Part 2: Multiobjective approximation models arising in radiotherapy treatment in medicine

1. Design of intensity modulated radiotherapy treatment

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1. Design of intensity modulated radiotherapy treatment

- Selection of beam angles (geometry problem)

- Computation of an intensity map for each selected beam angle (intensity problem)

- Finding a sequence of configurations of a multileaf collimator to deliver the treatment (realization problem)

H.W. Hamacher (1995), M. Ehrgott (2003), M. Ehrgott, C. Güler, H.W. Hamacher, L. Shao (2010)

Models in radiotherapy treatment

- beams $k = 1, ..., p$ are available for a treatment,
- each beam consists of bixels $j = 1, ..., n$,
- voxels are indexed by $i = 1, ..., m$,
- (a_{ijk}) denotes the dose deposited in voxel i at unit intensity for bixel j of beam k (or the rate at which radiation along sub-beam j in beam k is deposited into dose-point i), (a_{ijk}) is positive for each (i, j, k).

These rates are patient-specific constants, and hence, the mapping between intensity (or fluence) and dose is linear.

Notations:

- Dose deposition matrix A (defined by the values (a_{ijk})) by indexing rows by i and columns by (j, k).

- Beam intensity: $x \in \mathbb{R}^{np}$, x_{jk} represents the intensity of bixel j, $j = 1, ..., np$ of beam k, $k = 1, ..., p$.

Each voxel is assigned to a particular structure.

- T: represents the tumor,

- C: represents critical organs (K critical organs or organs at risk (OARs) are represented by $C_1, ..., C_K$),

- N: represents normal tissue,

- m: total number of voxels, $m = m_T + m_C + m_N$, where $m_C = m_{C_1} + \cdots + m_{C_K}$.

- A_T, A_C, A_N: A can be partitioned and reordered into submatrices $A_T \in \mathbb{R}^{m_T \times np}$, $A_C \in \mathbb{R}^{m_C \times np}$ and $A_N \in \mathbb{R}^{m_C \times np}$ (according to the rows corresponding to tumor, critical organ and normal tissue voxels (A_i: row i of A).

Treatment planning

$TG \in \mathbb{R}^{m_T}$: desired dose to tumor voxels,

$TLB \in \mathbb{R}^{m_T}$: lower bounds on the dose to tumor voxels,

$TUB \in \mathbb{R}^{m_T}$: upper bounds on the dose to tumor voxels,

$CUB \in \mathbb{R}^{m_C}$: upper bounds on the dose to critical organ voxels,

$NUB \in \mathbb{R}^{m_N}$: upper bounds on dose to normal tissue voxels.

Example Minimize the weighted sum of maximum deviation from tumor goal dose and maximum overdose to critical organs and normal tissue subject to nonnegativity constraints:

Lim et al (2007):

$$\min_{x\geq 0} w_T||A_Tx - TG||_\infty + w_C||(A_Cx - CUB)_+||_\infty + w_N||(A_Nx - NUB)_+||_\infty,$$

where $(\cdot)_+ = \max\{0, \cdot\}$ and w is a vector of weight factors.

Xing et al. (1998):

$$\min_{x\geq 0} \frac{w_T}{m_T}||A_Tx - TG||_2^2 + \frac{w_C}{m_C}||A_Cx - CUB||_2^2 + \frac{w_N}{m_N}||A_Nx - NUB||_2^2.$$

Multiobjective optimization models

Desired dose distribution can not always be obtained, due to physical limitations and trade-offs between the various conflicting treatment goals $\Longrightarrow$ multiobjective characteristic of inverse planning (Cotrutz et al (2001) and Lahanas et al (2003)):

$$f(x) \to \min \qquad \text{w.r.t. } \mathbb{R}^3_+, \tag{P}$$

where

$$f(x) := \begin{pmatrix} \frac{1}{m_T}\|A_T x - TG\|_2^2 \\ \frac{1}{m_N}\|A_N x\|_2^2 \\ \frac{1}{m_C}\|(A_C x - CUB)_+\|_2^2 \end{pmatrix},$$

$x \in \mathbb{R}^s$, $\|x\|_2 = \sqrt{\sum_{i=1}^s x_i^2}$.

$f_T(x) := \frac{1}{m_T}\|A_T x - TG\|_2^2$:
Average squared deviation from the prescribed dose to the tumor.

$f_N(x) := \frac{1}{m_N}\|A_N x\|_2^2$:
Average squared dose to the normal tissue.

$f_C(x) := \frac{1}{m_C}\|(A_C x - CUB)_+\|_2^2$:
Average squared overdose to the critical organ.

3. Multiobjective approximation problems

Scalar approximation problem:

$$(c, x) + \sum_{i=1}^{m} \alpha_i \|A_i(x) - a^i\|_{(i)}^{\beta_i} \to \min_{x \in D}. \qquad \text{(P1)}$$

Multiobjective approximation problem:

$$C(x) + \begin{pmatrix} \alpha_1 \|A_1(x) - a^1\|_{(1)}^{\beta_1} \\ \cdots \\ \alpha_m \|A_m(x) - a^m\|_{(m)}^{\beta_m} \end{pmatrix} \to \min_{x \in D} \quad \text{w.r.t. } \mathbb{R}^m_+. \qquad \text{(PV)}$$

Solution concept for multiobjective optimization problems:

Consider $f : D \to \mathbb{R}^m$, $D \subset X$, a proper closed convex and pointed cone $K \subset \mathbb{R}^m$.

An element $f(x) \in f(D)$, where $f : D \to \mathbb{R}^m$, $D \subset \mathbb{R}^s$, is called Pareto minimal point of $f(D)$ with respect to K, if

$$f(D) \cap (f(x) - (K \setminus \{0\})) = \emptyset.$$

We denote the set of Pareto minimal points of $f(D)$ with respect to K by

$$\mathrm{Min}(f(D), K).$$

Suppose $\mathrm{int}\, K \neq \emptyset$. An element $f(x) \in f(D)$ is called weakly minimal point of $f(D)$ with respect to K, if

$$f(D) \cap (f(x) - \mathrm{int}\, K) = \emptyset.$$

We denote the set of weakly minimal points of $f(D)$ with respect to K by

$$\mathrm{WMin}(f(D), K).$$

An element $x \in D$ with $f(x) \in \mathrm{WMin}(f(D), K)$ is called weakly efficient element.

Assume that X, U and Y are real Banach spaces; $K \subset Y$ is a proper pointed closed convex cone. Vector-valued norm (see Jahn (2004)) $|\!|\!| \cdot |\!|\!| : U \to K$ which for all $u, u_1, u_2 \in U$ and for all $\lambda \in \mathbb{R}$ satisfies:

(1) $|\!|\!|u|\!|\!| = 0 \Longleftrightarrow u = 0$;

(2) $|\!|\!|\lambda\ u\ |\!|\!| = |\ \lambda\ |\ \ |\!|\!|u|\!|\!|$;

(3) $|\!|\!|u_1 + u_2|\!|\!|\ \in\ |\!|\!|u_1|\!|\!| + |\!|\!|u_2|\!|\!| -\ K.$

Suppose $g : X \to Y$ is a cost function, $A_i \in L(X, U)$ and $\alpha_i \geq 0$ $(i = 1, \ldots, m)$. We consider for $x \in D \subset X$ and $a^i \in U$ $(i = 1, \ldots, m)$ the vector-valued approximation problem

$$\text{Determine} \quad \text{WMin}(f(D), K), \tag{1}$$

where $f(x) := g(x) + \sum_{i=1}^{m} \alpha_i |\!|\!|A_i(x) - a^i|\!|\!|$ and $D \subset X$ is closed.

Theorem: Suppose that X, U, Y are reflexive Banach spaces, D is a closed subset of X and $K \subset Y$ is a proper convex Daniell cone with a weakly compact base and nonempty interior. Let $\overline{x} \in D$ be a weakly efficient point of (1). Assume that g is K-bounded from above around $\bar{x}$, g is K-convex and $\|\!| \cdot |\!\|$ is continuous. Then there exist $y^* \in K^+ \setminus \{0\}$ and $T_i \in L(U, Y)$ with

$$T_i(A_i(\overline{x}) - a^i) = \|\!|A_i(\overline{x}) - a^i|\!\|, \; \|\!|v|\!\| - T_i(v) \in K \; \forall v \in U$$

$(i = 1, \dots, m)$ such that

$$0 \in \partial \langle y^*, g(\overline{x}) \rangle + \sum_{i=1}^{m} \alpha_i A_i^* y^* T_i + N_L(\overline{x}; D).$$

(Vu Anh Tuan, Chr. Tammer, C. Zălinescu (2016))

4. Algorithms for solving multiobjective approximation problems

4.1 A proximal point algorithm for the scalar problem

(Minty (1962), Rockafellar (1976), Idrissi, Lefebvre, Michelot (1988), Bonnel, Iusem, Svaiter (2004))

Consider (P1): $\quad (c,x) + \sum\limits_{i=1}^{m} \alpha_i \|A_i x - a^i\|_{(i)}^{\beta_i} \to \min_{x \in D}$,

where $\|\cdot\|_{(i)}$, norms in $\mathbb{R}^{k_i}$; $c, x \in \mathbb{R}^s$, $a^i \in \mathbb{R}^{k_i}$, $\alpha_i > 0$, $\beta_i \geq 1$, $A_i \in L(\mathbb{R}^s, \mathbb{R}^{k_i})$, $D = \bigcap\limits_{j=1}^{\ell} D_j$, $D_j \subset \mathbb{R}^s$ closed and convex, $(j = 1, \ldots, \ell)$. Assume that a constraint qualification is fulfilled.

Indicator function: $\chi_M(x) := \begin{cases} 0 & \text{if } x \in M \\ +\infty & \text{if } x \notin M \end{cases}$.

(P1) $\Longrightarrow$ Unconstraint minimization problem (P'):

$$F(x) = (c, x) + \sum_{i=1}^{m} \alpha_i \|A_i x - a^i\|_{(i)}^{\beta_i} + \sum_{j=1}^{\ell} \chi_{D_j}(x) \to \min_{x \in \mathbb{R}^s} .$$

Under the given assumptions:

$$x^0 \text{ solves } (P') \Longleftrightarrow 0 \in \partial F(x^0) \tag{2}$$

$$(5) \Longleftrightarrow \begin{aligned} & q_i \in \partial(\alpha_i \|A_i x^0 - a^i\|_{(i)}^{\beta_i}), \quad i = 1, 2, \ldots, m, \\ & r_j \in \partial \chi_{D_j}(x^0), \qquad j = 1, 2, \ldots, \ell, \\ & c + \sum_{i=1}^{m} q_i + \sum_{j=1}^{\ell} r_j \ = \ 0. \end{aligned} \tag{3}$$

Introduce

$$E := \mathbb{R}^{k_1} \times \mathbb{R}^{k_2} \times \ldots \times \mathbb{R}^{k_m} \times \underbrace{\mathbb{R}^s \times ... \times \mathbb{R}^s}_{\ell+1}$$

and the subspaces

$$\mathcal{A} := \{y \in E : y = (\underbrace{A_1(x), \ldots, A_m(x), x, \ldots, x)}_{\ell+m+1}, x \in \mathbb{R}^s\},$$

$$\mathcal{B} := \{p \in E \mid p = (p_1, p_2, \ldots, p_{m+\ell+1}), p_i \in \mathbb{R}^{k_i} \text{ (i=1,...,m)},$$
$$p_j \in \mathbb{R}^s \; (j = m+1, \ldots, m+\ell+1) : \sum_{i=1}^{m} A_i^T p_i + \sum_{j=m+1}^{m+\ell+1} p_j = 0\},$$

and the operator T defined on E by

$$\begin{aligned} T_i(y_i) &:= \partial(\alpha_i \|y_i - a^i\|_{(i)}^{\beta_i}), && i = 1, \ldots, m, \\ T_{m+j}(x) &:= N_{D_j}(x) && j = 1, \ldots, \ell, \\ T_{m+\ell+1}(x) &:= c\,. \end{aligned}$$

Algorithm *(PPA)* (Special case: $\beta_i = 1$ (i=1,...,m))

- Choose the starting points: $x^1 \in \mathbb{R}^s$ and $p^1 \in E$ with $\sum_{i=1}^{m} A_i^T p_i^1 + \sum_{j=m+1}^{m+\ell+1} p_j^1 = 0$, $p_i^1 \in \mathbb{R}^{k_i}$, $p_j^1 \in \mathbb{R}^s$.

- Compute y^{k+1} and p^{k+1} from

$$\tilde{p}_i^k = \begin{cases} b_i & \text{if} \quad \|b_i\|_{i^*} \leq \alpha_i \\ \alpha_i P_{B_i}(b_i/\alpha_i) & \text{if} \quad \|b_i\|_{i^*} > \alpha_i \end{cases}$$

$(b_i := y_i^k + p_i^k - a^i,$ (i=1,...,m))

$\tilde{y}_{m+j}^k = P_{D_j}(p_{m+j}^k + y_{m+j}^k)$, $(j = 1, \ldots, \ell)$, $\tilde{p}_{m+\ell+1}^k = c$,

$\tilde{p}_{m+j}^k = p_{m+j}^k + y_{m+j}^k - \tilde{y}_{m+j}^k$ and $\tilde{y}_i^k = p_i^k + y_i^k - \tilde{p}_i^k$,

such that $p^{k+1} := P_{\mathcal{B}}(\tilde{p}^k)$ and $y^{k+1} := P_{\mathcal{A}}(\tilde{y}^k)$.

4.2 Interactive algorithm for multiobjective approximation problems

Consider the problem:

$$C(x) + \begin{pmatrix} \tilde{\alpha}_1 \|A_1(x) - a^1\|_{(1)}^{\beta_1} \\ \cdots \\ \tilde{\alpha}_m \|A_m(x) - a^m\|_{(m)}^{\beta_m} \end{pmatrix} \to \min_{x \in D} \qquad \text{w.r.t. } K \qquad \text{(PV)}$$

under the assumptions given above with $C \in L(\mathbb{R}^s, \mathbb{R}^m)$, $K \subset \mathbb{R}^m$ is a closed pointed convex cone with $K + (\mathbb{R}^m_+ \setminus \{0\}) \subset \operatorname{int} K$.

$$\sum_{i=1}^{m} \lambda_i (C_i(x) + \tilde{\alpha}_i \|A_i(x) - a^i\|_{(i)}^{\beta_i}) \to \min_{x \in D}, \qquad (PV(\lambda))$$

where $\lambda \in \Lambda \subset \operatorname{int} K^+$.

Algorithm for the multiobjective approximation problem (PV)

Step 1: Choose $\bar{\lambda} \in \operatorname{int} K^+$. Compute an approximate solution (y^0, p^0) of $(PV(\bar{\lambda}))$ with algorithm *(PPA)*. If (y^0, p^0) is accepted by the *decision maker*, then Stop.

Step 2: Put $k = 0, t_0 = 0$. Choose $\bar{\bar{\lambda}} \in \operatorname{int} K^+$, $\bar{\bar{\lambda}} \neq \bar{\lambda}$. Go to Step 3.

Step 3: Choose t_{k+1} with $t_k < t_{k+1} \leq 1$, set $\lambda_k = \bar{\lambda} + t_{k+1}(\bar{\bar{\lambda}} - \bar{\lambda})$ and compute an approximate solution (y^{k+1}, p^{k+1}) of $(PV(\lambda_k))$ with *(PPA)* and (y^k, p^k) as starting point. If an approximate solution of $(PV(\lambda_k))$ cannot be found for $t > t_k$, then go to Step 1. Otherwise go to Step 4.

Step 4: (y^{k+1}, p^{k+1}) is to be evaluated by the *decision maker* . If it is accepted, then Stop. Otherwise go to Step 5.

Step 5: If $t_{k+1} \geq 1$, then go to Step 1. Otherwise set $k = k + 1$ and go to Step 3.

4. Further Research: Application to inverse problems

Inverse Stefan problem (Crank, Reemtsen and Jahn):

Consider: Process of melting ice in the water, temperature distribution $u(x,t)$ in the water at the time t.
Heat-flow equation:

$$u_{xx}(x,t) - u_t(x,t) = 0.$$

Problem: Heat input $g(t)$ is to be determined such that the melting interface moves in the prescribed way: $x = \delta(t)$, $t \geq 0$.

Suppose: $\delta \in C^1[0,T]$, $T > 0$, is a given function, $0 \leq t \leq T$, $0 \leq x \leq \delta(t)$, and $\delta(0) = 0$. Put

$$D(\delta) := \{(x,t) \in \mathbb{R}^2 \mid 0 < x < \delta(t),\ 0 < t \leq T\} \quad \delta \in C^1[0,T].$$

Consider the parabolic boundary value problem

$$u_{xx}(x,t) - u_t(x,t) = 0, \ (x,t) \in D(\delta), \tag{4}$$

$$u_x(0,t) = g(t), \ 0 < t \le T, \tag{5}$$

where $g \in C([0,T])$, $g(0) < 0$, is to be determined,

$$u(\delta(t),t) = 0, \quad \dot{\delta}(t) = -u_x(\delta(t),t), \quad 0 < t \le T. \tag{6}$$

Characterization of approximate solutions of the inverse Stefan problem (4), (5), (6) using approximation theory!
Settings:

$$\bar{u}(x,t,a) = \sum_{i=0}^{l} a_i w_i(x,t), \quad l > 0 \text{ integer, fixed,}$$

$$\text{with} \quad w_i(x,t) = \sum_{k=0}^{[\frac{i}{2}]} \frac{i!}{(i-2k)!k!} x^{i-2k} t^k, \quad i = 0, \dots, l,$$

and $g(t) = c_0 + c_1 t + c_2 t^2,\ c_0 \le 0, c_1 \le 0, c_2 \le 0$.

Error functions:

$$\begin{aligned}
\varphi_1(t,a,c) &:= \bar{u}(\delta(t),t,a) - 0, \\
\varphi_2(t,a,c) &:= \bar{u}_x(0,t,a) - g(t), \\
\varphi_3(t,a,c) &:= \bar{u}_x(\delta(t),t,a) - (-\dot{\delta}(t)), \\
\varphi(a,c) &:= \begin{pmatrix} \|\varphi_1(\cdot,a,c)\|_1 \\ \|\varphi_2(\cdot,a,c)\|_2 \\ \|\varphi_3(\cdot,a,c)\|_3 \end{pmatrix}.
\end{aligned}$$

Moreover, assume $D \subset \mathbb{R}^{l+1} \times \mathbb{R}^3$ and $D := \{d \in \mathbb{R}^{l+1} \times \mathbb{R}^3 \mid d_i \in \mathbb{R}\ \forall\, i = 0, 1, \ldots, l+3;\ d_i \le 0\ \forall\, i = l+1, \ldots, l+3\}$.

Compute the set $\mathrm{Min}(f(D), \mathbb{R}^3_+)$, with

$$f(d) := \begin{pmatrix} \|A_1(\cdot, d) - a^1\|_1 \\ \|A_2(\cdot, d) - a^2\|_2 \\ \|A_3(\cdot, d) - a^3\|_3 \end{pmatrix},$$

where $A_i \in L(\mathbb{R}^{l+1} \times \mathbb{R}^3, Y_i)$, Y_i are reflexive L_q-spaces,

$$\begin{aligned}
A_1(t) \quad &= (w_0(\delta(t), t), w_1(\delta(t), t), \ldots, w_l(\delta(t), t), 0, 0, 0), \\
A_2(t) \quad &= (w_{0x}(0, t), w_{1x}(0, t), \ldots, w_{lx}(0, t), -1, -t, -t^2), \\
A_3(t) \quad &= (w_{0x}(\delta(t), t), w_{1x}(\delta(t), t), \ldots, w_{lx}(\delta(t), t), 0, 0, 0), \\
d^T \quad &= (a_0, a_1, a_2, \ldots, a_l, c_0, c_1, c_2), \\
a^1 \quad &= (0, \ldots, 0) \in Y_1, \quad a^2 = (0, \ldots, 0) \in Y_2, \\
a^3 \quad &= -\dot{\delta} \in Y_3 = L_q[0, T],
\end{aligned}$$

$\|\cdot\|_i$ $(i = 1, 2, 3)$ norms in reflexive L_q-spaces Y_i.

Methods for the Elastography Inverse Problem of Locating Tumors

Cancer is the second deadliest disease. For its successful treatment, cancer must be diagnosed in the earliest possible stages of the disease's progression. In living soft tissue, differences in molecular makeup as well as in microscopic and macroscopic structure result in significant differences in tissue stiffness. Many cancers appear as hard nodules within the surrounding softer tissue.

Such diseases are often detectable by the standard medical practice of palpation, but palpation remains a subjective technique and is mostly limited to the detection of large, stiff tissue abnormalities that lie near the skin's surface.

A tool like ultrasound can be used to diagnose tumors deeper within the body, but it can also fail to find lesions that lack certain acoustical properties. The potential for using varying elastic properties to differentiate between healthy and diseased tissue in a more quantitative manner is clear and has been recognized by many authors.

The elasticity imaging inverse problem is a novel approach that uses the varying elastic properties of healthy and diseased tissue to identify lesions similar to palpation. This approach consists of exerting a small, external, and quasistatic compression force to the tissue and measuring its axial displacement field or, more indirectly, the tissue's overall motion. From this measurement, a tumor can be identified by solving the so-called elasticity imaging inverse problem of determining the tissue's underlying elasticity.

This inverse problem builds upon a combination of mathematical, computational, and experimental techniques based on linear elasticity models.

Underlying mathematical model for this inverse problem:
System of partial differential equations that describes the response of an isotropic elastic object to certain body forces and traction applied to its boundary:

$$
\begin{aligned}
-\nabla\cdot\sigma &= f \quad \text{in } \Omega, && \text{(7a)}\\
\sigma &= 2\mu\epsilon(u)+\lambda \mathrm{div} u\, I, && \text{(7b)}\\
u &= g \quad \text{on } \Gamma_1, && \text{(7c)}\\
\sigma n &= h \quad \text{on } \Gamma_2. && \text{(7d)}
\end{aligned}
$$

Here the domain Ω is a subset of $\mathbb{R}^2$ or $\mathbb{R}^3$ and $\partial\Omega = \Gamma_1 \cup \Gamma_2$ is its boundary. In (7), the vector-valued function $u = u(x)$ represents the displacement of the elastic object, f is the applied body force, n is the unit outward normal, and $\epsilon(u) = \frac{1}{2}(\nabla u + \nabla u^{\top})$ is the linearized strain tensor. The resulting stress tensor σ in the stress-strain law (7b) is obtained under the assumption that the elastic object is isotropic and the displacement is small enough so that a linear relationship holds. The coefficients μ and λ are the Lamé parameters that quantify the elastic properties of the material.

In this setting, the direct problem for (7) is to find the displacement u when functions g, h, the variable coefficients μ and λ, and the body force f are known.
In the elasticity imaging inverse problem, the focus, however, is on the inverse problem of identifying the parameter μ when a certain measurement z of the displacement u is available. Since cancerous tumors differ markedly in their elastic properties from the surrounding healthy tissue, these tumors are then located by solving the inverse problem of identifying the variable parameters that describe the elastic properties of the tissue.
From a mathematical standpoint, this inverse problem seeks μ from a measurement of the displacement vector u under the assumption that the parameter λ is very large. The elastography inverse problem mathematically mimics the practice of palpation by making use of the differing elastic properties of healthy and unhealthy tissue to identify tumors.

The ill-conditioning of the Hessian matrix in this method was eliminated employing the Tikhonov regularization technique.

However, the choice of regularization parameter was largely heuristic.

The study of error estimates for inverse problem of parameter identification in PDEs is challenging and have been mostly carried out in the context of simpler elliptic problem

$$-\nabla\left(a\nabla u\right) = f \text{ in } \Omega, \tag{8}$$

usually subject to Neumann boundary conditions, where the parameter a is to be identified.

Tikhonov regularization:

$$J(a) := \frac{1}{2}\|u - z\|^2 + \frac{\rho}{2}\|a\|^2_{H^1(\Omega)} \to \min, \qquad \text{(PT)}$$

where z is the data (the measurement of u), $\|\cdot\|$ is a suitable norm and $u(a)$ solves the variational problem corresponding to the elliptic problem.

In the Tikhonov approach, it is necessary to choose the regularization weight ρ. We replace (PT) by

$$f(a) := \begin{pmatrix} \|u - z\|^2 \\ \|a\|^2_{H^1(\Omega)} \end{pmatrix} \to \min \quad \text{w.r.t. } \mathbb{R}^2_+. \qquad \text{(PTV)}$$

So, it is possible to apply our methods for solving (8).

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