Dynamic robust optimization for fractionated IMRT treatment planning

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Lung cancer

- Leading cause of cancer death in the US and Canada
- 180,000 deaths in last year; 25% of cancer deaths
Intensity modulated radiation therapy (IMRT)

- Very popular form of radiation therapy
- Several beams; each beam consists of smaller beams or beamlets
- Basic problem: find beamlet intensities that deliver at least some prescription dose to the tumour at minimal healthy tissue damage
Uncertainty

- For lung cancer, most significant uncertainty comes from breathing motion
- Patient breathes; tumour is not in the same position during treatment session
- Breathing pattern is not known precisely
Approaches to uncertainty

- **Nominal approach**: assume patient will breathe according to a single breathing pattern
  - If actual breathing pattern is different from planned, tumour underdose is very likely

- **Margin approach**: assume patient can breathe according to any breathing pattern
  - Tumour dose is guaranteed to be sufficient, but cost to healthy tissue is high

- **Robust optimization**: Given a set of breathing patterns, find the treatment that minimizes damage to healthy tissue and meets tumour dose constraints under those breathing patterns
Robust optimization - uncertainty

- $X$: a set of breathing motion states
- $\mathbf{p} = (p(x))_{x \in X}$: a breathing motion probability distribution
- $p(x)$: proportion of time patient spends in state $x$ during a treatment session
- $P$: uncertainty set; collection of $\mathbf{p}$ vectors that we wish to protect ourselves against

Mišić and Chan: *Dynamic robust IMRT optimization (Montréal, 2011)*
Robust optimization - decision variables and parameters

- $\mathcal{B}$: set of beamlets to be used for treatment
- $w_b$: intensity of beamlet $b \in \mathcal{B}$
- $\mathcal{V}$: set of all voxels; $\mathcal{T}$: set of tumour voxels
- For each voxel $v$, motion state $x$ and beamlet $b$, a dose deposition coefficient $\Delta_{v,x,b}$
- Dose to voxel $v$ under PMF $p$:

$$\sum_{x \in X} \sum_{b \in \mathcal{B}} \Delta_{v,x,b} p(x) w_b$$

- $\theta_v$: minimum prescription dose of tumour voxel $v \in \mathcal{T}$
Robust optimization - model

Formulation is

\[
\begin{align*}
\text{minimize} & \quad \sum_{v \in V} \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} \bar{p}(x) w_b \\
\text{subject to} & \quad \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p(x) w_b \geq \theta_v, \quad \forall \ v \in T, \ \forall \ p \in P, \\
& \quad \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p(x) w_b \leq \gamma \theta_v, \quad \forall \ v \in T, \ \forall \ p \in P, \\
& \quad w_b \geq 0, \quad \forall \ b \in B,
\end{align*}
\]

where \( \bar{p} \) is a PMF representative of the patient’s overall breathing and \( \gamma \geq 1 \).
Robust optimization - properties

- If patient’s PMF \( p \) is in \( P \) while \( w^* \) (optimal solution for RO problem with \( P \)) is being delivered, then

\[
    d_v = \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p(x) w_b^* \geq \theta_v
\]

for every tumour voxel \( v \)

- Generally, the larger \( P \) is, the more dose is delivered to healthy tissue under \( w^* \). (If \( P_1 \supseteq P_2 \), then

\[
    \text{Obj. value with } P_1 \geq \text{Obj. value with } P_2
\]

holds)
... so what’s the problem?

Fractionation:

- Prescribed dose is divided up into smaller amounts (fractions)
- Each fraction is delivered once a day every day for a period of 4 - 6 weeks
- Healthy tissue heals faster than cancerous tissue
Fractionation (continued)

- Usually, planner solves one problem before start of treatment, gets \( w \), delivers \( w/n \) in every fraction (static) ...
- ... but what if patient’s \( p \) changes over treatment?
  - Patient may be nervous in the beginning, but become more relaxed by the end
  - Progression of disease may change patient’s breathing
- ... what if uncertainty set \( P \) was determined inappropriately?
  - \( P \) may be very large, but patient’s \( p \)’s are actually tightly clustered around a single value
Our idea: Solve a sequence of robust optimization problems (one for each fraction), with the uncertainty set updated using the most recent PMF each time, and deliver the resulting solutions.
Our approach - I

Initialization:

1. Select an initial uncertainty set $P^1$

2. Solve the robust problem associated with $P^1$ to obtain beamlet weight vector $w^1$ for the first fraction
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In iteration (fraction) \( i \ (\in \{1, \ldots, n\}) \):

1. Deliver \( w^i/n \) to the patient
2. Measure the patient’s breathing, obtain \( p^i \)
3. Generate new uncertainty set \( P^{i+1} \) from previous set \( P^i \) and just observed \( p^i \)
4. Solve the robust problem with \( P^{i+1} \) to obtain beamlet weight vector \( w^{i+1} \) for the next fraction
5. Set \( i = i + 1 \)
In iteration (fraction) $i \ (\in \{1, \ldots, n\})$:

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In iteration (fraction) $i \ (\in \{1, \ldots, n\})$:

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Our approach - II

In iteration (fraction) $i \ (\in \{1, \ldots, n\})$:

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Our approach - II

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Uncertainty sets

- The set of all probability distributions on $X$:

$$\mathcal{P} = \left\{ p \in \mathbb{R}^{\lvert X \rvert} \mid \forall x \in X, \ p(x) \geq 0; \sum_{x \in X} p(x) = 1 \right\}$$

- An uncertainty set $P$ is specified by a lower bound vector $\ell$ and upper bound vector $u$:

$$P = \{ p \in \mathcal{P} \mid \forall x \in X, \ \ell(x) \leq p(x) \leq u(x) \}.$$
Updating the uncertainty set

- **Exponential smoothing:**

\[
\ell^{k+1} = (1 - \alpha)\ell^k + \alpha p^k \\
u^{k+1} = (1 - \alpha)u^k + \alpha p^k
\]

where \( \alpha \in [0, 1] \).

- **Running average:**

\[
\ell^{k+1} = \frac{1}{k + 1} (\ell^1 + \sum_{i=1}^{k} p^i) \\
u^{k+1} = \frac{1}{k + 1} (u^1 + \sum_{i=1}^{k} p^i)
\]
Prescient algorithms

- To analyze our results later, we also consider “prescient” algorithms

  - Daily prescient algorithm:
    - On day $i$, set $\ell^i = u^i = p^i$, so $P^i = \{p^i\}$
    - On each day, tumour voxel $v$ receives at least $\theta_v/n$, so by end it receives at least $\theta_v$

  - Average prescient algorithm:
    - Calculate the average PMF: $p_{\text{avg}} = \frac{1}{n} \sum_{i=1}^{n} p^i$
    - On day $i$, set $\ell^i = u^i = p_{\text{avg}}$, so $P^i = \{p_{\text{avg}}\}$
    - By end of treatment, each tumour voxel $v$ receives at least $\theta_v$
Computational results - I

Sequence of real patient PMFs: $p^1, p^2, \ldots, p^n$

Select initial uncertainty set

- Nominal; $P = \{\tilde{p}\}$
- Margin; $P = \mathcal{P}$
- Robust; in between $\{\tilde{p}\}$ and $\mathcal{P}$. 

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Computational results - first PMF sequence

Minimum tumor dose versus mean left lung dose

- Static
- Exponential smoothing, $\alpha = 0.1$
- Exponential smoothing, $\alpha = 0.5$
- Exponential smoothing, $\alpha = 0.9$
- Running average
- Daily prescient
- Average prescient

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Computational results - first PMF sequence (zoomed in)

Minimum tumor dose versus mean left lung dose

- Static
- Exponential smoothing, $\alpha = 0.1$
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Computational results - takeaways

- Dynamic solutions are in general better than static solutions
- Choice of initial uncertainty set is less important than it is for static robust method
- Solutions are very close in quality to the prescient solution
Theoretical results

Suppose

\[ p^n \to p^* \]

as \( n \to \infty \). What can we say about

\[ \frac{1}{n} \sum_{i=1}^{n} \Delta p^i w^i \]

as \( n \to \infty \)?

(\( \Delta pw = \left[ \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p(x) w_b \right]_{v \in V} \))
Call an uncertainty set update algorithm convex-convergent if:

1. Each update is a convex combination of the most recent $p$ and most recent $\ell/u$: for every $n \in \mathbb{Z}_+$, there exists $\alpha_n \in [0, 1]$ such that

   \[
   \ell^{n+1} = (1 - \alpha_n)\ell^n + \alpha_n p^n, \\
   u^{n+1} = (1 - \alpha_n)u^n + \alpha_n p^n.
   \]

2. The updates inherit the convergence of the PMF sequence:

   \[
   p^n \to p^* \Rightarrow \ell^n \to p^*, \ u^n \to p^*.
   \]
Let

- $w^*(p^*)$ be the set of optimal solutions to the robust problem with $P = \{p^*\}$, and

- $w^*(\ell, u)$ be the set of optimal solutions to the robust problem with $P$ defined by $\ell$ and $u$. 
Optimal dose distribution set

Let

\[ D = \{ d \mid d = \Delta p^* w \text{ for some } w \in w^*(p^*) \}. \]

\( D \) is the set of dose distributions that are obtained when a \( w \) from \( w^*(p^*) \) is delivered and \( p^* \) is realized during delivery.

Every \( d \in D \) meets the minimum tumour dose constraint (for every \( v \in T \), \( d_v \geq \theta_v \)).
Convergence of dose distributions

**Theorem**

Suppose $p^n \to p^*$ and $(\ell^n)_{n=1}^{\infty}$ and $(u^n)_{n=1}^{\infty}$ are obtained by a convex-convergent update algorithm. Suppose $w^i \in w^*(\ell^i, u^i)$ for each $i$.

Then for every $\epsilon > 0$, there exists an $N \in \mathbb{Z}_+$ such that for all $n > N$,

$$\frac{1}{n} \sum_{i=1}^{n} \Delta p^i w^i \in U(D, \epsilon),$$

where

$$U(A, \epsilon) = \bigcup_{x \in A} B(x, \epsilon),$$

and $B(x, \epsilon)$ is the $\epsilon$-ball at $x$. 
Convergence of dose distributions (continued)

- For daily and average prescient, same theorem holds
- For static robust:

\[
\frac{1}{n} \sum_{i=1}^{n} \Delta p^i w = \Delta \sum_{i=1}^{n} \frac{p^i}{n} w \to \Delta p^* w
\]

as \( n \to \infty \).

- \( \Delta p^* w \) may have some underdosed tumour voxels, depending on where \( p^* \) is with respect to the uncertainty set \( P \) of \( w \).
Summary

- Dynamic robust method greatly improves on the static robust method
- Method achieves performance comparable to optimal prescient algorithms
- Simple and does not require a large amount of information pre-treatment (but does require work during treatment)
Future work

- Stress-testing under pathological PMF sequences
- Reducing the frequency of adaptation
- Adaptation in a distributionally-robust setting
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Thank you for listening!

Questions/comments?
Extras
Minimum tumor dose versus mean left lung dose

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**Computational results - second PMF sequence (zoomed in)**

Mean left lung dose as percentage of static margin dose

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Define $d^1$ as $d^1_v = \theta_v$ for $v \in \mathcal{T}$, $u^1$ as $u^1_v = \gamma \theta_v$ for $v \in \mathcal{T}$. Start with $i = 1$.

1. Solve to obtain $w^i$:

   $$\begin{align*}
   &\text{minimize} \quad \sum_{v \in \mathcal{V}} \sum_{x \in \mathcal{X}} \sum_{b \in \mathcal{B}} \Delta_{v,x,b} \bar{p}(x) w_b \\
   &\text{subject to} \quad \sum_{x \in \mathcal{X}} \sum_{b \in \mathcal{B}} \Delta_{v,x,b} p(x) w_b \geq d^i_v, \quad \forall v \in \mathcal{T}, \ p \in \mathcal{P}, \\
   &\sum_{x \in \mathcal{X}} \sum_{b \in \mathcal{B}} \Delta_{v,x,b} p(x) w_b \leq u^i_v, \quad \forall v \in \mathcal{T}, \ p \in \mathcal{P}, \\
   &w_b \geq 0, \quad \forall b \in \mathcal{B}.
   \end{align*}$$

2. Deliver $w^i/(n - i + 1)$.

3. Observe $p^i$. 
4. Set $d^{i+1}$ as

$$d^{i+1}_v = \max\{0, d^i_v - \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p^i(x) w^i_b / (n - i + 1)\},$$

and $u^{i+1}_v$ as

$$u^{i+1}_v = \max\{0, u^i_v - \sum_{x \in X} \sum_{b \in B} \Delta_{v,x,b} p^i(x) w^i_b / (n - i + 1)\}.$$

5. Generate $P^{i+1}$ from $P^i$ and $p^i$.
6. Set $i = i + 1$. 
Mean and max. underdose by fraction – non-reactive

Mean and maximum underdose as a percentage of 2.4Gy by fraction (robust)

- (ES(0.1),R) --- Max. underdose
- (ES(0.5),R) --- Max. underdose
- (ES(0.9),R) --- Max. underdose
- (ES(0.1),N) --- Mean underdose
- (ES(0.5),R) --- Mean underdose
- (ES(0.9),R) --- Mean underdose

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Mean and maximum underdose as a percentage of 2.4Gy by fraction (robust, reactive)

- (RX3ES(0.1),R) --- Max. underdose
- (RX3ES(0.5),R) --- Max. underdose
- (RX3ES(0.9),R) --- Max. underdose
- (RX3ES(0.1),R) --- Mean underdose
- (RX3ES(0.5),R) --- Mean underdose
- (RX3ES(0.9),R) --- Mean underdose

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