameters are calculated for P_{B}, P_{I} and P_{+}, and the dose that maximises EP_{+} is used as the new optimal treatment dose.

The process is then iterated, by using this optimal treatment dose for the next patient, sampling $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ again from the true distributions, inserting into (2) and (3), generating outcomes from the Bernoulli distribution and updating the posterior means and variances for the radiobiological parameters as well as the optimal dose.

In section 9 the numbers of tumor controls, normal tissue injuries and complication free tumor controls achieved by the updating model are compared to the numbers achieved under the historical and the true model. The results from the historical and true models are calculated similarly to the procedure just described, except here there is no updating of the treatment dose. Instead the historical or true optimal dose is used for all patients in the study.

8 Simulation studies

Simulation studies performed for studying the effect of sequentially updating a partially suboptimal model towards a model defined by the true average radiobiological parameters for the given population are presented. The purpose of the simulations is to evaluate the convergence properties of the feedback system in terms of the number/fraction of complication free tumor controls as a function of the parameters in the model.

In all simulations the fixed values of $N_{0\mathrm{B}}$ and $N_{0\mathrm{I}}$ are set to 441 and 22100, respectively. These are values taken from a clinical data set on head and neck cancer treated in [Ågren et al. (1990)] The true mean values for $D_{0\mathrm{B}}$ and $D_{0\mathrm{I}}$ are set to 12 Gy and 8.2 Gy. Also these values are taken from [Ågren et al. (1990)].

Two historical sets of radiobiological parameters are used, one with mean radiobiological parameters $(D_{0\mathrm{B}}, D_{0\mathrm{I}}) = (14\text{ Gy},10\text{ Gy})$, resulting in a historical optimal dose that is higher than the optimal dose under the true model, and one with mean radiobiological parameters $(D_{0\mathrm{B}}, D_{0\mathrm{I}}) = (10\text{ Gy},7\text{ Gy})$, resulting in a historical optimal dose that is lower than the optimal dose under the true model. We also tested the true mean radiobiological parameters as historical.

In the simulation studies the standard deviations of the true radiobiological parameters are in one case 1 %, in all other cases 10 % of the mean values. Standard deviations of the historical radiobiological parameters vary between 1 % and 10 % of the mean values. One patient is treated in each sequence before updating but the total number of patients is varied. In order to get stable results the whole feedback system is repeated from the same historical model a number of times. Mostly it is 10 but also 20 and 40 repeats are done.

An infile containing information on mean values and standard deviations of the historical radiobiological parameters is read into Splus [Insightful]. In appendix D an example of an infile is given (corresponds to example 13 in tables 2 and 3) where the mean values of the historical radiobiological parameters are set to $(D_{0\mathrm{B}}, D_{0\mathrm{I}}) = (14\text{ Gy}, 10\text{ Gy})$, and the standard deviations to 10 % of the mean values. The infile also contains information about the updating process, the number of patients to be treated in each sequence (1 in example 13), the number of sequences, which is then the number of patients to be treated, (200 in example 13), and the number of repeats (10 in example 13).

In figure 3 are shown the probability curves, P_{B}, P_{I} and P_{+} for the mean historical, true and updated radiobiological parameters from the example in appendix D. Note that the updated curves lie between the historical and the true curves. Convergence is not fully achieved.

Software and programs are described in more detail in appendix D.

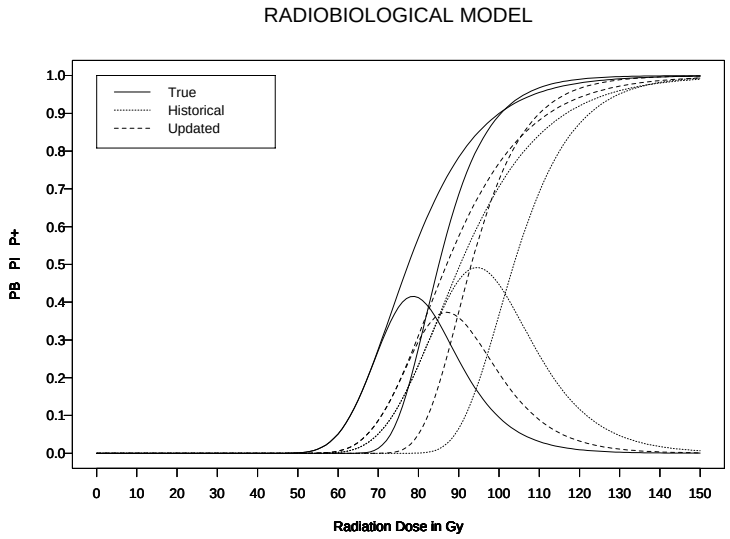

Figure 3: Illustrating true, historical and updated models for example 13 in tables 2 and 3.

9 Results and interpretation

Results of the simulation studies are given in tables 2 - 5.

Table 2 contains a reference number in the column to the left followed by simulation setup information on the means and standard deviations of the historical radiobiological parameters, and the total number of patients treated. Unless otherwise stated the standard deviations of the true radiobiological parameters are set to 10 % and the number of repeats to 10. Table 2 reports the achieved mean number of complication free tumor controls, the standard deviations (in parenthesis) and the mean fraction of complication free tumor controls (in brackets) compared to the number of patients being treated, taken over the repeats. Table 3 similarly contains a reference number in the column to the left, corresponding to the reference number from table 2, followed by the mean numbers of tumor controls and normal tissue injuries as well as their standard deviations and the mean fractions of tumor controls and normal tissue injuries compared to the number of patients being treated, taken over repeats.

As expected it is seen, that by updating the radiobiological parameters, complication free tumor control is achieved for more people than would have been the case using the historical optimal dose under the true model, cf. table 2. Below we consider the speed of convergence from the historical model to the true model measured in terms of the number of patients to be treated before the numbers of complication free tumor controls, tumor controls and normal tissue injuries are at the true level. The standard deviations of the radiobiological parameters are important when considering the speed of convergence, since the higher the standard deviations on the historical radiobiological parameters, the more the parameters values are allowed to change in the updating procedure when calculating posterior distributions. This in turn influences the optimal dose changes and hereby also the treatment outcomes.

Starting out with a historical dose that is too high compared to the true optimal dose, $(D_{0\mathrm{B}},D_{0\mathrm{I}})$=(14Gy,10Gy), the sequential updating results in a gain in the number of compli-

cation free tumor controls, achived by both fewer tumor controls and much fewer injuries than if using the historical optimal dose under the true model (since the optimal dose is lowered over sequences). With a 10 % standard deviation on the radiobiological parameters the number of complication free tumor controls are the same as in the true model already after 20 patients but both the numbers of tumor controls and normal tissue injuries are still higher than in the true model. However, after 50 and 200 patients also the numbers of tumor controls and normal tissue injuries are getting closer to the true model. The results for the simulation studies with standard deviations on the radiobiological parameters equal to 10 % and 5 % are very close to each other, and the number of complication free tumor controls for the updating models are about the same. When lowering the standard deviations to 1 % the number of complication free tumor controls are much lower and closer to the historical model than in the cases with 5 % and 10 % as are the numbers of tumor controls and normal tissue injuries. The convergence is slower than in the previous cases.

When starting out with a historical dose that is too low compared to the true optimal dose, $(D_{0\mathrm{B}},D_{0\mathrm{I}})$=(10Gy,7Gy), the dose is escalated over sequences. Both the numbers of tumor controls and injuries increase, the former faster than the latter, to obtain a higher number of complication free tumor controls than for the historical model. Also here the number of achieved complication free tumor controls are very close to the true model when standard deviations on the historical radiobiological parameters are 5 % and 10 %. When lowering the standard deviations from 5 % to 1 % the convergence is slowed down, and after 200 patients the updated model has still not converged.

	historical parameters D_{0B}	D_{0I}	(sd)	# patients treated in total	# complication free tumor controls under historical treatments (sd) [%]	true	updating
1	14	10	(10%)	20	4.5 (2.0) [.23]	6.9 (2.2) [.35]	7.9 (2.0) [.40]
2	14	10	(10%)	20	4.5 (2.0) [.23]	6.9 (2.2) [.35]	7.4 (1.7) [.37]
3	14	10	(10%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	18.4 (3.5) [.37]
4	14	10	(5%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	18.4 (3.4) [.37]
5	14	10	(5%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	16.0 (2.7) [.32]
6	14	10	(5%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	15.7 (1.8) [.31]
7	14	10	(1%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	9.7 (3.8) [.19]
8	14	10	(1%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	9.8 (1.6) [.20]
9	14	10	(1%)	50	11.2 (2.7) [.22]	18.3 (3.6) [.37]	7.7 (2.8) [.15]
10	14	10	(10%)	200	43.1 (6.4) [.22]	75.1 (5.7) [.38]	79.5 (7.1) [.40]
11	14	10	(10%)	200	43.1 (6.4) [.22]	75.1 (5.7) [.38]	83.2 (6.3) [.42]
12	14	10	(5%)	200	43.1 (6.4) [.22]	75.1 (5.7) [.38]	76.6 (4.6) [.38]
13	14	10	(1%)	200	43.1 (6.4) [.22]	75.1 (5.7) [.38]	53.9 (4.1) [.27]
14	14	10	(10%)	200[1)]	43.1 (6.4) [.22]	75.1 (5.7) [.38]	81.8 (6.6) [.41]
15	14	10	(10%)	200[2)]	43.1 (6.4) [.22]	75.1 (5.7) [.38]	81.8 (7.0) [.41]
16	14	10	(10%)	200[2)]	43.1 (6.4) [.22]	75.1 (5.7) [.38]	80.6 (6.5) [.40]
17	14	10	(5%)	200[3)]	36.8 (4.7) [.18]	80.2 (6.5) [.40]	77.8 (6.8) [.39]
18	10	7	(10%)	50	9.4 (2.4) [.19]	18.3 (3.6) [.37]	19.4 (3.8) [.39]
19	10	7	(5%)	50	9.4 (2.4) [.19]	18.3 (3.6) [.37]	17.9 (2.1) [.36]
20	10	7	(1%)	50	9.4 (2.4) [.19]	18.3 (3.6) [.37]	14.0 (3.0) [.28]
21	10	7	(10%)	200	41.9 (5.9) [.21]	75.1 (5.7) [.38]	77.8 (4.4) [.39]
22	10	7	(5%)	200	41.9 (5.9) [.21]	75.1 (5.7) [.38]	81.3 (8.4) [.41]
23	10	7	(5%)	200	41.9 (5.9) [.21]	75.1 (5.7) [.38]	78.2 (2.4) [.39]
24	10	7	(1%)	200	41.9 (5.9) [.21]	75.1 (5.7) [.38]	57.0 (5.8)[.29]
25	12	8.2	(10%)	50	18.3 (3.6) [.37]	18.3 (3.6) [.37]	19.6 (3.0) [.39]
26	12	8.2	(10%)	200	75.3 (6.5) [.38]	75.3 (6.5) [.38]	81.0 (4.7) [.41]
27	12	8.2	(10%)	200	75.3 (6.5) [.38]	75.3 (6.5) [.38]	79.0 (5.5) [.41]
28	12	8.2	(1%)	200	75.3 (6.5) [.38]	75.3 (6.5) [.38]	86.2 (5.0) [.41]
29	12	8.2	(1%)	200	75.3 (6.5) [.38]	75.3 (6.5) [.38]	79.6 (4.5) [.41]

The standard deviations of the true radiobiological parameters are 10 % if nothing else stated.

The number of repeats is 10 if nothing else is stated.

1) 20 repeats were done.

2) 40 repeats were done.

3) Only 5% sd on true parameters.

Table 2: Results of simulation studies. Complication free tumor controls.

	# tumor controls under			# injuries under		
	historical	true treatments (sd)	updating	historical	true treatments (sd)	updating
1	16.1 (1.6) [.81]	9.7 (2.2) [.49]	14.0 (2.3) [.70]	14.3 (2.0) [.72]	5.3 (1.6) [.27]	8.3 (1.4) [.42]
2	16.1 (1.6) [.81]	9.7 (2.2) [.49]	13.9 (1.7) [.70]	14.3 (2.0) [.72]	5.3 (1.6) [.27]	8.4 (1.5) [.42]
3	40.4 (2.8) [.81]	25.6 (3.3) [.49]	30.2 (3.9) [.60]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	18.3 (3.2) [.37]
4	40.4 (2.8) [.81]	25.6 (3.3) [.51]	35.5 (2.5) [.71]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	23.4 (2.2) [.47]
5	40.4 (2.8) [.81]	25.6 (3.3) [.51]	34.4 (2.2) [.69]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	25.6 (2.8) [.51]
6	40.4 (2.8) [.81]	25.6 (3.3) [.51]	33.6 (2.4) [.67]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	26.7 (2.5) [.53]
7	40.4 (2.8) [.81]	25.6 (3.3) [.51]	42.0 (3.1) [.84]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	38.5 (3.4) [.77]
8	40.4 (2.8) [.81]	25.6 (3.3) [.51]	40.1 (2.3) [.80]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	38.0 (1.9) [.76]
9	40.4 (2.8) [.81]	25.6 (3.3) [.51]	41.5 (2.8) [.83]	36.3 (2.7) [.73]	14.1 (3.2) [.28]	40.3 (2.5) [.81]
10	162.4 (5.4) [.81]	103.8 (7.0) [.52]	110.5 (3.8) [.55]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	53.6 (7.2) [.27]
11	162.4 (5.4) [.81]	103.8 (7.0) [.52]	115.1 (6.2) [.58]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	55.5 (3.8) [.28]
12	162.4 (5.4) [.81]	103.8 (7.0) [.52]	125.2 (3.2) [.63]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	75.3 (3.1) [.38]
13	162.4 (5.4 [.81])	103.8 (7.0) [.52]	156.4 (4.0) [.78]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	130.6 (6.7) [.65]
14	162.4 (5.4) [.81]	103.8 (7.0) [.52]	113.9 (4.8) [.57]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	54.7 (6.9) [.27]
15	162.4 (5.4) [.81]	103.8 (7.0) [.52]	115.2 (5.7) [.58]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	55.1 (7.3) [.28]
16	162.4 (5.4) [.81]	103.8 (7.0) [.52]	112.7 (5.1) [.56]	146.5 (6.8) [.73]	55.7 (6.3) [.28]	56.0 (6.7) [.28]
17	166.9 (5.5) [.81]	106.1 (6.6) [.53]	124.4 (6.2) [.62]	155.7 (4.4) [.78]	48.4 (5.2) [.24]	73.7 (7.4) [.37]
18	9.7 (2.5) [.19]	25.6 (3.3) [.51]	23.7 (3.6) [.47]	1.4 (1.2) [.03]	14.1 (3.2) [.28]	8.2 (2.6) [.16]
19	9.7 (2.5)[.19]	25.6 (3.3) [.51]	19.6 (2.2) [.39]	1.4 (1.2) [.03]	14.1 (3.2) [.28]	4.4 (.8) [.09]
20	9.7 (2.5) [.19]	25.6 (3.3) [.51]	14.2 (3.3) [.28]	1.4 (1.2) [.03]	14.1 (3.2) [.28]	.7 (.8) [.01]
21	43.3 (6.0) [.22]	103.8 (7.0) [.52]	99.7 (5.9) [.50]	5.9 (2.2) [.03]	55.7 (6.3) [.28]	42.1 (4.1) [.21]
22	43.3 (6.0) [.22]	103.8 (7.0) [.52]	96.8 (6.1) [.48]	5.9 (2.2) [.03]	55.7 (6.3) [.28]	30.6 (4.6) [.15]
23	43.3 (6.0) [.22]	103.8 (7.0) [.52]	93.7 (2.4) [.47]	5.9 (2.2) [.03]	55.7 (6.3) [.28]	33.4 (3.7) [.17]
24	43.3 (6.0) [.22]	103.8 (7.0) [.52]	57.7 (5.6) [.29]	5.9 (2.2) [.03]	55.7 (6.3) [.28]	2.2 (1.5) [.01]
25	25.6 (3.3) [.51]	25.6 (3.3) [.51]	25.3 (3.6) [.51]	14.1 (3.2) [.28]	14.1(3.2) [.28]	11.4 (1.5) [.23]
26	107.8 (6.7) [.54]	107.8 (6.7) [.54]	105.3 (5.7) [.53]	60.7 (6.5) [.30]	60.7(6.5) [.30]	42.8 (4.7) [.21]
27	107.8 (6.7) [.54]	107.8 (6.7) [.54]	105.3 (5.2) [.53]	60.7 (6.5) [.30]	60.7(6.5) [.30]	49.1 (5.1) [.25]
28	107.8 (6.7) [.54]	107.8 (6.7) [.54]	105.4 (5.0) [.53]	60.7 (6.5) [.30]	60.7(6.5) [.30]	37.4 (4.0) [.19]
29	107.8 (6.7) [.54]	107.8 (6.7) [.54]	101.4 (8.2) [.51]	60.7 (6.5) [.30]	60.7(6.5) [.30]	40.5 (6.0) [.20]

Table 3: Results of simulation studies. Tumor controls and normal tissue injuries.

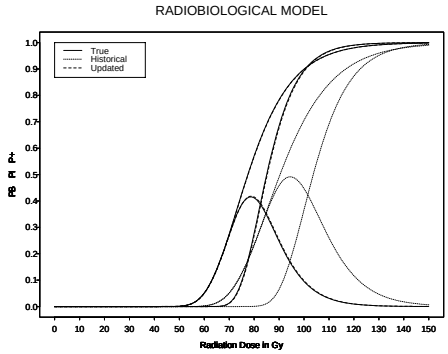

Figure 4: Illustrating true, historical and updated models for example 15 in tables tables 2 and 3.

In figure 4 the historical, true and final updated probability curves are drawn for example 15 from tables 2 and 3. Since the standard deviations are large and many patients are treated, the final updated model is overlapping the true model. Convergence is achieved.

To convince ourselves that results over 10 repeats in tables 2 and 3 capture the performance of the updating procedure we compared in table 4 the standard deviations of means and the means of standard deviations over repeats for the final radiobiological parameters for some of the simulations. The columns to the left are the reference number (corresponding to the reference number in table 2), the historical mean values and standard deviations of the radiobiological parameters, and the number of repeats in the simulations. It is seen that the standard errors are closer to the mean of the standard deviations when 40 repeats are done than when 10 repeats are done. However, when comparing with the results in tables 2 and 3 the estimates of tumor controls, injuries to the normal tissues and complication free tumor controls are similar for 10 repeats (reference numbers 10 and 11) and for 40 repeats (reference numbers 15 and 16) concluding that the 10 repeats done in most simulations are enough.

In table 5 optimal doses are given for different values of the means and the standard deviations of the radiobiological parameters when simulating the optimal dose from the left-hand side of (7) and when approximating from the right-hand side of (7). Comparing the two methods it is seen that the approximation works very well.

We conclude that the standard deviations for the historical radiobiological parameters are important factors for controlling the updating speed of the radiobiological parameters and hereby the optimal doses. In reality it is not known whether the historical dose is too high or too low compared to the true optimal dose. Regardless of which is the case the results presented here show a gain in the number of complication free tumor controls from sequentially updating the dose.

refers to numbers in tables 2 and 3	historical parameters D_{0B}	D_{0I}	(sd)	# patients treated	# repeats	standard deviations of means of the radiobiological parameters D_{0B}	D_{0I}	means of standard deviations of the radiobiological parameters D_{0B}	D_{0I}
3	14	10	(10%)	50	10	.319	.156	.348	.139
4	14	10	(5%)	50	10	.182	.110	.310	.123
10	14	10	(10%)	200	10	.155	.087	.182	.074
12	14	10	(5%)	200	10	.110	.043	.174	.066
15	14	10	(10%)	200	40	.191	.069	.179	.071
18	10	7	(10%)	50	10	.321	.184	.376	.148
19	10	7	(5%)	50	10	.350	.165	.340	.134
21	10	7	(10%)	200	10	.169	.041	.200	.076
22	10	7	(5%)	200	10	.219	.091	.195	.084

Table 4: Standard errors and means of standard deviations.

setups	radiobiological parameters D_{0B}	D_{0I}	(sd)	optimal dose (simulated) in Gy	optimal dose (approximated) in Gy
true/historical	12	8.2	(10%)	79.6	78.7
true/historical	12	8.2	(1%)	78.7	78.7
historical	14	10	(10%)	95.5	94.5
historical	14	10	(5%)	94.8	94.5
historical	14	10	(1%)	94.5	94.5
historical	10	7	(10%)	67.3	66.6
historical	10	7	(5%)	66.8	66.6
historical	10	7	(1%)	66.6	66.6

Table 5: Optimal doses simulated according to criteria and approximation in (7).

10 Discussion

A simple radiobiological model built into a feedback-system has been presented. Information from previous treated patients was built into the model and used to forwardly taylor a treatment to the future patients coming in for treatment.

When designing an optimal updating procedure for clinical use there are a number of issues worth exploring further. Distributions on N_{0B} and N_{0I} may be imposed and should be carefully chosen in order to reflect the complexity of different cells and cell structures in both tumor and normal tissues described in section 3. The normality assumption for the parameters in the linear predictor could be released and the covariance structure between all the radiobiological parameters could be further explored. From a substantive point of view it is reasonable to assume that the radiation sensitivity in the tumor cells and the normal tissues are correlated, cf. [Geara et al (1996)], but it remains unclear at present whether inclusions of the correlation structure in the updating procedure would substantially increase convergence speed for the optimal dose. Together with the exploration of a covariance structure the hyperprior structure could be built in. Comments on software needs for these extensions can be found in appendix D.

It is desirable to account for the dose fractionation by compensating for the between fractions tumor growth, cell repair and reoxygenation which will violate the Poisson assumption. Different endpoints for normal tissues could be considered and a competing risk moment between the tumor and the injury side be built in. The dose concept may be extended to account for non-uniform dose distributions. Other objective functions than the one in equation

(7) could be considered. For example [Löf J (2000)] consider maximizing the probability of tumor control subject to an upper restriction on the probability of inducing injury to the normal tissues. This extension will change the likelihood part of (8) and introduce additional posterior correlation between the tumor and the injury part.

Besides convergence from the historical model to the true model, there are convergence issues due to Monte Carlo error when calculating the posterior distributions using MCMC. In the simple model presented here the latter is a minor problem, but for more complicated models the number of chains may be extended and formal convergence diagnostics built into the process.

In order for the model to be clinically relevant the dose must be monitored in a clinically acceptable way. For implementing the feedback model in the clinic only a short dose interval will be of relevance. The prior historical variance controls the changes of the radiobiological parameters and the optimal dose. It should reflect the number of patients that were used to derive the parameters estimates. However, other things need to be taken into account, too. If treatment techniques have changed or the target population differ from the original one a flat prior with large standard deviations will let changes happen fast. The first patients will then have a huge effect on the treatment for the next patients. An informative prior, with minor standard deviations, will protect the new patients from odd acting historical patients but also slow down changes. Other control mechanisms can be built in, for example by limiting the size of the dose change between two sequences.

For taking the last step from section 1 and implementing the dynamic dose optimization procedure into a clinical setting in Sweden routines are needed for storing dose information as well as information on old and new tumor molecular markers. Inclusion of patient individual molecular information in the model, e.g. on molecular markers for sensitivity to radiation, cf. [Haghdoost et al. (2001), Friesland et al. (2002)], can be used to get the subgroups in the population under study more homogeneous. This allows for more individualized treatment schedules and a decrease in the variance of the model parameters. With new molecular information for tumor classification the need for individually targeted treatment planning and for new knowledge of optimal treatment allocation in subgroups will increase. The statistical tools proposed here are a first step in building a procedure for sequentially updating treatment schemes.

APPENDICES

A Interpreting the radiobiological model as a generalized linear mixed model

Defining a univariate *generalized linear model*. A GLM is fully characterized by three components (to be explained below): The type of the exponential family, the link function and the design vector [McCullagh & Nelder (1989), Fahrmeir & Tutz (1997)].

Assume that y is an observation on a stochastic variable Y and that a set of observations is given. To each observation is attached an m-dimensional covariate vector x. Assume that the conditional mean of Y given x is equal to μ, $E(Y|x) = \mu$, that the $Y|x$'s, are conditionally independent given μ and that the distribution of $Y|x$ belongs to a simple exponential family. For an *exponential family* the density function of Y can always be written as

$$f(y|\theta, \phi, \omega) = exp\left\{\frac{y\theta - b(\theta)}{\phi}\omega + c(y, \phi, \omega)\right\}, \tag{10}$$

where θ is called the canonical parameter, ϕ is the additional dispersion parameter, $b(\cdot)$ and $c(\cdot)$ are specific functions defining the type of exponential family distribution, and ω is a known weight. If data are grouped with n persons in each group and if the average of the individual responses is used as the group response then $\omega = n$, if the sum of the individual responses is used as the group response then $\omega = 1/n$. For ungrouped data $\omega = 1$. It can be shown that $E(Y|x) = \mu = b'(\theta)$ and that $Var(Y|x) = (b''(\theta)\phi)\omega$ where $b'(\theta) = \partial b(\theta)/\partial\theta$ and $b''(\theta) = \partial^2 b(\theta)/\partial\theta^2$. Assume further that the conditional means $E(Y|x) = \mu$ are related to the *linear predictor* $\eta = z'\beta$ by

$$E(Y|x) = \mu = h(\eta) = h(z'\beta) \qquad \text{resp.} \qquad \eta = z'\beta = g(\mu) \tag{11}$$

where h is a known one-to-one, monotone, sufficiently smooth response function, g is the *link* function i.e. the inverse of h, β is a vector of unknown parameters of dimension m, and z is a *design vector* of dimension m, which is determined as an appropriate function $z = z(x)$ of the covariates x.

The Binomial distribution. Assume that Y is binomially distributed with index n and parameter π. Y belongs to the exponential family since the density function can be written

$$\begin{aligned} f(y|\pi) &= \binom{n}{y}(\pi)^y(1-\pi)^{n-y} \\ &= exp\left\{ylog(\frac{\pi}{1-\pi}) + nlog(1-\pi) + log\binom{n}{y}\right\} \\ &= exp\left\{\frac{\frac{y}{n}log(\frac{\pi}{1-\pi}) - log[(1-\pi)^{-1}]}{1}n + log\binom{n}{n\frac{y}{n}}\right\} \\ &= exp\left\{\frac{\widetilde{y}log(\frac{\pi}{1-\pi}) - log[(1-\pi)^{-1}]}{1}n + log\binom{n}{n\widetilde{y}}\right\} \end{aligned} \tag{12}$$

where $\widetilde{y} = y/n$. Treating the average as response and identifying the canonical parameter $\theta = log(\frac{\pi}{1-\pi})$, the dispersion parameter $\phi = 1$, $b(\theta) = log(1 + e^\theta)$, $c(\widetilde{y}, \phi, \omega) = log\binom{\omega}{\omega\widetilde{y}}$ and $\omega = n$ it is seen that Y is also a GLM. For the special case where Y is Bernoulli distributed (n=1) with parameter π

$$f(y|\pi) = exp\left\{\frac{ylog(\frac{\pi}{1-\pi}) - log[(1-\pi)^{-1}]}{1}1 + 0\right\} \tag{13}$$

the canonical parameter $\theta = log(\frac{\pi}{1-\pi})$, the dispersion parameter $\phi = 1$, $b(\theta) = log(1 + e^\theta)$, $c(y, \phi, \omega) = 0$ and $\omega = 1$.

The radiobiological model is recognized as a (GLM) with a Bernoulli response, Y_{B}, and a log-log link function for the probability, P_{B},

$$\text{log-log}(P_{\mathrm{B}}) = \log(N_{0\mathrm{B}}) + \left(\frac{-1}{D_0 B}\right) D, \tag{14}$$

where log-log(P_{B}) = log(-log(P_{B})). The right-hand side of equation 14 is the linear predictor, $(log(N_{0\mathrm{B}}), -1/D_{0\mathrm{B}})$ corresponds to the β vector, $(1, D)$ to the z vector in (11).

Population heterogeneity can be captured by assuming a distribution on the mean value P_{B}, resulting in a Generalized Linear *Mixed* Model (GLMM) with a mixing distribution on the mean value.

The Beta-binomial model - a simple GLMM. Assume that Y is a stochastic variable, binomially distributed with index n and parameter π, and that π is Beta distributed with parameters α and β. Then the posterior distribution of π given the observed data y of Y is given by:

$$\begin{aligned} P(\pi|y) &\propto p(\pi)p(y|\pi) \\ &= \left(\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\pi^{\alpha-1}(1-\pi)^{\beta-1}\right) \cdot \left(\binom{n}{y}\pi^{y}(1-\pi)^{n-y}\right) \\ &\propto \pi^{(\alpha+y)-1}(1-\pi)^{(\beta-y+n)-1}, \end{aligned} \tag{15}$$

which is again a Beta distribution, this time with parameters $\alpha + y$ and $\beta + n - y$. When the prior and posterior have similar distributional form the prior is said to be a *conjugate* distribution for the likelihood. The Beta prior on the probability π is thus conjugate for the binomial likelihood.

To force a Beta distribution on P_{B} is very restrictive. A more flexible and generalizable family of models, *random effects models* is obtained by assuming distributions on (functions of) the radiobiological parameters as in (8). The posterior distribution of P_{B} then no longer has a known distributional form but numerical methods facilitates calculating the posterior distribution of P_{B} and similarly P_{I}.

B Priors and posteriors

Assume that Y is a stochastic variable and that y is the observed outcome of Y. The likelihood $p(y|\pi)$ is a function of the distribution parameter π conditional on the observed outcome. In the Bayesian framework the parameter π is treated as a stochastic variable with prior distribution $p(\pi)$. By *Bayes rule* the posterior distribution for the parameter π, given the observed data Y, $p(\pi|Y)$ is proportional to the prior, $p(\pi)$, multiplied by the likelihood of the data given π, $p(Y|\pi)$:

$$p(\pi|Y)^{B)} = \frac{p(\pi)p(Y|\pi)}{p(Y)} \propto p(\pi)p(Y|\pi) \tag{16}$$

where B) indicates the definition of Bayes rule.

The *joint posterior distribution* of the radiobiological parameters is given in (8). *Marginal posterior distributions* of one of the radiobiological parameters are obtained by integrating over the righthand side in (8) with respect to all the other parameters. Also the posterior distributions of the probabilities of achieving tumor control and inducing injury to the normal tissue, can be calculated.

C Computation using Markov chain Monte Carlo simulation

Gibbs sampling, an algorithm performing Markov chain Monte Carlo simulation, can be used to calculate the posterior distributions [Gilks et al. (1996)] of the radiobiological parameters and of the probabilities of achieving tumor control and inducing injury. The Gibbs sampler was given its name by [Geman & Geman (1984)] who used it for analyzing Gibbs distributions on lattices in connection with image analysis. It is known from statistical physics as the *heat-bath algorithm.* [Geman & Geman (1984)] based their work on work by [Metropolis et al. (1953)] and [Hastings (1970)] but it was articles by [Gelfand & Smith(1990)] and [Gelfand et al. (1990)] that explained how MCMC could be of widespread and important use in Bayesian statistics as a tool for calculating posteriors which was not possible before.

A short description of algorithms and how the theory of Markov chains Monte Carlo integration can be used to get information about the posterior distributions of the random parameters in the radiobiological model is given. For more detailed descriptions with references see for example [Gilks et al. (1996)]. Denote by X be the set of random parameters from the radiobiological model, let f be a function of X that we want to evaluate (the mean, the variance, upper percentile, etc), and denote by $\tau(\cdot)$ the posterior distribution of X.

First a remark on Markov chains. A *stochastic process* is a sequence of h-dimensional stochastic variables $\{X_0, X_1, X_2, ...\}$ and a *Markov Chain* is a stochastic process with a transition distribution $P_t(\cdot|\cdot)$ that satisfies

$$P_t(X_{t+1}|X_t, X_{t-1}, ..., X_0) = P_t(X_t + 1|X_t), \tag{17}$$

i.e. at time t the probability of going to X_{t+1} only depends on the position at time t, X_t, not on the whole history of steps from the start at X_0. The transition probabilities might or might not depend on t. If the Markov chain is *irreducible* (the chain can reach any non-empty set with positive probability in some number of iterations), *aperiodic* (preventing it from oscillating between different sets of states in a regular movement), and *positive recurrent* (if the initial value X_0 is sampled from the stationary distribution $\tau(\cdot)$ then all subsequent iterates will also be sampled according to $\tau(\cdot)$) then the distribution of X_t will converge to a *unique* stationary distribution which does not depend on t and X_0. cf. for example [Roberts (1996), Meyn & Tweedie(1996)].

If $f(X)$ is hard or impossible to calculate analytically *Monte Carlo integration* can be used to get information about the mean value of f given by

$$E[f(X)] = \frac{\int f(x)\tau(x)dx}{\int \tau(x)dx}. \tag{18}$$

When performing Monte Carlo integration the samples $\{X_t, t = 1, 2, ..., m\}$ are drawn *independently* from $\tau(\cdot)$ and then the mean value, $E[f(X)]$, is approximated by the sample

mean,

$$E[f(X)] \approx \frac{1}{m}\sum_{t=1}^{m} f(X_t), \tag{19}$$

the Monte Carlo estimate. By increasing the number of samples the estimate can be made as accurate as desired. If the samples $\{X_t\}$ are drawn by running a Markov chain having $\tau(\cdot)$ as its stationary distribution the method is called *Markov chain Monte Carlo*. Thus after a sufficiently long *burn-in* of say k iterations, the points $\{X_t, t = k+1, ..., m\}$ will be *dependent* samples approximately from $\tau(\cdot)$. The output from the Markov chain can then be used to estimate $E[f(X)]$, the Markov chain Monte Carlo estimate, by

$$E[f(X)] \approx \overline{f} = \frac{1}{m-k}\sum_{t=k+1}^{m} f(X_t) \tag{20}$$

where $\overline{f}$ is called the ergodic average. The variance of $\overline{f}$ is called the *Monte Carlo variance*. Convergence to the required expectation is ensured by the ergodic theorem, cf. for example [Roberts (1996), Meyn & Tweedie(1996)].

There are several algorithms for sampling by running a Markov chain such that its unique stationary distribution is the distribution of interest $\tau(\cdot)$, cf. for example [Gilks et al. (1996)], [Gilks (1996)], [Gelr

First consider the *Metropolis-Hastings sampler* [Hastings (1970)] which is a generalization of the Metropolis algorithm. Denote by X the set of stochastic variables in the radiobiological model, $X = (N_{0\mathrm{B}}, D_{0\mathrm{B}}, N_{0\mathrm{I}}, D_{0\mathrm{I}}, P_{\mathrm{B}}, P_{\mathrm{I}})$ At each time t the next state X_{t+1} of the Markov chain is chosen by first sampling a candidate point $\tilde{X}$ from a *proposal distribution*, $q(\cdot|X_t)$. The candidate point $\tilde{X}$ is then accepted with probability $\alpha(X_t, \tilde{X})$ where

$$\alpha(X_t, \tilde{X}) = \min\left(1, \frac{\tau(\tilde{X})q(X_t|\tilde{X})}{\tau(X_t)q(\tilde{X}|X_t)}\right) \tag{21}$$

τ being the posterior distribution of interest. If the candidate point is accepted the next state becomes $X_{t+1} = \tilde{X}$. If the candidate is rejected, the chain does not move.

The *Metropolis sampler* [Hastings (1970)] only considered symmetric proposal distributions leading to the following acceptance probability

$$\alpha(X_t, \tilde{X}) = \min\left(1, \frac{\tau(\tilde{X})}{\tau(X_t)}\right). \tag{22}$$

The *single-component component Metropolis-Hastings sampler* updates one component of the h-dimensional state vector X at a time, thus if at time $t+1$ an update component i is wanted, and if $X_{t+1}^{-i} = (X_{t+1}^1, X_{t+1}^2, ..., X_{t+1}, ^{i-1}, X_t^{i+1}, ..., X_t^h)$ and $\tilde{X}^i$ is the candidate for the i'th component then equation 21 becomes

$$\alpha(X_{t+1}^{-i}, \tilde{X}^i|X_{t+1}^i) = \min\left(1, \frac{\tau(\tilde{X}^i|X_{t+1}^{-i})q(X_{t+1}^i|\tilde{X}^i, X_{t+1}^{-i})}{\tau(X_{t+1}^i|X_{t+1}^{-i})q(\tilde{X}^i|X_{t+1}^i, X_{t+1}^{-i})}\right). \tag{23}$$

Here $\tau(X_{t+1}^i|X_{t+1}^{-i})$ is the full conditional distribution for X_{t+1}^i under $\tau(\cdot)$, i.e. the distribution of X_{t+1}^i given all other stochastic quantities in the model. If $\tilde{X}^i$ is accepted set $X_{t+1}^i = \tilde{X}^i$,

otherwise set $X_{t+1}^i = X_t^i$. The remaining components are not changed at step i. That the single-component Metropolis-Hastings algorithm does indeed generate samples from the target distribution $\tau(\cdot)$ follows from the fact that $\tau(\cdot)$ is uniquely determined by the set of its full conditional distributions [Besag (1974)].

The *Gibbs sampler* is a special case of the single-component Metropolis-Hastings sampler. The proposal distribution for updating the i'th component of X is

$$q_i(\tilde{X}^i|X_t^i, X_t^{-i}) = \tau(\tilde{X}^i|X_t^{-i}) \tag{24}$$

where $\tau(\tilde{X}^i|X_t^{-i})$ is the full conditional distribution. Substituting (24) into (21) gives an acceptance probability of 1.

Thus the Gibbs sampler proceeds by visiting the stochastic quantities in the model drawing a sample from the full conditional distribution of the stochastic variable in question given values of all the other variables from the previous round. Since the walk is constructed as a Markov chain the probability of visiting a variable in the model only depends on the previous position. The candidate points are always accepted and after a number of rounds (the burn-in), the samples will constitute dependent draws from the posterior distribution in question. From the sampled joint posterior distribution of the stocheastic quantities in the model the marginal posterior distributions of the radiobiological parameters and the posterior distributions of tumor control and injury can be calculated.

Methods for assessing convergence of the chain exist, cf. for example [Gelman et al. (1995), Raftery and Lewis (1996), Gelman (1996)]. Notice that this area is still developing. For example block updating of the Gibbs sampler has made it more efficient, but also new algorithms are continuously being developed.

D Software and programs

The simulation study is built into an S-plus [Insightful] program that is run on the Linux platform. The optimal way to run it is by specifying a number of characteristics such as link function (logit or log-log), objective function, number of patients to be treated, number of repeats (to ensure stable estimates), values and standard deviations on true and historical radiobiological parameters and treatment doses (optimal or fixed) in an infile, and then running the program in batch mode. For every update (i.e. every time a patient is treated) subprograms are called for example for getting ready for posterior calculations. The posterior calculations are done in the program Bugs [Spiegelhalter et al. (1995)], that implements Gibbs sampling, cf. appendix C, via *Adaptive Rejections Sampling* [Gilks (1996), Spiegelhalter et al. (1995), Gilks (1992), Gilks & Wild (1992)]. A unix shell script is written in order for the program to escape to unix, run the script and calculate the posterior distributions and then getting the results back into Splus. For the simple model reported here, the model is run without regular MCMC convergence tests. The convergence of the MCMC model in each sequence of the posterior model can be checked in the program BOA [Smith (2000)]. Sporadic checks have been done, showing fine quadratic posterior distributions, but for more complicated models regular checks should be done!

Bugs assumes a full probability model when calculating posterior distributions using Gibbs sampling. A full probability model representation incorporates hyperpriors on the mean

values and the variances of the radiobiological parameters. Typical choices of noninformative hyperpriors choices are a normal distribution for the mean value, ξ and a Wishart distribution for the inverse of the variance, Σ^{-1}. We tested a simplified form of the radiobiological model in the simulation studies ignoring the hyperlevel uncertainty, outomes were sampled from the true distribution, and the prior mean and variance of the radiobiological parameters were incorporated directly in the program calculating posteriors without integration with respect to the hyperprior distribution.

The pros of the program Bugs are that it is readily available to do posterior calculations. The cons are that since it is a general purpose program there are many restrictions on what is possible, and other software might do the job more effective. For example some kind of block-updating of some of the variables in the model would likely be more effetive, cf. appendix C. One of the restrictions in the model has been that the multivariate normal prior distribution for the radiobiological parameters on the Linux platform did not work. Another awkward restriction was the need to define the normal distributions for the variables in the linear predictor. For the radioresistances we might have wanted other distributions, such as a truncated normal distribution on $D_{0\mathrm{B}}$. A number of tricks have been introduced now to overcome some of the limitations in Bugs. At the time when this project was initiated one major force was to get familiar with modern tools for Bayesian posterior inference. During the course of the work it turned out that simulations involving the radiobiological model are rather too complex for Bugs, and if starting anew it would be important to write new computationel subroutines.

In subsections D1 - D10 (seperate appendix) we have documented the Splus, Bugs and shell scripts used in the simulation studies. D1 contains an example of an infile, (example 13 from tables 2 and 3), D2 contains the main program for the simulation studies and calls all the other subprograms and routines to be executed. D3 contains a subprogram preparing for posterior calculations, D4 contains the Bugs program file for calculating posteriors, D5 contains a shell script getting the Bugs program and command files ready for executing and D6 contains the Bugs command file. D7 contains a shell script to run the Bugs program, D8 contains Splus functions called by the main program in D2, D9 contains a shell script to start the simulation program and D10 contains parts of the result file from simulating according to the model in D1. The programs have been written such that extension of the model was possible.

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