Online Supplement to: Adjustable robust treatment-length optimization in radiation therapy

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A Results exact biomarker information: out-of-sample performance

To investigate the out-of-sample performance of the methods, we assume a uniform distribution for \((\rho, \tau)\) over a larger set than \(Z\). We can write \(Z\) as

\[
Z = \{(\rho, \tau): \rho_L \leq \rho \leq \rho_U, \tau_L \leq \tau \leq \tau_U\} = \{(\rho, \tau): |\rho - \bar{\rho}| \leq \varepsilon_{\rho}, |\tau - \bar{\tau}| \leq \varepsilon_{\tau}\},
\]

where \((\varepsilon_{\rho}, \varepsilon_{\tau})\) is the maximum deviation from the nominal scenario \((\bar{\rho}, \bar{\tau})\). This allows us to define

\[
Z_c = \{(\rho, \tau): |\rho - \bar{\rho}| \leq c \varepsilon_{\rho}, |\tau - \bar{\tau}| \leq c \varepsilon_{\tau}\},
\]

where \(c > 0\) is a parameter. We assume a uniform distribution over the new set \(Z_c\). If \(c = 1\), we have \(Z_c = Z\), so we sample exactly from \(Z\). If \(c > 1\), we sample from an interval that is \(c^2\) times as large as \(Z\) (\(c\) times larger for both \(\rho\) and \(\tau\)). For \(c = 2\) we obtain the results in Table A.1. The stage-1 dose \(d_1\) is the same as in ??? in the main manuscript for all methods except PI, because PI is the only method that is aware that the sample is not taken from uncertainty set \(Z\) but from \(Z_c\). For NOM, the maximum violation percentage has increased slightly. All other methods are able to deal with the out-of-sample realizations and do not have any OAR constraint violations.

Due to the larger sampling space (the area of \(Z_c\) is four times the area of \(Z\)), the difference between sample mean and sample worst-case performance is much larger than in ??? for all methods. The true worst-case objective value in \(Z\) is still lower than the sample worst-case in \(Z_c\). The reason for this is that the true worst-case scenario can differ per patient.

NOM-FH and ARO are near optimal for the worst-case sample scenario, and are also close to PI in the sample 5% quantile and sample mean. The relative performance of the adaptive methods remains
Table A.1: Results for experiments with exact biomarker information and uniform sampling of \((\rho, \tau)\) over \(Z_2\). For each scenario, results are averaged over 20 patients\(^*\). All methods optimize for worst-case tumor BED in \(Z\), which is displayed in bold.

\(^*\): the maximum OAR violation is computed over all patients and scenarios.

![Cumulative scenario-tumor BED graph for experiments with exact biomarker information and uniform sampling of \((\rho, \tau)\) over \(Z_2\) (200 scenarios). A point \((x, y)\) indicates that in \(y\)% of scenarios the tumor BED (averaged over 20 patients) is at least \(x\) Gy. ARO and NOM-FH are very close to PI.](image_url)

Fig. A.1 shows the complete cumulative scenario-tumor BED graph for the ‘average patient’. Compared to \(\rho\), NOM and RO have poor performance across the sample. This indicates bad performance of the static methods on scenarios outside of \(Z\).

Mostly unchanged, RO-FH performs slightly worse than NOM-FH and ARO, similar to \(\rho\). Compared to \(\tau\), NOM and RO have poor performance across the sample. This indicates bad performance of the static methods on scenarios outside of \(Z\).

Figure A.1 shows the complete cumulative scenario-tumor BED graph for the ‘average patient’. Compared to \(\rho\) in the main manuscript, the main difference is the decrease in performance of NOM. Naturally, the performance of static nominal optimization is directly related to the magnitude of possible deviations from the nominal scenario, which is higher in \(Z_2\) than in \(Z\).
B Extra analyses and proofs

For convenience, we repeat the definitions of functions $B, g$ and $f$:

\[
B(d', N'; \rho) = \phi D \left(1 + \frac{\rho D}{D'}\right) - \sigma d_1 N_1 - \sigma^2 \rho d_1^2 N_1 \quad \text{(B.1a)}
\]

\[
g(d', N', N'', \rho) = \frac{-1 + \sqrt{1 + \frac{\rho}{B(d', N'; \rho)}}}{2\sqrt{\rho}} \quad \text{(B.1b)}
\]

\[
f(d_1, N_2; \rho, \tau) = \begin{cases} N_1 d_1 + N_2 g(d_1, N_1, N_2; \rho) + \tau (N_1 d_2^1 + N_2 g(d_1, N_1, N_2; \rho)^2) & \text{if } d_1 \in [0, g(0, 0, N_1; \rho)] \\
\infty & \text{otherwise,}
\end{cases} \quad \text{(B.1c)}
\]

see (??), (??) and (??).

B.1 Proof ??

First, we show that for fixed $d_1$, feasible to (??), and given $(\rho, \tau)$, it is optimal to minimize the number of stage-2 fractions if $\tau \geq \sigma \rho$, and it is optimal to maximize the number of stage-2 fractions otherwise. After that, we show that with stage-2 dose $d_1$ such that (??) holds with equality, $N_2(\rho, \tau) = N_2^{\text{min}}$ is feasible if $\tau \geq \sigma \rho$ and $N_2(\rho, \tau) = N_2^{\text{max}}$ is feasible otherwise.

Consider problem (??). At the start of stage 2, we have delivered $N_1$ fractions with dose $d_1$ per fraction. Let $(\rho, \tau)$ be the realization of the uncertain parameters. The stage-2 problem reads

\[
N_1 d_1 + \tau N_2 d_1^2 + \max_{d_2, N_2} N_2 d_2 + \tau N_2 d_2^2 \quad \text{(B.2a)}
\]

\[
\text{s.t. } \sigma N_2 d_2 + \rho \sigma^2 N_2 d_2^2 \leq B(d_1, N_1, \rho) \quad \text{(B.2b)}
\]

\[
d_2 \geq d_{\text{min}} \quad \text{(B.2c)}
\]

\[
N_2 \in \{N_2^{\text{min}}, \ldots, N_2^{\text{max}}\}. \quad \text{(B.2d)}
\]

This is a static fractionation problem. Constraint (B.2b) will hold with equality at the optimum, because it is the only dose-limiting constraint. This yields

\[
d_2^*(d_1, N_2; \rho) = g(d_1, N_1, N_2; \rho). \quad \text{(B.3)}
\]

Secondly, this allows us to rewrite the objective to

\[
\max_{d_2, N_2} N_2 d_2 \left(\frac{\sigma \rho - \tau}{\sigma \rho}\right) + \frac{\tau B(d_1, N_1, \rho)}{\sigma^2 \rho} \quad \text{(B.4)}
\]

which implies that if $\tau > \sigma \rho$ it is optimal to minimize $d_2 N_2$. If $\tau < \sigma \rho$ it is optimal to maximize $d_2 N_2$, and if $\tau = \sigma \rho$ the objective value is independent of the value of $N_2$. Similar results are obtained in [Mizuta et al. 2012; Bortfeld et al. 2015]. As given in (??) at the optimum

\[
N_2 d_2^*(d_1, N_2; \rho) = N_2 g(d_1, N_1, N_2; \rho) = -N_2 + \sqrt{N_2^2 + 4N_2 \rho B(d_1, N_1; \rho)} \quad \text{(B.5)}
\]

and it is straightforward to show that

\[
\frac{\partial N_2 g(d_1, N_1, N_2; \rho)}{\partial N_2^*} \geq 0. \quad \text{(B.6)}
\]

Hence, if $\tau > \sigma \rho$, it is optimal to minimize the number of fractions, and if $\tau < \sigma \rho$ it is optimal to maximize the number of fractions. If $\tau = \sigma \rho$, every feasible number of fractions is optimal.
For the second part, we must show that for any \((p, \tau) \in Z \cap \{ \tau \geq \sigma p \}\) resp. \((p, \tau) \in Z \cap \{ \tau < \sigma p \}\), it is indeed possible to deliver \(N_{i}^{\text{min}}\) resp. \(N_{i}^{\text{max}}\) fractions with dose according to \((B.3)\) in stage 2. That is, we must show

\[
g(d_{i}, N_{i}, N_{i}^{\text{min}}; p_{i}) \geq d_{i}^{\text{min}}, \quad \forall (p, \tau) \in Z \cap \{ \tau \geq \sigma p \}\]
\[
g(d_{i}, N_{i}, N_{i}^{\text{max}}; p_{i}) \geq d_{i}^{\text{min}}, \quad \forall (p, \tau) \in Z \cap \{ \tau < \sigma p \}\]  

(B.7a)
\[
(B.7b)
\]

which is equivalent to

\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{min}}, N_{i}; p_{i}), \quad \forall (p, \tau) \in Z \cap \{ \tau \geq \sigma p \}\]  

(B.8a)
\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{max}}, N_{i}; p_{i}), \quad \forall (p, \tau) \in Z \cap \{ \tau < \sigma p \}\]  

(B.8b)

Lemma 3 states that \(g\) is increasing or decreasing in \(p\) for a fixed first argument. Hence, it is sufficient to consider only the largest and smallest value of \(p\) in either subset of \(Z\). Therefore, \((B.5)\) is equivalent to

\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{min}}, N_{i}; p_{i})\]  

(B.9a)
\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{max}}, N_{i}; p_{i})\]  

(B.9b)
\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{max}}, N_{i}; \min \{ \frac{\tau}{\sigma} \})\]  

(B.9c)
\[
d_{i} \leq g(d_{i}^{\text{min}}, N_{i}^{\text{max}}, N_{i}; \rho_{i})\]  

(B.9d)

From \((B.5)\) we see that function \(g\) is decreasing in its second argument, so \((B.9b)\) is redundant. The remaining three conditions in \((B.9)\) hold true due to \((B.3)\). Hence, an optimal decision rule for \(N_{2}(\cdot)\) is given by

\[
N_{2}(p, \tau) = \begin{cases} 
N_{i}^{\text{min}} & \text{if } \tau \geq \sigma p \\
N_{i}^{\text{max}} & \text{otherwise,}
\end{cases}
\]

(B.10)

and

\[
d_{2}(d_{2}; p, \tau) = \begin{cases} 
g(d_{i}, N_{i}, N_{i}^{\text{min}}; p_{i}) & \text{if } \tau \geq \sigma p \\
g(d_{i}, N_{i}, N_{i}^{\text{max}}; p_{i}) & \text{otherwise.}
\end{cases}
\]

(B.11)

are optimal decision rules for \(N_{2}(\cdot)\) and \(d_{2}(\cdot)\), respectively. For \(\tau \neq \sigma p\), these give the unique optimal decisions. For \(\tau = \sigma p\) any \(N_{2} \in \{N_{i}^{\text{min}}, \ldots, N_{i}^{\text{max}}\}\) is optimal, and the corresponding optimal \(d_{2}\) follows according to \((B.3)\).

### B.2 Proof \((\ast)\)

Due to \((\ast)\) a stage-1 decision \(d_{1}\) is \(\mathcal{PARO}\) according to \((\ast)\) if conditions \((\ast)\) hold with \((d_{2}(\cdot), N_{2}(\cdot))\) plugged in. Thus, we must show that for any \(d_{1} \in \mathcal{X}_{\mathcal{PARO}}\) there is no \(\mathcal{ARO}\) \(d_{1}\) such that

\[
f(d_{1}, N_{1}(\cdot), \rho_{1}; \rho, \tau) \leq f(d_{1}, N_{2}(\cdot), \rho_{1}; \rho, \tau) \quad \forall (p, \tau) \in Z \]  

(B.12a)
\[
f(d_{1}, N_{2}(\cdot), \rho_{2}; \rho, \tau) < f(d_{1}, N_{2}(\cdot), \rho_{2}; \rho, \tau) \quad \text{for some } (\rho, \tau) \in Z. \]  

(B.12b)

If \(|\mathcal{X}_{\mathcal{PARO}}| = 1\), then the single element yields a strictly better objective value than all other elements in \(\mathcal{X}_{\mathcal{ARO}}\) in either scenario \((\rho_{\text{min}}, \tau_{\text{min}})\) or \((\rho_{\text{max}}, \tau_{\text{max}})\) or both, so it is \(\mathcal{PARO}\). For the remainder of this proof we assume \(|\mathcal{X}_{\mathcal{PARO}}| \geq 2\).

Consider \(\tau_{\text{min}}\). By construction of \((\rho_{\text{aux-min}}, \tau_{\text{aux-min}})\) it holds that \(\tau_{\text{aux-min}} \neq \rho_{\text{aux-min}}\). Hence, according to Lemma 4 there can be at most two values for \(d_{1}\) in \(\mathcal{X}_{\text{aux-min}}\) that yield the same objective value \(f\) in scenario \((\rho_{\text{aux-min}}, \tau_{\text{aux-min}})\). Hence, \(|\mathcal{X}_{\text{aux-min}}| = |\mathcal{X}_{\mathcal{PARO}}| = 2\). Denote the two elements of \(\mathcal{X}_{\mathcal{PARO}}\) by \(d_{1}'\) and \(d_{1}''\), let \(d_{1}' < d_{1}''\). Solutions \(d_{1}'\) and \(d_{1}''\) are both optimal to \((\ast)\) and \((\ast)\). Hence, according to Lemma 4 it holds that

\[
d_{1}' = t(d_{1}'; \rho_{\text{aux-min}}, \tau_{\text{aux-min}})\]  

(B.13a)
\[
d_{1}'' = t(d_{1}''; \rho_{\text{aux-max}}, \tau_{\text{aux-max}}).\]  

(B.13b)
From the definition of $t$ (see (C.21)) we derive for $\sigma \rho \neq \tau$:

$$\frac{\partial t(d_i; \rho, \tau)}{\partial \rho} = \frac{2N_2^i(\rho, \tau)}{N_1 + N_2^i(\rho, \tau) - \frac{\partial g(d_i, N_1, N_2^i(\rho, \tau); \rho)}{\partial \rho}},$$  \hspace{1cm} (B.14)

because $N_2^i(\rho, \tau)$ is constant in $\rho$ unless $\sigma \rho = \tau$. According to Lemma 3b if for given $N_2$ it holds that $d_1 \neq d_1^i(N_2)$ and $d_1 \neq d_2^i(N_2)$ (defined in (C.11)), then function $g(d_i, N_1, N_2^i(\rho, \tau); \rho)$ is strictly increasing or decreasing in $\rho$. By construction, it holds that $d_1^i(N_2) = t(d_i'(N_2); \rho, \tau)$ for any $\rho$. According to Lemma 3a we have $d_1^i(N_2) \neq d_1^i(N_2^\min)$, so $d_1^i$ cannot be equal to both. Additionally, it cannot hold that $d_2^i \neq d_2^i(N_2^\min)$ or $d_2^i \neq d_2^i(N_2^\max)$, because it would imply $d' \leq d"$. Hence, either $d_1^i \neq d_1^i(N_2^\min)$ or $d_1^i \neq d_1^i(N_2^\max)$ holds (or both).

We show that in either case, we can construct two new scenarios where $d_1^i$ outperforms $d_2^i$ in one scenario, and vice versa in the other. Suppose $d_1^i \neq d_1^i(N_2^\min)$ or $d_1^i \neq d_1^i(N_2^\max)$ holds. In this case, it holds that

$$\frac{\partial t(d_i'; \rho_{\text{aux-min}}, \tau_{\text{aux-min}})}{\partial \rho} \neq 0.$$

We consider two new scenarios. Let $\epsilon > 0$ be a sufficiently small number and define

$$(\rho_1, \tau_1) = (\rho_{\text{aux-min}} - \epsilon, \tau_{\text{aux-min}}), \hspace{1cm} (\rho_{\text{aux-min}}, \tau_{\text{aux-min}}) \in \text{int}(Z^{\min})$$

(B.16a)

$$(\rho_2, \tau_2) = (\rho_{\text{aux-min}} + \epsilon, \tau_{\text{aux-min}}), \hspace{1cm} (\rho_{\text{aux-min}}, \tau_{\text{aux-min}}) \in \text{int}(Z^{\min})$$

(B.16b)

This is visualized in Figure B.1. Due to (B.15) and (B.16), it holds that

$$(t(d_i'; \rho_1, \tau_1) > d" \wedge t(d_i'; \rho_2, \tau_2) < d") \vee (t(d_i'; \rho_1, \tau_1) < d" \wedge t(d_i'; \rho_2, \tau_2) > d")$$

(B.17)

If the first clause is true, we obtain

$$f(d_i', N_2^\min; \rho_1, \tau_1) > f(d_i', N_2^\min; \rho_1, \tau_1),$$

$$f(d_i', N_2^\min; \rho_2, \tau_2) > f(d_i', N_2^\min; \rho_2, \tau_2),$$

where we used convexity of $f(d_i, N_2^\min, \rho, \tau)$ for $(\rho, \tau) \in \text{int}(Z^{\min})$. Similarly, if the second clause of (B.17) is true, we obtain

$$f(d_i', N_2^\min; \rho_1, \tau_1) < f(d_i', N_2^\min; \rho_1, \tau_1),$$

$$f(d_i', N_2^\min; \rho_2, \tau_2) > f(d_i', N_2^\min; \rho_2, \tau_2).$$

In either case, there is a scenario in $Z^{\min}$ where $d_1^i$ outperforms $d_2^i$ and a scenario in $Z^{\min}$ where $d_1^i$ outperforms $d_2^i$. Hence, both $d_1^i$ and $d_2^i$ are $\mathcal{P}_R\mathcal{A}_R$. Using similar arguments, we can show that in case $d_1^i \neq d_1^i(N_2^\max)$, $d_2^i(N_2^\max)$ also both $d_1^i$ and $d_2^i$ are $\mathcal{P}_R\mathcal{A}_R$.

B.3 Proof ??

Consider problem (??). At the start of stage 2, we have delivered $N_1$ fractions with dose $d_1$ per fraction. Let $(\rho, \tau)$ be the observation. The resulting stage-2 problem for (??) reads

$$\max_{d_2; N_2} \min_{(\rho, \tau) \in Z_\rho \tau} (N_1 d_1 + N_2 d_2) + \tau(N_1 d_2^i + N_2 d_2^i)$$

(B.20a)

s.t. \hspace{0.5cm} \sigma N_2 d_2 + \rho^2 N_2 d_2^2 \leq B(d_1, N_1, \rho) \forall (\rho, \tau) \in Z_\rho \tau$$

(B.20b)

$$d_2 \geq d_{\text{min}}$$

(B.20c)

$$N_2 \in \{N_2^\min, \ldots, N_2^\max\}.$$ (B.20d)

This is a static robust optimization problem. Constraint (B.20b) will hold with equality at the optimum, because it is the only dose-limiting constraint. Solving for $d_2$ yields the constraint

$$d_2 = g(d_1, N_1, N_2; \rho), \hspace{0.5cm} \forall (\rho, \tau) \in Z_\rho \tau.$$  \hspace{1cm} (B.20c)
and this is used to rewrite (B.20a) and (B.20b) in terms of functions $f$ and $g$. Problem B.20 is equivalent to

\[
\max_{N_2} \min_{(\rho, \tau) \in Z_{\rho, \tau}} f(d_1, N_2, \rho, \tau) \quad \text{s.t.}\ g(d_1, N_1, N_2; \rho) \geq d_{\min}, \ \forall (\rho, \tau) \in Z_{\rho, \tau} \quad \text{(B.22a)}
\]

\[
N_2 \in \{N_{\min}^2, \ldots, N_{\max}^2\}. \quad \text{(B.22c)}
\]

Similar to the exact case (72), in any worst-case realization it will hold that $\tau$ is at its lowest value, so it is sufficient to consider only those observations $(\rho, \tau) \in Z_{\rho, \tau}$ with $\tau = \tau_L$. Additionally, according to Lemma 5, functions $f$ and $g$ are increasing or decreasing in $\rho$. Hence, there are two candidate worst-case scenarios: $(\rho_L, \tau_L)$ and $(\rho_U, \tau_U)$. We can rewrite (B.22a) to

\[
\max_{N_2} \min_{(\rho, \tau) \in Z_{\rho, \tau}} \{ f(d_1, N_2, \rho_L, \tau_L), f(d_1, N_2, \rho_U, \tau_U) \} \quad \text{s.t.}\ g(d_1, N_1, N_2; \rho_L) \geq d_{\min}, \quad g(d_1, N_1, N_2; \rho_U) \geq d_{\min}, \quad N_2 \in \{N_{\min}^2, \ldots, N_{\max}^2\}. \quad \text{(B.23a)}
\]

\[
\text{(B.23b)}
\]

\[
\text{(B.23c)}
\]

\[
\text{(B.23d)}
\]

We distinguish three cases:

1. Case $(\rho, \tau) \in Z_{\rho, \tau}^*$. Analogous to the proof of (72), one can show that for any realization $(\rho, \tau) \in Z_{\rho, \tau}^*$ it is optimal to maximize the number of fractions in stage 2. We plug in $N_2^* (\rho, \tau) = N_{\max}^2$ and show that it is feasible. Constraints (B.23b) and (B.23c) reduce to

\[
\min_{(\rho, \tau) \in Z_{\rho, \tau}} \{ g(d_1, N_1, N_{\max}^2; \rho_L), g(d_1, N_1, N_{\max}^2; \rho_U) \} \geq d_{\min}. \quad \text{(B.24)}
\]

which is equivalent to

\[
d_1 \leq \min \{ g(d_{\min}, N_{\max}^2; \rho_L), g(d_{\min}, N_{\max}^2; \rho_U) \}. \quad \text{(B.25)}
\]

It holds that $\rho_L \geq \frac{d_L}{d_{\min}} \geq \frac{\tau_L}{d_{\min}}$, and $\rho_U \leq \rho_L$. According to Lemma 5, function $g$ is either increasing or decreasing in $\rho$ for other arguments fixed. Hence, by (72) condition (B.25) holds. Hence, $N_2^* (\rho, \tau) = N_{\max}^2$ is feasible and optimal. Thus, (B.22a) equals

\[
\min_{N_2} \{ f(d_1, N_{\max}^2; \rho_L, \tau_L), f(d_1, N_{\max}^2; \rho_U, \tau_U) \}. \quad \text{(B.26)}
\]
Combining the above three cases, we arrive at the optimal decision rules \( d_2 = \min \{ g(d_1, N_1, N_2^{\text{max}}, \hat{\rho}_L), g(d_1, N_1, N_2^{\text{max}}, \hat{\rho}_U) \} \). (B.27)

- Case \((\hat{\rho}, \hat{\tau}) \in Z_{U}^{\text{min}}\): Similar to the previous case. Analogous to the proof of \((\rho, \tau) \in Z_{U}\), one can show that for any realization \((\rho, \tau) \in Z_{U}\), it is optimal to minimize the number of fractions in stage 2. We plug in \( N_2(\rho, \tau) = N_2^{\text{min}} \) and show that it is feasible. Similar to the previous case, constraints (B.23b) and (B.23c) reduce to

\[
d_1 \leq \min \{ g(d_{\text{min}}, N_2^{\text{max}}, N_1; \hat{\rho}_L), g(d_{\text{min}}, N_2^{\text{max}}, N_1; \hat{\rho}_U) \}. \tag{B.28}
\]

It holds that \( \hat{\rho}_L \geq \rho_L \), and \( \hat{\rho}_U \leq \rho_U \). Hence, by \((\rho, \tau) \in Z_{U}\) and using the fact that function \( g \) is decreasing in its second argument, condition (B.28) holds. Hence, \( N_2(\rho, \tau) = N_2^{\text{min}} \) is feasible and optimal. Similar to the previous case, we find

\[
d_2 = \min \{ g(d_1, N_1, N_2^{\text{min}}, \hat{\rho}_L), g(d_1, N_1, N_2^{\text{min}}, \hat{\rho}_U) \}. \tag{B.29}
\]

- Case \((\hat{\rho}, \hat{\tau}) \in Z_{U}^{\text{max}}\): The optimal number of fractions in stage 2 is not known a priori. By definition of \( Z_{U}^{\text{max}} \), it holds that \( \hat{\rho}_L \geq \max\{\rho_L, \frac{3}{2} - 2\hat{\rho}_L\} \) and \( \hat{\rho}_U \leq \rho_U \). By \((\rho, \tau) \in Z_{U}\) it holds that

\[
d_1 \leq \min \{ g(d_{\text{min}}, N_2^{\text{max}}, N_1; \max\{\rho_L, \frac{3}{2} - 2\hat{\rho}_L\}), g(d_{\text{min}}, N_2^{\text{max}}, N_1; \hat{\rho}_U) \}. \tag{B.30}
\]

Lemma \(3a\) the fact that function \( g \) is decreasing in its third argument and (B.30) together imply that (B.23b) and (B.23c) hold for any feasible \( N_2 \). Hence, from problem (B.23) we derive

\[
N_2^*(d_1; \hat{\rho}, \hat{\tau}) = \arg\max_{N_2 \in \{N_2^{\text{min}}, N_2^{\text{max}}\}} \min \{ f(d_1, N_2, \hat{\rho}_L, \hat{\tau}_L), f(d_1, N_2, \hat{\rho}_U, \hat{\tau}_U) \}. \tag{B.31}
\]

and by definition of \( f \) the corresponding value for \( d_2 \) is

\[
d_2 = \min \{ g(d_1, N_1, N_2^*(d_1; \hat{\rho}, \hat{\tau}); \hat{\rho}_L), g(d_1, N_1, N_2^*(d_1; \hat{\rho}, \hat{\tau}); \hat{\rho}_U) \}. \tag{B.32}
\]

Combining the above three cases, we arrive at the optimal decision rules \((\rho, \tau, \hat{\rho}, \hat{\tau})\) for fixed \( d_1 \).

### B.4 Extra analysis to ??

This analysis makes use of the lemmas in Appendix \(C\). Consider problem \((\rho, \tau, \hat{\rho}, \hat{\tau})\). For given \( d_1 \), the optimal stage-2 decision rules are given by \((\rho, \tau) \in Z_{U}\). As stated in ??, we split the uncertainty set \( Z \) into three subsets. This enables us to exploit the fact that depending on \((\hat{\rho}, \hat{\tau})\) the value \( N_2(d_1; \hat{\rho}, \hat{\tau}) \) may be known in advance. The split \((\rho, \tau) \in Z_{U}\) is repeated here for convenience

\[
Z_{U}^{\text{min}} = \{ (\hat{\rho}, \hat{\tau}) \in Z : \hat{\tau} \geq \sigma \hat{\rho}_U \} \quad \tag{B.33a}
\]

\[
Z_{U}^{\text{int}} = \{ (\hat{\rho}, \hat{\tau}) \in Z : \sigma \hat{\rho}_L < \hat{\tau} < \sigma \hat{\rho}_U \} \quad \tag{B.33b}
\]

\[
Z_{U}^{\text{max}} = \{ (\hat{\rho}, \hat{\tau}) \in Z : \hat{\tau} \leq \sigma \hat{\rho}_L \} \quad \tag{B.33c}
\]

so that \( Z = Z_{U}^{\text{min}} \cup Z_{U}^{\text{int}} \cup Z_{U}^{\text{max}} \). The associated sets of observation-realization pairs \((\rho, \tau, \hat{\rho}, \hat{\tau})\) are given by

\[
U' = \bigcup_{i \in \{\text{min, int, max}\}} \{ (\rho, \tau, \hat{\rho}, \hat{\tau}) : (\hat{\rho}, \hat{\tau}) \in Z_{U}^{i} \}, \quad i \in \{\text{min, int, max}\}, \tag{B.34}
\]

so it holds that \( U = U' \cup \bigcup_{\text{min, int, max}} U' \). Set \( U' \) can be interpreted as the set of observation-realization pairs for which the observation \((\hat{\rho}, \hat{\tau})\) is in set \( Z_{U}^{i} \). ?? illustrates the subsets \( Z_{U}^{i} \). Set \( U^{\text{min}} \) consists of those observation-realization pairs \((\rho, \tau, \hat{\rho}, \hat{\tau})\) for which \( N_2(d_1; \hat{\rho}, \hat{\tau}) = N_2^{\text{min}} \). If \((\rho, \tau, \hat{\rho}, \hat{\tau}) \in U^{\text{max}} \), then based
on the observation \((\tilde{\rho}, \tilde{\tau})\) it is clear what fractionation is worst-case optimal. Last, if \((\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{max}\) we know \(N^*_2(d; \tilde{\rho}, \tilde{\tau}) = N^\text{max}_2\). Problem (??) is equivalent to

\[
\max_{d_1, q} q
\text{ s.t. } q \leq f(d_1, N^\text{min}_2; \rho, \tau), \quad \forall (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{min}\]

(B.35a)

\[
q \leq f(d_1, N^\text{max}_2(d; \tilde{\rho}, \tilde{\tau}); \rho, \tau), \quad \forall (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{int}\]

(B.35b)

\[
q \leq f(d_1, N^\text{max}_2; \rho, \tau), \quad \forall (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{max}\]

(B.35c)

Similar to the exact case (??), in any worst-case realization it will hold that \(\tau = \tau_i\). Therefore, any observation with \(\tilde{\tau} - r^T > \tau_i\) cannot yield the worst-case realization. Define

\[
U^*_i = U_i \cap \{(\rho, \tau, \tilde{\rho}, \tilde{\tau}) : \tilde{\tau} - r^T \leq \tau_i\}, \quad i \in \{\text{min, int, max}\},
\]

(B.36)

which is the subset of \(U^*_i\) of observation-realization pairs for which \(\tau_i\) is a possible realization of \(\tau\). Constraints (B.35b)–(B.35e) can be replaced by

\[
q \leq f(d_1, N^\text{min}_2; \rho, \tau), \quad \forall (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{min}\]

(B.37a)

\[
q \leq f(d_1, N^\text{max}_2; \rho, \tau), \quad \forall (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{max}\]

(B.37b)

For (B.37a) and (B.37c) it remains to find the worst-case realization of \(\rho\) for which the observation-realization pair is in \(U^\text{min}_i\) and \(U^\text{max}_i\), respectively. According to Lemma 3a, function \(f\) is increasing or decreasing in \(\rho\) for fixed \(d_1\), so it is sufficient to check the maximum and minimum realization of \(\rho\) for which the observation-realization pair is in those sets. These are

\[
\min\{\rho : (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{min}_i\} = \rho_L, \quad \max\{\rho : (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{min}_i\} = \rho_R.
\]

(B.38a)

\[
\min\{\rho : (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{max}_i\} = \rho_L, \quad \max\{\rho : (\rho, \tau, \tilde{\rho}, \tilde{\tau}) \in U^\text{max}_i\} = \rho_R.
\]

(B.38b)

Plugging in \(\rho = \frac{\sigma_L}{\sigma}\) in (B.37a) and (B.37c) yields \(q \leq K\), with \(K\) defined by (??). Lemma 3b provides a conservative approximation of constraint (B.37b). Putting everything together, the optimum of the following problem is a lower bound to the optimum of (B.35) (or, equivalently, (??)):

\[
\max_{d_1, q} q
\text{ s.t. } q \leq f(d_1, N^\text{min}_2; \rho_L, \tau_i) \quad \text{(B.39a)}

q \leq f(d_1, N^\text{max}_2; \rho_L, \tau_i) \quad \text{(B.39b)}

q \leq K \quad \text{(B.39c)}

q \leq p(d_1) \quad \text{(B.39d)}

d^\text{min}_1 \leq d_1 \leq d^\text{max}_1 \quad \text{(B.39f)}

\]

with \(p(d_1)\) defined by (??). Constraint (B.35c) is the only conservative constraint, all other constraints are exact reformulations. In particular, this means that if for a solution the objective value equals \(K\), it is certain that this is an optimal solution. It is easy to obtain other straightforward conservative approximations of (B.35c). For instance, a policy that delivers \(N^\text{min}_2\) or \(N^\text{max}_2\) fractions (or any number in between, for that matter) for any observation \((\tilde{\rho}, \tilde{\tau})\) in \(Z^\text{ID}_2\) is a conservative approximation. However, these perform less good and do not use all available information, as explained in the proof of Lemma 5.

### C Extra lemmas

This appendix states and proves several frequently used properties of functions \(g\) and \(f\).
Lemma 1 (Convexity/concavity f w.r.t. $d_1$) Let $\rho > 0$, $\tau > 0$ and $N_1, N_2 \in \mathbb{N}_+$. Let $d_1 \in [0, g(0,0,N_1;\rho)]$. The following properties hold for function $f$:

- Function $f(d_1, N_2; \rho, \tau)$ is strictly convex in $d_1$ if $\tau > \rho \sigma$, with unique minimizer $g(0,0,N_1 + N_2;\rho)$;
- Function $f(d_1, N_2; \rho, \tau)$ is strictly concave in $d_1$ if $\tau < \rho \sigma$, with unique maximizer $g(0,0,N_1 + N_2;\rho)$;
- Function $f(d_1, N_2; \rho, \tau)$ is constant in $d_1$ if $\tau = \rho \sigma$, with value $\frac{1}{\sigma} B(0,0,\frac{\tau}{\sigma})$.

Proof The partial derivative of $f$ w.r.t. $d_1$ is given by

$$\frac{\partial f(d_1, N_2; \rho, \tau)}{\partial d_1} = N_1 + N_2 \frac{\partial g(d_1, N_1, N_2; \rho)}{\partial d_1} + \tau \left( 2N_1 d_1 + 2N_2 g(d_1, N_1, N_2; \rho) \frac{\partial g(d_1, N_1, N_2; \rho)}{\partial d_1} \right),$$

(C.1)

where the partial derivative of $g$ w.r.t. $d_1$ is given by

$$\frac{\partial g(d_1, N_1, N_2; \rho)}{\partial d_1} = -\frac{1}{N_2} (N_1 + 2N_1 d_1 \sigma \rho) \left( 1 + \frac{\Delta \rho}{N_2} \frac{g(d_1, N_1, N_2; \rho)}{\partial d_1} \right)^{-\frac{1}{2}},$$

(C.2)

Define $h(d_1, N_2; \rho) = 1 + 4 \frac{\rho \sigma}{N_2} B(d_1, N_1; \rho)$. Then, plugging (C.2) in (C.1), we obtain

$$\frac{\partial f(d_1, N_2; \rho, \tau)}{\partial d_1} = \left( N_1 - (N_1 + 2N_1 d_1 \sigma \rho) h(d_1, N_1, N_2; \rho) \right)^{-\frac{1}{2}}$$

$$+ \tau \left( 2N_1 d_1 + 2 \frac{\sigma \rho}{N_2} (N_1 + 2N_1 d_1 \sigma \rho) h(d_1, N_1, N_2; \rho)^{-\frac{1}{2}} N_2 \left( 1 + h(d_1, N_2; \rho) \right)^{\frac{1}{2}} \right)$$

$$= \frac{N_1}{\sigma \rho} \left( h(d_1, N_2; \rho)^{-\frac{1}{2}} \left( 2 \sigma \rho d_1 + 1 \right) - 1 \right) (\tau - \rho \sigma).$$

Further elementary math shows that $h(d_1, N_2; \rho)^{-\frac{1}{2}} \left( 2 \sigma \rho d_1 + 1 \right) - 1 = 0$ if and only if $d_1 = g(0,0,N_1 + N_2;\rho)$. For the second derivative of $f$ w.r.t. $d_1$, we obtain:

$$\frac{\partial^2 f(d_1, N_2; \rho, \tau)}{\partial d_1^2} = \left( \frac{\tau - \rho \sigma}{\sigma \rho} \right) \frac{\partial}{\partial d_1} h(d_1, N_2; \rho)^{-\frac{1}{2}} \left( 2 \sigma \rho d_1 + 1 \right)$$

$$= \left( \frac{\tau - \rho \sigma}{\sigma \rho} \right) \left[ h(d_1, N_2; \rho)^{-\frac{1}{2}} 2 \sigma \rho + \frac{2 \rho}{N_2} (2 \sigma \rho d_1 + 1) h(d_1, N_2; \rho)^{-\frac{1}{2}} \left( \sigma N_1 + 2 \sigma \rho^2 d_1 N_1 \right) \right],$$

and the second part of this product is positive. Hence, its sign depends only on the term $\tau - \rho \sigma$. Combining the result for the first and second derivative, we obtain

- Function $f(d_1, N_2; \rho, \tau)$ is strictly convex in $d_1$ if $\tau > \rho \sigma$, with unique minimizer $g(0,0,N_1 + N_2;\rho)$;
- Function $f(d_1, N_2; \rho, \tau)$ is strictly concave in $d_1$ if $\tau < \rho \sigma$, with unique maximizer $g(0,0,N_1 + N_2;\rho)$;
- Function $f(d_1, N_2; \rho, \tau)$ is constant in $d_1$ otherwise.

If $\tau = \rho \sigma$, we can rewrite $f(d_1, N_2; \frac{\tau}{\sigma}, \tau)$ to

$$f(d_1, N_2; \frac{\tau}{\sigma}, \tau) = \max_{d_1} \left\{ d_1 N_1 + d_2 N_2 + \tau (d_1^2 N_1 + d_2^2 N_2) \mid \sigma (d_1 N_1 + d_2 N_2) + \rho \sigma^2 (d_1^2 N_1 + d_2^2 N_2) \leq B(0,0,\rho) \right\}$$

$$= \max_{d_1} \left\{ d_1 N_1 + d_2 N_2 + \tau (d_1^2 N_1 + d_2^2 N_2) \mid \sigma (d_1 N_1 + d_2 N_2) + \rho \sigma^2 (d_1^2 N_1 + d_2^2 N_2) = B(0,0,\rho) \right\}$$

$$= \max_{d_1} \left\{ d_1 N_1 + d_2 N_2 + \tau (d_1^2 N_1 + d_2^2 N_2) \mid d_1 N_1 + d_2 N_2 = \frac{1}{\sigma} B(0,0,\frac{\tau}{\sigma}) \right\};$$

$$= \frac{1}{\sigma} B(0,0,\frac{\tau}{\sigma}).$$
Lemma 2 (Properties \(d_i^-\) and \(d_i^+\)) Let \(N, T \in \mathbb{N}_+\).

(a) Let \(N_i \in \mathbb{N}_+.\) If \(p_1 \neq p_2\), the equation

\[
 f(d_1, N_1; p_1, \tau) = f(d_1, N_2; p_2, \tau),
\]

has the following real roots for \(d_1\) on the interval \([0, d_{1a}]:\)

- \(d_i^- (N_2)\) and \(d_i^+ (N_2)\) if \(N_1 + N_2 \geq T, N_2 \leq T \land N_1 \leq T\) \hspace{1em} (C.6a)
- \(d_i^-(N_2)\) if \(N_1 + N_2 \geq T, N_2 \leq T \land N_1 > T\) \hspace{1em} (C.6b)
- \(d_i^+(N_2)\) if \(N_1 + N_2 \geq T, N_2 > T \land N_1 \leq T\) \hspace{1em} (C.6c)
- no roots on interval if \(N_1 + N_2 \geq T, N_2 > T \land N_1 > T\) \hspace{1em} (C.6d)
- no real roots otherwise. \hspace{1em} (C.6e)

(b) Let \(N_{i1}, N_{i2} \in \mathbb{N}_+\) such that \(N_{i2} < N_{i1}\). It holds that

(i) If \(d_i^- (N_{i1})\) and \(d_i^- (N_{i2})\) are both finite, then \(d_i^- (N_{i1}) > d_i^- (N_{i2})\);
(ii) If \(d_i^+ (N_{i1})\) and \(d_i^+ (N_{i2})\) are both finite, then \(d_i^+ (N_{i1}) \leq d_i^+ (N_{i2})\).

Proof

By definition of \(f\), the equation \(f(d_1, N_1; p_1, \tau) = f(d_1, N_2; p_2, \tau)\) reduces to \(g(d_1, N_1; p_1) = g(d_1, N_2, p_2)\) with \(d_1 \in [0, \min\{g(0,0,N_1;\rho_1), g(0,0,N_2;\rho_2)\}]\). By construction of \(g\), this means we are interested in the pairs \((d_1, d_2)\) that solve the system

\[
 \sigma(N_1 d_1 + N_2 d_2) + p_1 \sigma^2(N_1 d_1^2 + N_2 d_2^2) = \phi D(1 + p_1 \frac{D}{\phi}) \tag{C.7a}
\]
\[
 \sigma(N_1 d_1 + N_2 d_2) + p_2 \sigma^2(N_1 d_1^2 + N_2 d_2^2) = \phi D(1 + p_2 \frac{D}{\phi}) \tag{C.7b}
\]
\[
 d_1 \geq 0, \ d_2 \geq 0. \tag{C.7c}
\]

We subtract \(\frac{\phi D}{\sigma} \) times (C.7a) from (C.7b) and solve for \(d_1\) to obtain

\[
 d_1 = \frac{\sigma D - \sigma N_2 d_2}{\sigma N_1} \tag{C.8}
\]
We know that \( d_2 = g(d_1, N_1, N_2; \rho_1) \). Plugging in (C.3) in this expression and simplifying yields the following roots for \( d_2 \):

\[
\begin{align*}
    r_{2}^+ (N_2) &= \frac{\phi D + \phi D \left( 1 + (N_1 + N_2) \left( \frac{N_1}{N_2} - 1 \right) \right)}{\sigma(N_1 + N_2)} \left( \frac{N_1}{N_2} \right) \left( N_1 + N_2 \right) \\
    r_{2}^- (N_2) &= \frac{\phi D - \phi D \left( 1 + (N_1 + N_2) \left( \frac{N_1}{N_2} - 1 \right) \right)}{\sigma(N_1 + N_2)} \left( \frac{N_1}{N_2} \right) \left( N_1 + N_2 \right)
\end{align*}
\]  

(C.9a)

(C.9b)

Plugging (C.3) in (C.8) and simplifying yields the following roots for \( d_1 \):

\[
\begin{align*}
    r_{1}^+ (N_2) &= \frac{\phi D - \phi D \left( 1 + (N_1 + N_2) \left( \frac{N_2 - T}{N_2} \right) \right)}{\sigma(N_1 + N_2)} \left( \frac{N_1}{N_2} \right) \left( N_1 + N_2 \right) \\
    r_{1}^- (N_2) &= \frac{\phi D + \phi D \left( 1 + (N_1 + N_2) \left( \frac{N_2 - T}{N_2} \right) \right)}{\sigma(N_1 + N_2)} \left( \frac{N_1}{N_2} \right) \left( N_1 + N_2 \right)
\end{align*}
\]  

(C.10a)

(C.10b)

These roots need not be real-valued, nor in the interval \([0, \min \{ g(0,0,N_1;\rho_1), g(0,0,N_1;\rho_2) \}] \). For both \( r_{1}^- (N_2) \) and \( r_{1}^+ (N_2) \) to be real-valued, we require

\[1 + (N_1 + N_2) \left( \frac{N_1}{N_2} - 1 \right) \geq 0 \]

which reduces to \( N_1 + N_2 \geq T \). Furthermore, for nonnegativity of \( r_{1}^- (N_2) \) and \( r_{1}^+ (N_2) \) it suffices to check nonnegativity of the former. This is equivalent to

\[
\phi D - \sigma \phi \sigma N_2 d_{2}^- \geq 0
\]

which reduces to \( N_2 \leq T \). Moreover, it needs to hold that \( r_{1}^+ (N_2) \leq g(0,0,N_1;\rho_1) \) and \( r_{1}^- (N_2) \leq g(0,0,N_1;\rho_2) \).

This is equivalent to \( r_{2}^+ (N_2) \geq 0 \), which can be rewritten to

\[1 + (N_1 + N_2) \left( \frac{N_1}{N_2} - 1 \right) / N_2 \leq 1,\]

and this reduces to \( N_1 \leq T \). Parameters \( d_{1}^+ (N_2) \) resp. \( d_{2}^+ (N_2) \) (see (C.3)) take the values of \( r_{1}^+ (N_2) \) resp. \( r_{1}^- (N_2) \) if they are a root of (C.5), and \( \pm \infty \) resp. \( \mp \infty \) otherwise. All together, we obtain the cases in (C.6).

It remains to show that the obtained roots are in the interval \([0,d_1\text{min}]\). It is already shown that, if they are (real-valued) roots to (C.5), then \( d_{1}^+ (N_2) \) and \( d_{2}^+ (N_2) \) are nonnegative. Furthermore, in that case \( d_{1}^- (N_2) \leq d_{1}^+ (N_2) \). It holds that

\[
\frac{\partial g(0,0,N_1;\rho)}{\partial \rho} \leq 0 \iff N_1 \leq T.
\]

Hence, if \( d_{1}^+ (N_2) \) is a real-valued root to (C.5) it follows that

\[
d_1\text{min} = \min \left\{ \rho : (0,0,N_1;\rho) \geq 0 \right\} = \lim_{\rho \to -\infty} g(0,0,N_1;\rho) = \frac{\phi D}{\sigma \sqrt{N_1 T}} \geq d_{1}^+ (N_2),
\]

where the second equality follows from the definition of \( g \). This implies that indeed \( d_{1}^- (N_2), d_{1}^+ (N_2) \in [0,d_1\text{min}] \).

**Proof Lemma 20**

Assume \( N_2^A, N_2^B \in N_+ \) such that \( N_2^A \leq N_2^B \), and assume \( N_1 + N_2^A \geq T \). Statements (i) and (ii) are proved individually.

**Proof part (i)**

Assume \( d_{1}^- (N_2^A) \) and \( d_{1}^- (N_2^B) \) are both finite. The denominator of \( d_{1}^- (N_2) \) (see (C.3a)) is increasing in
Lemma 3 (Derivative of part of within the square root in the numerator of (C.3a)) is given by 
\((N_1 T)^{-1} (N_1 + 2N_2 - T) \geq 0\), because \(N_1 + N_2 \geq T\). Hence, the numerator is decreasing in \(N_2\), while the 
denominator is increasing in \(N_2\). This implies \(d_1^+ (N_2^2) \geq d_1^+ (N_2^3)\).

Proof part (ii)
Assume \(d_1^+ (N_2^2)\) and \(d_1^+ (N_2^3)\) are both finite. One can show that
\[
\frac{\partial d_1^+ (N_2^2)}{\partial N_2} = \phi D \frac{(N_1 + N_2)(N_1 + 2N_2 - T) - 2N_1T}{2N_1T} \sqrt{\frac{N_1^2(N_1 + N_2 - T)}{N_1T}}.
\]
This implies
\[
\frac{\partial d_1^+ (N_2)}{\partial N_2} \geq 0
\]
\[
\Leftrightarrow (N_1 + N_2)(N_1 + 2N_2 - T) - 2N_1T \sqrt{\frac{N_1^2(N_1 + N_2 - T)}{N_1T}} - 2N_2(N_1 + N_2 - T) \geq 0
\]
\[
\Leftrightarrow N_1(N_1 + N_2 - T) + TN_2 \geq \sqrt{\frac{N_1^2(N_1 + N_2 - T)}{N_1T}}
\]
\[
\Leftrightarrow \left(\frac{N_1(N_1 + N_2 - T) + TN_2}{2N_1T}\right)^2 \geq \frac{N_1(N_1 + N_2 - T)}{N_1T}
\]
\[
\Leftrightarrow \left(\frac{N_1 - T}{2N_1T}\right)^2 \frac{(N_1 + N_2)^2}{2N_1T} \geq 0,
\] where the fourth line is obtained by using the fact that \(N_1 + N_2 \geq T\), and squaring on both sides. The last line follows from simple algebraic manipulations. Condition (C.12) clearly holds, so \(d_1^+ (N_2^2) \leq d_1^+ (N_2^3)\).

Lemma 3 (Derivative \(f\) and \(g\) w.r.t. \(\rho\)) Let \((\rho, \tau) \in \mathbb{Z}^2\).
(a) Let \(N', N'' \in \mathbb{N}_+\). Let \(d' \in [0,d_{1\|}]\). If \(N' + N'' < T\), then
\[
\frac{\partial g(d', N', N'', \rho)}{\partial \rho} < 0 \quad \text{for all} \quad d' \in [0,d_{1\|}].
\] (C.13)
If \(N' + N'' \geq T\), then
\[
\frac{\partial g(d', N', N'', \rho)}{\partial \rho} \begin{cases} < 0 & \text{if} \quad d' \in [0,d_1^+ (N')] \cup (d_1^+ (N'), d_{1\|}] \\ = 0 & \text{if} \quad d' \in [0,d_{1\|}] \cap (d_1^+ (N'), d_1^+ (N'')) \\ > 0 & \text{if} \quad d' \in [0,d_{1\|}] \cap (d_1^+ (N''), d_1^+ (N'))) \end{cases}
\] (C.14)
(b) Let \(N_1, N_2 \in \mathbb{N}_+\). Let \(d_1 \in [0,d_{1\|}]\). If \(N_1 + N_2 < T\), then
\[
\frac{\partial f(d_1, N_1; \rho, \tau)}{\partial \rho} < 0 \quad \text{for all} \quad d_1 \in [0,d_{1\|}].
\] (C.15)
If \(N_1 + N_2 \geq T\), then
\[
\frac{\partial f(d_1, N_1; \rho, \tau)}{\partial \rho} \begin{cases} < 0 & \text{if} \quad d_1 \in [0,d_1^+ (N_1)] \cup (d_1^+ (N_1), d_{1\|}] \\ = 0 & \text{if} \quad d_1 \in [0,d_{1\|}] \cap (d_1^+ (N_1), d_1^+ (N_2)) \\ > 0 & \text{if} \quad d_1 \in [0,d_{1\|}] \cap (d_1^+ (N_2), d_1^+ (N_1)) \end{cases}
\] (C.16)
We distinguish 2 cases:

- \( \phi D \geq d'N' \sigma \). In this case, squaring (C.18) on both sides and simplifying results in

\[
- \sigma^2 N'(N' + N'')d'^2 + 2\phi D N'\sigma d' + \left( \frac{N'}{T} \right)^2 \phi^2 D^2 \geq 0,
\]

which is a condition independent of \( \rho \). If \( N' + N'' < T \), this inequality has no roots for \( d' \), and (C.19) holds for all \( d' \in [0, \phi D/T] \). If \( N' + N'' \geq T \) one can verify that \( d_1 = d_1'(N'') \) and \( d_1 = d_1''(N'') \) are the roots of this concave parabola if they are finite. The smaller root, \( d_1''(N'') \), is finite if and only if \( N'' \leq T \). The larger root, \( d_1'(N'') \), is finite if and only if \( N'' < T \).

- \( \phi D < d'N' \sigma \). In this case, \( B(d', N'; \rho) > 0 \) only if \( N'' > T \). In this case, the delivered dose exceeds the dose that is used to set the BED tolerance, which is only possible if the number of fractions \( N'' \) is strictly larger than the reference number of fractions \( T \). Condition (C.18) clearly holds, so \( g(d', N', \rho, \phi) \) is increasing in \( \rho \). Using the fact that \( N'' > T \) it is easily shown that \( d_1'' < \phi D/T < d' \). Additionally, it can be shown that \( d_1' < d_1''(N'') \). Hence this case satisfies (C.14).

Putting all of the above together yields the required result for \( g \), i.e., Lemma 3a.

The partial derivative of \( f \) w.r.t. \( \rho \) is given by

\[
\frac{\partial f}{\partial \rho}(d_1, N_1, N_2; \tau) = \frac{\partial g(d_1, N_1, N_2; \rho)}{\partial \rho} \left( N_2 + 2\tau N_2 g(d_1, N_1, N_2; \rho) \right).
\]

Hence, the sign of the partial derivative of \( f \) w.r.t. \( \rho \) is equal to the sign of the partial derivative of \( g \) w.r.t. \( \rho \). The result of Lemma 3a immediately follows.

For given \( (\rho, \tau) \) such that \( \tau \neq \sigma \rho \), define the twin point of \( d_1 \in W(\rho, \tau) \) as

\[
t(d_1; \rho, \tau) = \frac{\{N_1 - N_2(\rho, \tau)\} d_1 + 2N_2(\rho, \tau) g(d_1, N_1, N_2(\rho, \tau); \rho)}{N_1 + N_2(\rho, \tau)},
\]

where

\[
W(\rho, \tau) = \left[ \max\{0, t(0, \rho, \tau), g(0, 0, N_1; \rho)\}, \min\{t(0, \rho, \tau), g(0, 0, N_1; \rho)\} \right] \setminus \{0, g(0, 0, N_1; \rho)\}.
\]

Figure C.4 illustrates the relation between \( d_1 \) and \( t(d_1; \rho, \tau) \). Set \( W \) can be interpreted as the points \( d_1 \) for which there exists another point the graph of \( f \) that has the same value, we refer to such points as twin points. The following lemma proves that for fixed \( (\rho, \tau) \) any \( d_1 \) in the set \( W(\rho, \tau) \) has a twin point \( t(d_1; \rho, \tau) \) that is also in the set \( W(\rho, \tau) \), and their objective values are equal.

**Lemma 4** Let \( (\rho, \tau) \in Z \) such that \( \tau \neq \sigma \rho \), let \( N_2 = N_2(\rho, \tau) \) and let \( d_1 \in [0, g(0, 0, N_1; \rho)] \). The equation

\[
f(d_1, N_2; \rho, \tau) = f(d_1', N_2; \rho, \tau)
\]

has a solution \( d_1' \in [0, g(0, 0, N_1; \rho)] \) unequal to \( d_1 \) if and only if \( d_1 \in W(\rho, \tau) \). In that case, there is a unique solution \( d_1'' \) such that \( d_1'' = t(d_1; \rho, \tau) \in W(\rho, \tau) \), and it holds that \( d_1 = t(t(d_1; \rho, \tau); \rho, \tau) \).
Let $L$, $Q \in \mathbb{R}_+$ denote the linear and quadratic contribution of $d_1$ to $f$, i.e.,

$$L(d_1, N_2; \rho) = N_1 d_1 + N_2 g(d_1, N_1, N_2; \rho)$$  \hfill (C.24a)

$$Q(d_1, N_2; \rho) = N_1 d_1^2 + N_2 g(d_1, N_1, N_2; \rho)^2.$$  \hfill (C.24b)

We show that for any $d_1 \in [0, g(0,0, N_1; \rho)]$ unequal to $g(0,0, N_1+N_2; \rho)$ there is a unique solution $d_1'$ such that

$$L(d_1, N_2; \rho) = L(d_1', N_2; \rho)$$  \hfill (C.25a)

$$Q(d_1, N_2; \rho) = Q(d_1', N_2; \rho).$$  \hfill (C.25b)

Any such $d_1'$ has exactly the same objective value as $d_1$. Plug (C.24) in (C.25) to eliminate $g$, and plug this in the second equation to get

$$d_1' = \frac{L(d_1, N_2; \rho) \pm \sqrt{N_2 \left( (N_1 + N_2)(Q(d_1, N_2; \rho) - L^2(d_1, N_2; \rho) \right)}}{N_1 + N_2}$$

$$= \frac{N_1 d_1 + N_2 g(d_1, N_1, N_2; \rho) \pm N_2 (d_1 - g(d_1, N_1, N_2; \rho))}{N_1 + N_2}.$$  \hfill (C.26)

The ‘+’ solution to (C.26) returns $d_1' = d_1$, and the ‘–’ solution returns

$$d_1' = \frac{(N_1 - N_2) d_1 + 2 N_2 g(d_1, N_1, N_2; \rho)}{N_1 + N_2}.$$  \hfill (C.27)
and we denote this solution by $t(d_1; \rho, \tau)$. By construction, it holds that $d_1 = t(t(d_1; \rho, \tau); \rho, \tau)$. Because $\tau \neq \sigma \rho$, function $f(d_1, N_2; \rho, \tau)$ is a strictly convex or concave function according to Lemma 1, so $f(d_1, N_2; \rho, \tau) = z$ for some constant $z \in \mathbb{R}$ has either 0, 1 or 2 solutions. In particular, $d_1 = t(d_1; \rho, \tau)$ if and only if $d_1$ equals minimizer $g(0, 0, N_1 + N_2; \rho)$. Hence if there exists a solution $d'_1$ to (C.23) unequal to $d_1$, then this solution is $d'_1 = t(d_1; \rho, \tau)$.

Second part:

- Suppose $d_1 \notin W(\rho, \tau)$. We distinguish three cases. Case (i): ‘$d_1 = g(0, 0, N_1 + N_2; \rho)$’. Because this is the unique minimizer of $f$, there does not exist a $d'_1$ with equal objective value. Case (ii): ‘$d_1 > \min\{t(0, 0, \rho, \tau), g(0, 0, N_1; \rho)\}$’. Because $d_1 \in [0, g(0, 0, N_1; \rho)]$, this implies $d_1 > t(0, 0, \rho, \tau)$. As shown in the first part of the proof, it holds that $d_1 = t(t(d_1; \rho, \tau); \rho, \tau)$. Hence, $d_1 > t(0, 0, \rho, \tau)$ is equivalent to $t(t(d_1; \rho, \tau); \rho, \tau) > t(0, 0, \rho, \tau)$. Because $t(d_1; \rho, \tau)$ is decreasing in $d_1$, this implies $t(d_1; \rho, \tau) < 0$, so according to (C.37d) it holds that $f(t(d_1; \rho, \tau), N_2; \rho, \tau) = -\infty$ and we have a contradiction. Case (iii): ‘$d_1 < \min\{0, t(g(0, 0, N_1; \rho); \rho, \tau)\}$’. Similar to case (ii), one can show that $f(t(d_1; \rho, \tau), N_2; \rho, \tau) = -\infty$.

- Suppose $d_1 \in W(\rho, \tau)$. From (C.26) one can see that, because the term $d_1 - g(d_1, N_1, N_2; \rho)$ is increasing in $d_1$, the function $t(d_1; \rho, \tau)$ is decreasing in $d_1$. Consequently,

$$d_1 \leq \min\{t(0, 0, \rho, \tau), g(0, 0, N_1; \rho)\} \Leftrightarrow d'_1 \geq \max\{0, t(g(0, 0, N_1; \rho); \rho, \tau)\}. \tag{C.28}$$

Furthermore, using the same argument,

$$d_1 \geq \max\{0, t(g(0, 0, N_1; \rho); \rho, \tau)\} \Leftrightarrow d'_1 \leq \min\{t(0, 0, \rho, \tau), g(0, 0, N_1; \rho)\}. \tag{C.29}$$

Therefore, it holds that $d'_1 \in W(\rho, \tau)$.

In the following lemma, let $I(\cdot|S)$ denote the indicator function for a set $S$:

$$I(x|S) = \begin{cases} 1 & \text{if } x \in S \\ 0 & \text{otherwise.} \end{cases} \tag{C.30}$$

**Lemma 5** For given $q \in \mathbb{R}_+$ and given $d_1 \in [0, d_1^\text{opt}]$,

$$q \leq f(d_1, N_2^*; d_1; \rho, \tau; \hat{\rho}, \hat{\tau}), \forall (\rho, \tau, \hat{\rho}, \hat{\tau}) \in U_{\text{int}}^\text{opt}, \tag{C.31}$$

holds if $\tau \leq p(d_1)$, with

$$p(d_1) = \sum_{\eta \in \{N_1^\text{min}, \ldots, N_1^\text{max}\}} \max\left\{f(d_1, \eta; \rho_1^\text{int}, \tau_1), f(d_1, \eta - 1; \rho_1^\text{int}, \tau_1)\right\} I(d_1|S_\eta) \tag{C.32}$$

$$+ f(d_1, N_2^\text{min}; \rho_1^\text{int}, \tau_1) I(d_1|S_{\text{min}}^\text{opt}) + f(d_1, N_2^\text{max}; \rho_1^\text{int}, \tau_1) I(d_1|S_{\text{max}}),$$

where sets $S_{\text{min}}, S_{\text{max}}$ and $S_\eta$ are defined in (C.37a), (C.37d) and (C.44), respectively, and $\rho_1^\text{int}, \rho_1^\text{max}$ are defined in (C.33).  

**Proof** By definition of $N_2^*(d_1; \rho, \tau)$ and $U_{\text{int}}^\text{opt}$, it holds that

$$q \leq f(d_1, N_2^*; d_1; \rho, \tau), \forall (\rho, \tau, \hat{\rho}, \hat{\tau}) \in U_{\text{int}} \tag{C.33}$$

is equivalent to

$$q \leq \max_{\eta \in \{N_2^\text{min}, N_2^\text{max}\}} \min\{f(d_1, \eta; \hat{\rho}, \hat{\tau}, \tau_1), f(d_1, \eta - 1; \hat{\rho}, \hat{\tau}, \tau_1)\}, \forall (\hat{\rho}, \hat{\tau}) \in Z_{\text{int}} \cap \{(\hat{\rho}, \hat{\tau}) : \hat{\tau} \leq \tau_1 + r\}, \tag{C.34}$$

and because function $f$ is increasing in $\tau$, we need to consider only those observations $(\hat{\rho}, \hat{\tau})$ with $\tau_1 = \tau_2$. For the first part of the proof, we fix the observation $(\hat{\rho}, \hat{\tau})$, plug in $\tau_2 = \tau_1$, and rewrite (C.34) for this fixed observation.
Because \((\rho, \tau) \in \mathcal{Z}_{\text{opt}}\), it holds that \(\sigma_{\rho_L} < \tau_L < \sigma_{\rho_U}\). Hence, by Lemma 2a, function \(f(d_1, \eta; \rho_L, \tau_L)\) is convex and \(f(d_1, \eta; \rho_U, \tau_U)\) is concave for any \(\eta \in \mathbb{N}_+\). We make use of results of Lemma 2b. Define
\[
E = \{ \eta : N_1 + \eta \geq T, \eta \leq T \} \cap \{ N_{\min}^{\text{min}}, \ldots, N_{\max}^{\text{max}} \} \tag{C.35a}
\]
and let \(\eta_{\min}, \eta_{\max}, \eta_{\min}^+, \eta_{\max}^+\) denote the smallest and largest elements of \(E^-\) and \(E^+\), respectively. If \(\eta \in E^-\) respectively \(\eta \in E^+\), then, according to Lemma 2b, \(d_1 = d_1^-(\eta)\) respectively \(d_1 = d_1^+(\eta)\) is a nonnegative real root of
\[
f(d_1, \eta; \rho_L, \tau_L) = f(d_1, \eta; \rho_U, \tau_U),
\]
and the corresponding objective value equals \(K\). From Lemma 2b we know that
\[
d_1^-(N_{\max}^{\text{max}}) < \ldots < d_1^-(N_{\min}^{\text{min}}) \leq d_1^+(N_{\max}^{\text{max}}) \leq \ldots \leq d_1^+(N_{\min}^{\text{min}}). \tag{C.36}
\]
We use this to split the domain \(0, d_{\text{UB}}\) as follows:
\[
S_{\text{min}} = \begin{cases}
(d_1^-(\eta_{\min}), d_1^+(\eta_{\min})) & \text{if } E^- \neq \emptyset, E^+ \neq \emptyset \\
(0, d_1^+(\eta_{\min})) & \text{if } E^- = \emptyset, E^+ \neq \emptyset \\
(d_1^-(\eta_{\min}), d_{\text{UB}}) & \text{if } E^- \neq \emptyset, E^+ = \emptyset \\
(0, d_{\text{UB}}) & \text{if } N_1 + N_{\max}^{\text{max}} < T \\
\end{cases}
\tag{C.37a}
\]
\[
S_{\eta}^- = \begin{cases}
[d_1^-(\eta - 1), d_1^-(\eta - 1)] & \text{if } \eta_{\min} \leq \eta - 1 < \eta \leq \eta_{\max} \forall \eta \in \{N_{\text{min}}^{\text{min}}, \ldots, N_{\max}^{\text{max}}\} \\
0 & \text{otherwise}
\end{cases}
\tag{C.37b}
\]
\[
S_{\eta}^+ = \begin{cases}
[d_1^+(\eta - 1), d_1^+(\eta - 1)] & \text{if } d_{\min} \leq \eta - 1 < \eta \leq d_{\max} \forall \eta \in \{N_{\text{min}}^{\text{min}}, \ldots, N_{\max}^{\text{max}}\} \\
0 & \text{otherwise}
\end{cases}
\tag{C.37c}
\]
\[
S_{\text{max}} = \begin{cases}
[d_1^-(\eta_{\max}), d_1^+(\eta_{\max})] & \text{if } E^- \neq \emptyset, E^+ \neq \emptyset \\
[d_1^+(\eta_{\max}), d_{\text{UB}}) & \text{if } E^- = \emptyset, E^+ \neq \emptyset \\
(0, d_{\text{UB}}) & \text{if } E^- \neq \emptyset, E^+ = \emptyset \\
\end{cases}
\tag{C.37d}
\]
We will reformulate (C.34) on each interval (set) separately, assuming it is nonempty.

1. “\(S_{\text{min}}\)”: If \(d_1 \in S_{\text{min}}\), then \(f(d_1, \eta; \rho_L, \tau_L) < f(d_1, \eta; \rho_U, \tau_U)\) for all \(\eta \in \{N_{\text{min}}^{\text{min}}, \ldots, N_{\max}^{\text{max}}\}\) according to Lemma 2b so it is optimal to deliver \(N_{\min}^{\text{min}}\) fractions. Hence, on this interval \(C.34\) is equivalent to
\[
q \leq f(d_1, N_{\min}^{\text{min}}, \rho_L, \tau_L). \tag{C.38}
\]

2. “\(S_{\eta}^-\)”:: From Lemma 2b we know that \(f(d_1, \eta; \rho_L, \tau_L) = f(d_1, \eta; \rho_U, \tau_U)\) if \(d_1 = d_1^-(\eta)\) or \(d_1 = d_1^+(\eta)\). In this case, the objective value equals \(K\). Furthermore, function \(f(d_1, \eta; \rho_U, \tau_U)\) is convex and \(f(d_1, \eta; \rho_L, \tau_L)\) is concave in \(d_1\). Consider the interval \([d_1^-(\eta), d_1^+(\eta - 1)]\). It holds that
\[
f(d_1, \eta; \rho_L, \tau_L) \leq K \leq f(d_1, \eta - 1; \rho_L, \tau_L). \tag{C.39a}
\]
\[
f(d_1, \eta - 1; \rho_L, \tau_L) \leq K \leq f(d_1, \eta; \rho_U, \tau_U). \tag{C.39b}
\]
This implies that if \(d_1 \in [d_1^-(\eta), d_1^+(\eta - 1)]\), it is optimal to deliver either \(\eta\) or \(\eta - 1\) fractions. If we deliver \(\eta\) fractions, the restricting worst-case scenario is \((\rho_L, \tau_L)\) and the value \(f\) is above \(K\) for the scenario \((\rho_U, \tau_U)\). If we deliver \(\eta' > \eta\) fractions, the value for the scenario \((\rho_U, \tau_U)\) decreases, while the value for the scenario \((\rho_L, \tau_L)\) increases even further. Hence, delivering \(\eta' > \eta\) fractions cannot be optimal. Similarly, delivering less than \(\eta - 1\) fractions cannot be optimal. Therefore, if \(d_1 \in [d_1^-(\eta), d_1^+(\eta - 1)]\) it is optimal to deliver either \(\eta\) or \(\eta - 1\) fractions. This implies that on the interval \(S_{\eta}^-\) constraint (C.34) is equivalent to
\[
q \leq \max\{f(d_1, \eta; \rho_L, \tau_L), f(d_1, \eta - 1; \rho_U, \tau_U)\}. \tag{C.40}
\]
Note that this result does not depend on the values \(\rho_L\) and \(\rho_U\), we only use that \(\rho_L < \frac{\Delta}{2} < \rho_U\).
3. “$S_\eta$” : Similar to the case for $S^+_\eta$, one can show that for $d_1 \in S^+_\eta$, constraint (C.34) is equivalent to (C.40).

4. $S_{\max}$ : If $d_1 \in S_{\max}$, then $f(d_1, \eta; \hat{\rho}_d, \tau_d) \geq f(d_1, \eta; \hat{\rho}_d, \tau_d)$ for all $\eta \in \{N^1_{\min}, \ldots, N^1_{\max}\}$ according to Lemma 3b, so it is optimal to deliver $N^1_{\max}$ fractions. Hence, on this interval (C.34) is equivalent to

$$q \leq f(d_1, N^1_{\max}, \hat{\rho}_d; \tau_d).$$

(C.41)

For sets $S^-\eta$ and $S^+\eta$ the reformulation is the same. Therefore, define

$$S_\eta = S^-\eta \cup S^+\eta.$$  

(C.42)

Putting everything together, for $d_1 \in [0, d_{\max}]$ the constraint (C.34) is equivalent to

$$q \leq \sum_{\eta \in \{N^2_{\min}, \ldots, N^2_{\max}\}} \max\{f(d_1, \eta; \hat{\rho}_d, \tau_d), f(d_1, \eta - 1; \hat{\rho}_d, \tau_d)\}I(d_1|S_\eta)
+f(d_1, N^2_{\max}; \hat{\rho}_d, \tau_d)I(d_1|S_{\max}) + f(d_1, N^2_{\max}; \hat{\rho}_d, \tau_d)I(d_1|S_{\max})$$

$$\forall \{\hat{\rho}, \hat{\tau}\} \in \mathbb{Z}^2 \cap \{\{\hat{\rho}, \hat{\tau}\} : \hat{\tau} \leq \eta + \gamma\}.$$  

(C.43)

In order to find a tractable conservative robust counterpart of (C.43), denote

$$p_1^{\max} = \max\{\hat{\rho}_d, \frac{\tau_d}{\sigma} - 2\sigma\}$$

(C.44a)

$$p_1^{\min} = \min\{\hat{\rho}_d, \frac{\tau_d}{\sigma} + 2\sigma\}$$

(C.44b)

and note that $p_1^{\min} \leq \hat{\rho}_d < \frac{\tau_d}{\sigma} \leq p_1^{\max}$. Only if $d_1 \in S_{\eta}$, the robust counterpart is conservative. By Lemma 3b, it holds that function $f$ is strictly decreasing, constant or strictly increasing in $\rho$ for fixed $d_1$, so

$$f(d_1, \eta; \hat{\rho}_d, \tau_d) \geq \min\{f(d_1, \eta; \hat{\rho}_d^{\max}, \tau_d), f(d_1, \eta; \frac{\tau_d}{\sigma}, \tau_d)\} = \min\{f(d_1, \eta; \hat{\rho}_d^{\max}, \tau_d), K\} = f(d_1, \eta; \hat{\rho}_d^{\max}, \tau_d),$$

where the second equality follows from (C.39). A similar result holds for $f(d_1, \eta - 1; \hat{\rho}_d, \tau_d)$. Furthermore, as shown before, $f$ is increasing in $\rho$ on $S_{\min}$ and decreasing in $\rho$ on $S_{\max}$. Therefore, a conservative approximation of (C.39) is given by

$$q \leq \sum_{\eta \in \{N^2_{\min}, \ldots, N^2_{\max}\}} \max\{f(d_1, \eta; \hat{\rho}_d^{\max}, \tau_d), f(d_1, \eta - 1; \hat{\rho}_d^{\max}, \tau_d)\}I(d_1|S_\eta)
+f(d_1, N^2_{\max}; \hat{\rho}_d^{\max}, \tau_d)I(d_1|S_{\min}) + f(d_1, N^2_{\max}; \hat{\rho}_d^{\max}, \tau_d)I(d_1|S_{\max})$$

(C.45)

and the RHS is $p(d_1)$.

Function $p(d_1)$ is a piece-wise function. On intervals defined by $S_{\min}$ and $S_{\max}$, it is convex and concave, respectively. On any interval $S_\eta$, function $p(d_1)$ is the maximum of a concave and convex function.

References
