Understanding the Relationship between Interactive Optimisation and Visual Analytics in the Context of Prostate Brachytherapy

Jie Liu, Tim Dwyer, Kim Marriott, Jeremy Millar and Annette Haworth

Abstract—The fields of operations research and computer science have long sought to find automatic solver techniques that can find high-quality solutions to difficult real-world optimisation problems. The traditional workflow is to exactly model the problem and then enter this model into a general-purpose "black-box" solver. In practice, however, many problems cannot be solved completely automatically, but require a "human-in-the-loop" to iteratively refine the model and give hints to the solver. In this paper, we explore the parallels between this interactive optimisation workflow and the visual analytics sense-making loop. We assert that interactive optimisation is essentially a visual analytics task and propose a *problem-solving loop* analogous to the sense-making loop. We explore these ideas through an in-depth analysis of a use-case in prostate brachytherapy, an application where interactive optimisation may be able to provide significant assistance to practitioners in creating prostate cancer treatment plans customised to each patient's tumour characteristics. However, current brachytherapy treatment planning is usually a careful, mostly manual process involving multiple professionals. We developed a prototype interactive optimisation tool for brachytherapy that goes beyond current practice in supporting *focal* therapy - targeting tumour cells directly rather than simply seeking coverage of the whole prostate gland. We conducted semi-structured interviews, in two stages, with seven radiation oncology professionals in order to establish whether they would prefer to use interactive optimisation for treatment planning and whether such a tool could improve their trust in the novel focal therapy approach and in machine generated solutions to the problem.

Index Terms—Visual analytics, interactive optimisation, interactive systems and tools, prostate brachytherapy

1 Introduction

Visual analytics combines automatic analysis with interaction and visualisation techniques to gain knowledge from data [28]. It is now an essential tool for decision support. Another widely-used tool for decision support is optimisation. This aims to find the best solution to a decision problem by modelling it mathematically using constraints and objective functions and then using constrained optimisation to find a solution [33]. Standard approaches to optimisation view the solution process as a "blackbox". However, driven by application requirements, there is a growing realisation within the optimisation community of the need for more *interactive optimisation* in which the user is actively engaged in the solution process.

There are several compelling reasons for interactive optimisation. Any mathematical model necessarily simplifies the real-world problem and so may not capture all aspects of that problem [4, 18]. As a result, solutions can be unsatisfying or even unrealistic. Involving the user allows them to bring their additional knowledge into the solution process. This is particularly important in multi-criteria optimisation as it allows the user to guide the system on how to trade-off the various objectives. A second reason is that the search space of candidate solutions may be huge: the user can help to direct the solver to more promising regions. Finally, involving the user allows them to build up trust and confidence in the solver.

Both visual analytics and interactive optimisation aim to leverage the complementary strengths of humans and computers to solve difficult real-world problems. This similarity of intent leads us to believe that there are opportunities to share and transfer experience and knowledge between the two fields. In particular, creating effective visual interfaces for humans to control and explore optimisation can be seen as an application of visual analytics. Yet, as we discuss below, there is little published research exploring it from this perspective.

The main contribution of this paper is to explore the relationship between the fields of visual analytics and interactive optimisation to identify their similarities and to understand the potential use of interactive visualisation in optimisation (Sect. 3). Our second contribution is an in-depth analysis of a use-case in prostate brachytherapy that allows us to further explore the relationship between these fields (Sect. 4). Current brachytherapy treatment planning is a careful, usually manual process involving multiple professionals. We developed a prototype interactive optimisation tool (Sect. 5) that goes beyond current practice by supporting *focal* therapy—which targets discrete tumour foci directly—rather than conventional *whole gland* therapy which simply seeks uniform coverage of the whole prostate gland. Interactive 2- and 3-D visualisations are core elements of the tool.

We conducted two studies, each involving semi-structured interviews in conjunction with a treatment planning activity, with seven radiation oncology professionals (eight, if we include our co-author who acted as pilot). The first study (Sect. 6) explored current workflows and the reasons why clinicians currently use manual rather than automatic treatment planning for whole gland therapy. This study fed into the development of a new theoretical framework for understanding the high-level user goals and tasks in interactive optimisation that we call the *problem-solving loop* (Sect. 7). It is analogous to the sense-making loop commonly used to formalise the visual analytics process.

The second study (Sect. 8) introduced focal therapy and allowed the professionals to compare manual, automatic, and interactive optimisation for focal therapy planning. Our results suggest that interactive optimisation did build trust in focal therapy and that professionals overwhelmingly prefer to use interactive optimisation to create focal therapy treatment plans.

2 Background Research in Optimisation

Interactive optimisation has been used in a wide range of applications: facility layout [6, 11, 35], vehicle routing [4, 40, 41, 47], user interface design problems [5, 49], animation design problems [12, 43], radiotherapy treatment planning [45], vehicle scheduling and planning problems [2, 10, 48], image segmentation [8, 39] and composition [1], daylight performance problems [3], environmental management [29] and many more.

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Most of these interactive optimisation application papers are focussed on algorithm or system and tool designs. For instance, a recent survey [31] focusses on the reasons and role of interactive visualisation, solver techniques and user preference gathering but is almost completely silent about visualisation and interaction techniques, the user experience or user studies evaluating systems. However, there are some exceptions. An early review from Jones [26] looked at visualisation usage in optimisation while Miettinen [32] surveyed visualisation used in multi-criteria optimisation.

One area that has received attention is the use of visualisation when debugging and profiling optimisation models. For instance, Goodwin *et al.* [21] investigated requirements for visualisation in profiling of search in constraint programming (a specific approach to optimisation), thus attempting to open up the 'black box' of the optimisation search process. Closely related are interactive visualisation tools for determining the best choice of parameters for image segmentation [46], simulation-based design [15], animation [13], weather forecasting [19] and sensitivity analysis for car engine design [7]. Sedlmair *et al.* [42] provided a conceptual framework for visual parameter space analysis for simulation and design.

A number of user studies have evaluated interactive optimisation systems [4, 5, 12, 14, 18, 27, 35, 41, 43, 45]. In particular, Anderson *et al.* [4] reported that better routes can be found by using the interactive optimisation system HuGSS to solve a vehicle routing problem. Bailly *et al.* [5] conducted a user study to compare the performance of manual and interactive optimisation in menu design and found that using interactive optimisation can reduce the editing effort to achieve equally good menu designs. The study closest to ours is of an optimisation system developed by Thieke *et al.* [45] that allows doctors to explore the Pareto front for multi-criteria treatment plans. They concluded that faster treatment planning is achieved.

However, virtually all user studies have evaluated interactive optimisation in terms of solution quality and time spent to find solutions aspects: user satisfaction is not considered. An exception is a study done by Patten and Ishii [35] evaluating the usability of their tangible human-computer interface Pico to solve a cellular telephone tower layout optimisation problem. An even bigger gap is that the possible effects of interaction on *trust* have, to the best of our knowledge, never been explored in a user study for interactive optimisation. This is in contrast to studies investigating user trust in recommendation systems [17, 22], adaptive agent systems [20], information security classification [36] and classification based on machine learning [38].

Another limitation of previous user studies is that very few use experts from a particular problem domain. Exceptions are Butler *et al.* [14] which asked professionals to develop flight-line maintenance schedules and Thieke *et al.* [45] which used clinical planners to evaluate treatment plans for two clinical test cases: a paraspinal and a prostate case. Also relevant to our application domain is Raidou *et al.* [37] which proposed a visual tool for sensitivity analysis of tumour control probability (TCP) models to compare different treatment strategies for prostate cancer using radiotherapy. While we used a TCP model in the second study our focus is on the use of interactive optimisation to generate treatment plans for one particular treatment strategy: *low-dose-rate (LDR) brachytherapy*. More loosely related are Brecheisen *et al.* [9] which presented interactive visualisations for parameter sensitivity analysis in brain fibre tracking and Nunes *et al.* [34] which presented an interactive tool to support image fusion of magnetic resonance spectroscopy imaging (MRSI) with other medical images.

Compared to the past work, through exploration of interactive optimisation in the context of a concrete application (*brachytherapy*) we propose a general model for interactive optimisation systems which is analogous to the visual analytics sense-making loop. The studies described in this paper are another significant contribution to the current literature on interactive optimisation because of the use of experts and because of the focus on trust and usability.

3 Interactive Optimisation and Visual Analytics

Optimisation solves a real-world decision problem (*real problem*) by building a *mathematical model* of the problem and using computational techniques such as linear programming, simulated annealing or constraint programming to try and find the best (or at least a good) solution to the model. The model has a set of *decision variables* for which the optimisation technique will find values, an *objective function* for measuring the quality of a solution, and a set of *constraints* that restrict the values that the decision variables can take. Usually the model is generic and *problem data* is needed to encode an actual instance of the problem. For instance, in staff rostering the decision variables are the names of the staff taking the various shifts, the objective function is to reduce staff costs and satisfy staff preferences while constraints capture work-force restrictions and skills required on each shift.

Improvements in optimisation solving technology and increased computational power mean that optimisation is now routinely used to solve a wide variety of decision problems in many different application areas. The standard approach of the optimisation community has been to build a fully automatic system in which the solver is a "black-box" and the user simply provides the problem data and then waits for the system to spit out a solution. However, for this approach to be practical it requires the model to adequately capture the actual real-world problem and for the solver to be powerful enough to find a sufficiently good solution in a reasonable time. For many, if not most, real-world problems these are not reasonable assumptions. As a result there is now a recognition by the optimisation community that in many applications there is a need to directly engage the user in the optimisation process. Such *interactive optimisation* (also known as *semi-automatic optimisation* or *human-in-the-loop optimisation*) has been used in practice for many decades but has only recently been recognised as a topic worthy of study in its own right.

A recent survey paper [31] clarifies the rationale for interactive optimisation: "the main goal of interactive optimisation is to turn efficient optimisation methods into effective decision tools." They identify the following reasons and roles for interactive optimisation:

Inherent limitations of mathematical models. A mathematical model is almost always a partial approximation to the real problem. The real problem may contain aspects that cannot easily be modelled mathematically [44], such as: multiple conflicting criteria whose complex tradeoffs cannot be captured in an objective function; uncertainty or probabilistic constraints; or constraints that model human preferences. The mathematical model may also be simplified for tractability, for instance by using linear approximations or a single weighted objective function. Or it may just be too expensive or impractical to find the necessary experts to properly understand and model the problem. Interaction allows the user to adjust the constraints or objective function or to enrich the model by adding new constraints or objectives. A particularly important case is for the user to guide how to trade-off conflicting criteria in multi-objective optimisation.

Solver performance. The quality and efficiency of the solving process are crucial to the use of optimisation tools. It is difficult for the designers of the generic model to predict how efficiently the model will be solved on real-world data and with incomplete heuristic methods, such as simulated annealing. The solver may never explore that part of the search space containing the best solution. Users can assist by providing feasible starting configurations, guiding the search, or tuning solver parameters for more efficient search.

Non-acceptance and misunderstanding of optimisation systems. The opacity of the black-box approach to optimisation may lead users to either lack trust or place too much trust in the quality of the solutions produced by the system. Interaction allows the user to modify solutions in order to better understand the quality of a solution as well as to explore what-if scenarios allowing them to build an appropriate level of trust in the system.

A key question is what are the appropriate visual representations and interaction techniques to support interactive optimisation. As discussed in Sect. 2, this is a subject that has received little attention from optimisation researchers. In contrast, the field of visual analytics ("the science of analytical reasoning facilitated by interactive visual interfaces" [16]) focusses on the design and evaluation of interactive visual interfaces and has many findings regarding how best to incorporate the human analyst in the data sense making and knowledge discovery process. We therefore believe there is considerable potential for sharing and transferring knowledge from visual analytics to interactive optimisation.

Both visual analytics and interactive optimisation aim to achieve better decision making by bringing humans into the analytics-loop. Visual analytics applications allow the analyst to interactively combine automatic and visual analysis to gain knowledge from data [28]. These are complementary. Automatic analysis allows analysts to fit mathematical models built through data mining or machine learning while visual analysis gives freedom to analysts to explore the data and model through interactive visualisation. Interactive optimisation and visual analytics share many similarities. In both disciplines the user may:

- interact with the system to bridge the gap between the inherent limits of a mathematical model and the real world problem;
- guide the search, either for a solution or for the right model and parameters;
- need interaction and visualisation to build their trust in the model or solution;
- need to find patterns and to understand complex and large datasets (in optimisation this is the solution space, fitness landscape or the solver search space);
- need to communicate the result to managers, policy makers and other stakeholders.

Thus, interactive optimisation can be seen as an application domain for visual analytics. Conversely, model fitting and classification can be regarded as a particular kind of optimisation problem and visual analytics applications utilising machine learning or data mining may therefore be regarded as a kind of interactive optimisation. We will now explore the relationship between interactive optimisation and visual analytics in more depth through an in-depth case-study.

4 Application Context

Our application context is the development of planning tools for the treatment of prostate cancer using LDR brachytherapy in which radioactive sources are placed inside the patient's body close to or in tumours in order to control or kill the tumour cells. The radioactive isotope is encased and sealed inside a tiny cylinder-shaped titanium "*seed*". Multiple seeds are connected by physical strand and assembled into a *needle*. Using the needle, the surgeon implants seeds into the patient's prostate gland where they remain permanently, though the radioactive strength decays exponentially over time. As shown in Fig. 1, a template grid is used to guide needle placement.

Whole gland therapy is the current standard clinical treatment method in LDR prostate brachytherapy. The aim is to give a good dose coverage to the entire prostate by uniformly distributing radiation to the prostate gland, while avoiding high doses to *organs at risk (OAR)*. In particular, such organs include the urethra, passing through the middle of the prostate, and the rectum, which runs below it (see Fig. 1). Whole gland therapy has great success in prostate tumour control and is supported by strong clinical evidence. However, whole gland therapy has the danger of over-treating patients if the number of tumours in the prostate is limited and the tumour size is relatively small.

For this reason, *focal therapy* has been proposed as an alternative to whole gland therapy. Instead of delivering a high dose to the entire gland, only those regions of the prostate with high likelihood of containing tumour cells are targeted for high-dose radiation. The potential benefit is a reduction of toxicity to other OAR especially the urethra and rectum, while still maintaining effective control of the prostate tumour cells. Approaches to focal therapy differ in the amount of radiation applied to regions of the prostrate deemed to be low-risk. In the 'focussed' approach the entire prostate gland is irradiated by a small but sufficient dose, while the tumour regions are irradiated with high dose [30]. Our research is part of an on-going project investigating the viability and effectiveness of focussed focal therapy. Our role is to investigate how to best support radiation oncology professionals when creating a treatment plan with this therapy.

Commercial treatment planning systems are used for treatment plan creation for whole gland LDR brachytherapy. *VariSeed* (Varian Medical Systems, Inc., Palo Alto, CA) is one of the most widely used. It provides

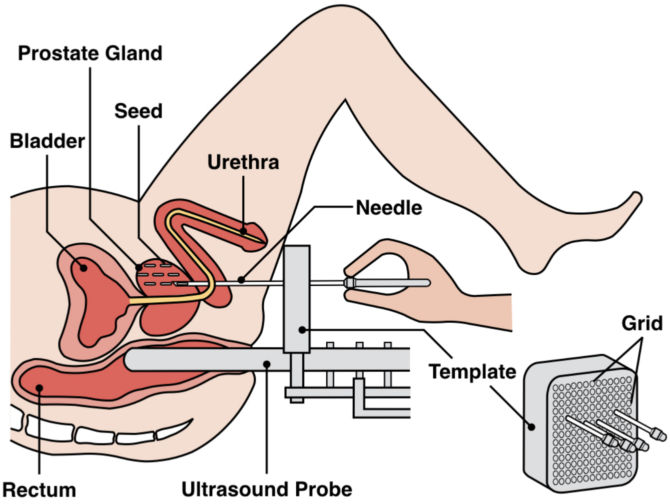

Fig. 1. Needle placement in LDR prostate brachytherapy. Note the physical template grid used to guide needle placement.

manual planning of seed placement as well as a module for automatic planning. The manual approach, often referred to as *forward planning*, presents the treatment planners with an initial auto-seed-loading pattern based on a simple template automatically generated from a pre-defined planning protocol that specifies where seeds are placed on the grid points and also defines forbidden areas for the seeds. The planning protocols often vary between clinical departments. The treatment planners manually adjust the loaded template by adding extra seeds to increase dosage coverage, or removing or moving seeds to avoid overdosing of other sensitive structures. The automatic optimisation approach (also named *inverse planning*) requires the treatment planner to set planning criteria such as the dosage coverage and then automatically generates a treatment plan. However, at least within Australia, the manual approach is typically used for whole gland LDR brachytherapy planning. Automatic optimisation is used for intra-operative LDR brachytherapy, i.e., the plan is re-optimised while the patient is undergoing the treatment when the actual needle placement varies from the planned position. Automatic optimisation is used because of the requirement to update the plan in real-time making manual planning impractical.

Our approach to the development of treatment plans for focal therapy is based on a new mathematical model of biological characteristics of prostate tumour cells [23,25]. The model introduces *TCP* as a biological planning objective that provides a relative measure of the likelihood of disease control following radiation. The calculation of TCP takes into account the radiation *dose* and the *tumour cell density (TCD)* within the prostate volume as well as tumour characteristics such as tumour aggressiveness and tumour hypoxia.

Because of the complex interaction between TCP and TCD, and the lack of clinical expertise, manually creating focal therapy treatment plans based on TCP had initially been regarded as impractical. As a result, automatic optimisation software based on the TCP model has recently been developed to produce focal treatment plans [24]. This aims to reach a desired TCP level while providing a safe level of dose to OAR. The optimisation software was effective, producing plans in a few minutes. However, due to the limitations of unsupervised optimisation identified in Sect. 3 (i.e., limitations of the underlying optimisation model, solving performance and lack of trust in automatically generated solutions) it was clear that an interactive-optimisation approach potentially offered several benefits over a black-box approach:

- Treatment planning requires multi-criteria optimisation as high TCP conflicts with low dosage to OAR. Human radiation oncology professionals are better able to manage this tradeoff by taking into account additional knowledge, e.g. patient age or previous medical history.
- The model is not guaranteed to find an optimal solution as it uses an

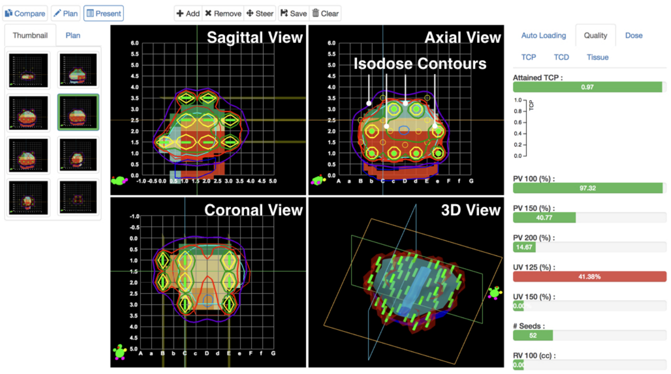

Fig. 2. A sample treatment plan shown in presentation mode after Study 1 & 2 improvements. The white text is not part of the interface but added for explanation purpose.

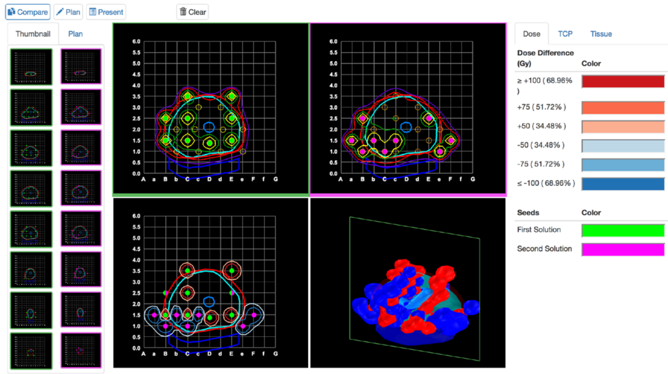

Fig. 3. The compare mode after Study 1 & 2 improvements. Top two view ports show the axial view slices of the two plans to be compared. Bottom two view ports show the difference map in 2D and 3D.

incomplete local search to find a solution above the desired TCP value. Humans can help guide the search to find better solutions.

• Finally, when the consequences of a poor optimisation can be extreme, clinicians are rightfully cautious in trusting the results of automatic optimisation. This is compounded by the fact that focal therapy and TCP are unfamiliar. Interaction potentially allows clinicians to build a better understanding of TCP and confidence in the underlying biological model as well as the underlying optimisation.

5 Prototype Interactive Optimisation Tool for Prostate Brachytherapy

In order to evaluate whether interactive optimisation is superior to manual or fully-automatic optimisation for TCP-based focal prostate brachytherapy, we developed a prototype interactive optimisation tool. The tool builds upon a local-search-based optimisation solver previously developed to test a fully-automatic (inverse planning) approach to focal therapy using TCP. The user interface for this new interactive tool, and the required interfacing to the algorithm, took more than a year to develop using a participative design process with a medical physicist and bioengineer.

The tool allows the user to generate and rank a set of candidate solutions (the solution *gallery*). The tool has three modes: *presentation mode* which allows the user to visualise a single candidate solution in the gallery; *compare mode* which allows the user to compare candidate solutions from the gallery; and *plan mode* in which the user can guide the solver to generate a new solution or improve an existing solution.

Presentation Mode (Fig. 2): It took a number of attempts to produce a satisfactory visualisation of a single solution. The initial visualisation used two view ports: one for the 3D prostate model and the other for *axial* views presented in small multiples. After discussion with our collaborating medical physicist and bioengineer, *sagittal* and *coronal* views (longitudinal and cross section views) of the prostate were added to give a complete overview of a treatment plan. The eventual solution was to provide an anatomical plane of the prostate (the *axial*, *sagittal* and *coronal* views) and the 3D model in four linked view ports on a single pane. Grids were added in all anatomical views to show the physical grids (see Fig. 1) used for treatment delivery. As the axial view is the primary view used by radiation oncology professionals when planning treatments, we also included a complete gallery of axial view slices on the left.

Contours are provided for the prostate, urethra, rectum and the *planning target volume (PTV)* defining the treatment margin around the prostate. The user can choose to overlay this with TCD, TCP or physical dose. First we used pixel and voxel representations of dose in 2- and 3-D views to show the different levels. After user feedback, we settled on an isodose contour representation (implemented using marching squares and marching cubes), similar to that used in commercial prostate brachytherapy planning tools. We also provided histograms on the right to summarise the dosage and planning objectives.

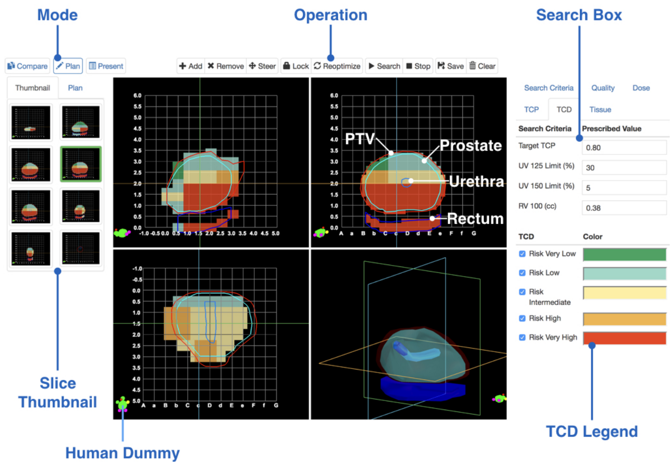

Fig. 4. The prototype interactive optimisation tool after Study 1 & 2 improvements. The prostate gland is divided by a grid with colour coding representing the TCD in each grid cell. A Human Dummy is used to indicate the patient's orientation.

Compare Mode (Fig. 3): Being able to review and verify a single treatment plan is essential. However, we felt that it would also be useful to be able to *compare* and *rank* candidate solutions. This is an activity that is typically not well supported in optimisation tools. Our tool provides a novel comparison mode in which the user can scroll through synchronised axial view slices of two solutions, with a third view port showing the difference between the two slices and a fourth showing a 3D visualisation of the difference. Like the presentation mode, the user can choose to show TCD, TCP, physical dose or a combination.

Initially we designed two view ports: a solution gallery for browsing all candidate plans and below a view of two candidate plans and their absolute dose differences. Our collaborators were very excited about this. However switching between slices caused significant delay because of the colour-washed difference representation. We replaced it with pixels to reduce the delay and keep the whole interface responsive. Later we changed the layout to more closely resemble the presentation mode, providing a more uniform interface and more flexible comparison with sagittal, coronal and 3D views as well as the difference in axial views. We used a point cloud for the 3D visualisation of difference.

Planning Mode (Fig. 4): The ability to generate new solutions or improve an existing solution must be supported by any true interactive optimisation tool. In our tool this is supported by the *planning mode*. Fig. 4 shows the planning mode before any plans have been created. In the figure, the user is viewing the TCD. They can use the pane on the right to generate a new solution. They can set values for the minimum desired TCP and the maximum allowed dose to both the urethra and the rectum, defined as three constraints ('prescribed dose' is declared as $145Gy$, *Gray (Gy)* being the unit used to measure the total amount of radiation a patient is exposed to):

1. *UV125*: Volume of the urethra receiving 125% of the prescribed dose ($145Gy \times 125\% = 181.25Gy$);
2. *UV150*: As above, but 150% of the prescribed dose ($145Gy \times 150\% = 217.5Gy$);
3. *RV100*: Volume of the rectum receiving the prescribed dose ($145Gy$).

By varying these parameters they can *guide* the solver by forcing it to generate solutions that have different tradeoffs between higher TCP and less irradiation to OAR. When the solution is generated a visualisation shows the solver's progress: this provides an indication of how difficult it is to find a solution meeting the specified criteria.

The planning mode also allows users to improve a solution by *adjusting/suggesting* changes to the placement of seeds and needles in the solution. Our tool provides both manual and semi-automatic adjustment of solutions as we were interested in finding out which techniques would be preferred by radiotherapy team members. The following adjustments are possible:

Add: Users can add a new seed to a grid point in the current slice. If there is no needle at the target grid point a new needle is created.

Remove: Users can also remove seeds. If the seed to be removed is the last in the needle, removing the seed also removes the needle.

Move: Users can select and move a needle which also moves the seeds on the needle.

Lock & Re-optimise: Users can lock the position of seeds and needles whose position they are happy with. They can then run the re-optimise which starts from the current solution and tries to improve it by moving the unlocked seeds. In combination with manual placement of seeds this is a powerful way of *steering/guiding* the solver to generate better solutions. By locking the position of some seeds the solver search space is reduced, speeding up the search for better solutions.

After users perform any of these operations, the treatment plan is refreshed and either physical dose or TCP contours are updated immediately to give users instant feedback.

6 Study 1: Whole Gland Therapy

We conducted two exploratory, formative user studies with radiotherapy team members to evaluate and inform the design of our prototype tool. We had originally planned a single study but based on feedback from our medical collaborators we decided to break the study into two parts because participants would have been overwhelmed by the need to understand focal therapy (recall from Sect. 4 that the current standard whole gland therapy), TCP (proposed in [23] and not yet part of clinical procedure) as well as our novel and therefore unfamiliar interactive optimisation tool. The first study was designed to present the tool in the context of treatment planning for whole gland therapy, a process they were extremely familiar with. Based on feedback from this study we could refine the design of the tool before conducting the second study investigating use of the tool for focal therapy planning.

This meant that we needed to modify the tool for the first study as traditional planning for whole gland therapy does not use TCP or TCD, only physical dose. The underlying solver was modified to optimise dose coverage rather than TCP and the interface of the tool was also appropriately modified to consider only physical dose.

Study 1 was designed to achieve three main aims:

1. Build a better understanding of the workflow of treatment planning;
2. Understand why radiation oncology professionals use a manual approach to create treatment plans rather than optimisation in whole gland therapy;
3. Evaluate and improve the prototype interactive optimisation tool, in particular the visualisations and interaction design.

6.1 Study Design

Apparatus & Materials: The modified interactive optimisation tool was used throughout the study. Two whole gland treatment plans were prepared for the study. The first was produced using automatic optimisation while the second was a plan created manually by a radiation therapist (not part of the study).

Participants: Seven participants were recruited for the study: 3 *radiation therapists (RT)*, 2 *medical physicists (MP)* and 2 *radiation oncologists (RO)* after we gave an introductory presentation about this project at the Alfred hospital. All participants completed the study except for one RO who did not do the plan improvement (due to time constraints). An initial pilot was conducted with a radiation oncologist who was a member of the research team. We have included the results from the pilot study (indicated as such) where relevant.

Procedure: Interviews were conducted at the participants' workplace. The study took about one hour on average. It had four parts:

1. *Introduction Activity:* The participants were asked about their experience in LDR brachytherapy, their current roles and responsibility in the brachytherapy team and the overall workflow, as well as their opinion on manually produced and optimisation generated treatment plans.

2. *Training Activity:* Next, our prototype tool was presented to participants. The operations of the tool were explained and demonstrated and participants were encouraged to ask questions and play with the tool until they were familiar with its operations.

3. *Planning Activity:* In the main part of the study participants were asked to evaluate two different types of treatment plan and to "think aloud" to explain the reasons and the evaluation criteria. They were not told how the plans had been produced. The two different types of treatment plan were:

(a) A manually-produced plan by another radiation oncology professional using their usual procedure;
(b) An automatically-produced plan (without interaction) using our solver software to optimise for dosage.

Then the participants were asked to improve the automatically produced treatment plan by using the operations introduced in the Training Activity. As before, they were asked to evaluate it and to give their reasons and evaluation criteria. The participants were also asked to give a rank to each treatment plan after evaluation.

4. *Recap Activity:* Finally, the participants were asked open-ended questions about the advantages and disadvantages of both manual and optimisation approaches to producing a treatment plan and to provide general comments about the prototype tool and suggestions for improvement. They were specifically asked to provide feedback on the comparison mode and the difference map visualisation as this was the most novel aspect of the tool.

6.2 Results & Discussion

Aim 1 (Understanding the treatment planning workflow) was investigated by asking participants to describe their roles and responsibilities in radiation treatment planning and to explain the process in the Introduction Activity.

The first step is that an RO contours the prostate gland and its surrounding organs and establishes the treatment margin based on the patient's ultrasound images. This is the 'Volume Study' process. The initial plan is usually created by an RT and reviewed by an MP before sending it to RO for the final review. However, to balance workload, sometimes an MP will create the initial plan that is reviewed by an RT before the final review. Both MPs mentioned they were in charge of the treatment plan quality assurance process and indicated that it was common to ask for revision or for another plan to be produced. On occasion more than one plan is produced when it is unclear how best to trade-off dose coverage and protecting OAR. What is striking about the workflow is the importance placed on checking and validation of the plan. This requires significant collaboration between the clinical professionals. Fig. 5 summarises the treatment planning workflow and the different roles.

Aim 2 (Understanding why radiation oncology professionals use a manual approach to create treatment plans rather than optimisation in whole gland therapy) was investigated through questions in the Introduction and Recap Activities as well as the "think aloud" ranking and planning in the Planning Activity.

Our study revealed a number of reasons why manually produced

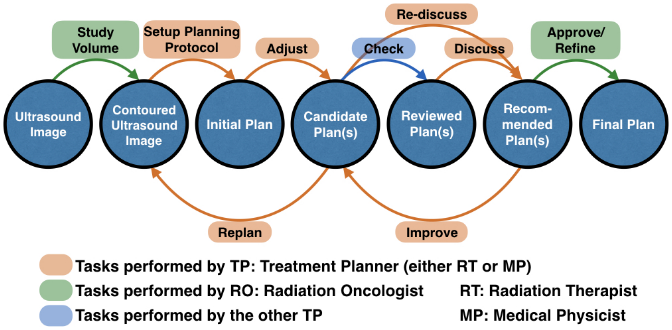

Fig. 5. The workflow to create and approve a treatment plan.

plans were preferred. One unexpected reason was a desire for plans to be symmetric. During the pilot the RO strongly criticised the automatically produced plan for not placing seeds and needles symmetrically on either side of the prostate gland. This was intriguing so we slightly modified the study procedure to further investigate symmetry. Subsequent participants where asked 'Do you like to keep the plan symmetric? If so, why?' and we modified the optimisation solver to produce more symmetric plans. For the last **4** participants we added an additional automatically produced plan that was more symmetric to the study and asked the participants to rank four plans (the original asymmetric automatically generated plan, the more symmetric automatically generated plan, the manually modified automatically generated plan and the manually produced plan).

All participants agreed on the importance of symmetry and this was reflected in the rankings with the manual plan (which was symmetric) and the symmetric automatic plan receiving higher ranks by most users. The importance of symmetry was also reflected in participants' improvements to the optimisation plan with some participants replacing existing seeds and needles with new ones placed evenly on both sides of the prostate.

A number of reasons were given for preferring symmetric plans. Aesthetic preference was one. Symmetry of the prostate was another: "*if it [the prostate] is symmetrical then it makes sense to have sort of the same kind of needle placement on both sides of the prostate.*" A third reason was treatment speed and simplicity. It was felt that surgeons liked symmetric plans because they were easier to remember, meaning that treatment could be faster and less error prone. Symmetry was also said to make the plan more robust. Finally, we suspect that symmetric plans make it easier for planners to understand the plan and build a mental model from the slices. It also reduces the search space when creating a plan manually.

In addition to lack of symmetry, fully automatic generation of treatment plans was criticised for a number of other reasons. One reason reflects the multi-criteria objectives in whole gland therapy planning. There is a conflict between delivering sufficient dose coverage to the prostate gland and reducing the dose toxicity to OAR. Participants felt this balance required human judgment and decision making. Another reason is that different clinical centres can differ in the planning protocol for dose constraints as well as allowed placement of seeds and needles. This makes it difficult for automatic optimisation to produce acceptable plans for all clinical centres. Yet another reason was that the underlying mathematical model restricts seed placement to grid points. While needles are inserted through a grid template, in practice surgeons may insert them at an angle so as to steer seeds away from OAR or to take into account physical constraints such as the pelvis. Thus seeds may actually be placed off the grid. Other comments reflected that participants were simply comfortable with the current processes. "*[Forward planning (manual planning) is] the robust way of planning. [We've] got years of results behind it.*"

The responses clearly show that the current preference for manual planning over automatic planning in whole gland therapy is because of the mismatch between the mathematical optimisation model used in automatic planning and the actual real-world problem. This provides strong support for using interactive optimisation rather than automatic optimisation in focal therapy planning.

Aim 3 (Evaluating and improving the prototype interactive optimisation tool, in particular the visualisations and interaction design) was achieved by asking questions in the Recap Activity and from comments made by participants during planning. Changes were made to visualisations, interaction and to the underlying optimisation model.

We improved the visualisations as the study progressed in light of participants' feedback. The first change was to use the clinic-specific colour scheme for treatment planning. Next, we rearranged the four view ports in the presentation mode so as to accord with the layout provided in Variseed (the commercial prostate brachytherapy planning tool used in the clinic). We also adjusted the grid labelling and alignments of images in each view port to better fit with the current treatment planning workflow as well as to synchronise with the alignment of the physical template for treatment delivery.

One of the most novel aspects of our prototype tool is the compare mode. Generally participants were positive: one participant said "*I think the comparison [where the difference map is used] could be really useful actually. That's one thing we are missing in VariSeed.*" However some participants found it initially confusing. "*[It's] hard because [I have] never seen this before.*" Another commented "*I don't think it's hard to understand. I think it takes a little bit of getting used to looking at it.*"

In response to user feedback we: moved the axial view slices of the two plans to be side-by-side in the top two view ports for easier comparison; replaced the pixel-based display of differences with isoline contours because of participant familiarity with isodose line usage in treatment planning and, for consistency, replaced the point cloud 3D difference visualisation with isosurface contours. We also reduced the use of colour and emphasised large differences in the 3D difference model. However, while participants liked the 2D difference view they did not make much use of the 3D difference model. In general we found they relied on the 2D views much more than 3D models.

Responsiveness was an issue raised by several participants. We removed the sliders along each anatomical view and replaced with scrolling and key stroke to support faster browsing of anatomical slices and improved responsiveness during planning by reducing refresh frequency for the axial view slices gallery, as this was viewed less frequently.

Finally, as discussed previously, we modified the underlying constraint model to produce more symmetric plans and also allowed the user to manually steer a needle away from a grid point to allow fine-tuning, better reflecting actual practice.

7 The Problem Solving Loop

Another way to understand the differences and similarities between visual analytics and interactive optimisation is to compare the high-level processes and aims of the user in these two endeavours. Informed by the first study we can now attempt this.

Sense-making is a widely used theoretical framework for understanding visual analytics tasks. It identifies the following steps in the analytical reasoning process:

- Information gathering (or foraging) to find relevant information
- Reformulation of the data to aid analysis
- Development of insight by interactive exploration of the data
- Formalisation of this insight by fitting schema or models to the data
- Generating hypotheses based on these schema or models
- Presentation of the findings

For instance, Pirolli and Card's sense-making loop (Fig. 6) captures the processes employed by intelligence analysts when making sense of information. An important observation is that at each step of the process the analyst may revisit earlier steps in light of new insights. To the best of our knowledge there is no analogue of the sense-making loop for interactive optimisation.

The *problem-solving loop* shown in Fig. 7 is our attempt to provide a similar theoretical framework for understanding the high-level user goals and processes in interactive optimisation. There are two main

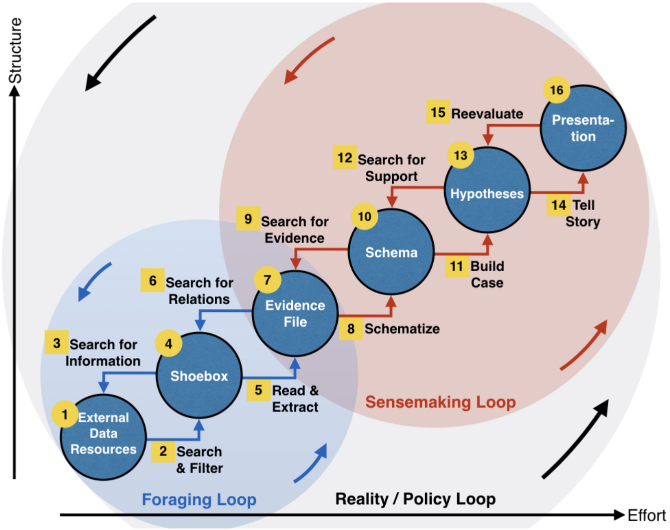

Fig. 6. Pirolli and Card's sense-making loop.

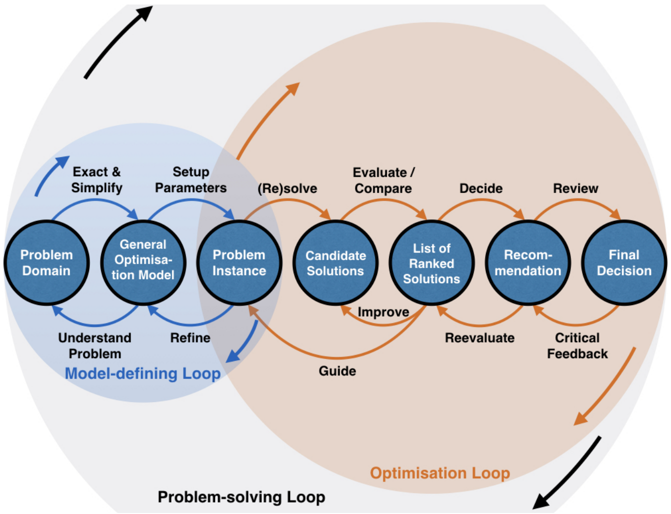

Fig. 7. The problem-solving loop.

loops: the *model-defining loop* captures the development of the generic mathematical optimisation model, typically by an expert in optimisation, while the second loop, the *optimisation loop* captures the use of the model by the end-user, typically the domain expert, to support their decision making. Our focus in this paper is on the optimisation loop. It has the following steps:

- Solving the generic model with the problem specific data to generate a pool of candidate solutions
- Evaluation and comparison of these candidates to give a ranked list of solutions
- Decide upon a recommendation which may be a single solution or solutions with an analysis of the tradeoffs between them
- Review by relevant stakeholders and decision makers to determine the final decision

Like the sense-making loop the problem-solving loop is interactive and the analyst will frequently return to earlier steps. For instance, after evaluating and comparing the solutions in order to rank the candidate solutions she may decide that none of them are good enough and try to generate better candidate solutions, either by refining the general model by guiding the solver, or by improving an existing solution manually by changing the values assigned to some of the decision variables. Thus, steering of the needle away from a grid point is an example of manual improvement.

Another important loop results from critical feedback from stakeholders and the final decision makers on the recommendations which may lead to reevaluation of the ranked list. Interactive optimisation is regularly employed to solve problems where the wrong decision can lead to significant loss or even death. As we have seen in the first study robust review is an important part of the problem solving process in such high-stake applications and will often lead to refinement or even rejection of the initial recommendation. This differs from many visual analytics applications in which findings of the analyst tend to be presented as a *fait accompli* rather than being the subject of robust collaborative review.

Examination of the optimisation loop and of the prototype tool developed for our case study clarifies the tasks for which interactive visualisation may be useful:

- *Evaluate:* Showing a single solution and its associated constraints and objective values in order to understand and evaluate it.
- *Compare:* Comparing multiple candidate solutions to rank them and to better understand the tradeoffs between them (this is especially important in multi-criteria optimisation).
- *Improve:* Manually manipulating a solution to improve it.
- *Guide*: Guiding the optimisation solver to search for new solutions in "interesting" regions of the search space of the problem instance.
- *Recommend:* Presenting recommended solutions including alternatives to decision makers and stakeholders.

There are a number of different kinds of multidimensional data that may need to be visualised. The first is a single solution and its "fitness". The second is the solution space, the set of allowed values for the decision variables. The third is the fitness landscape: the set of possible values for the objective criteria while a fourth is the search space being explored by the solver.

8 Study 2: Focal Therapy

In our second study we investigated the use of interactive optimisation for focal therapy. Our aims were fourfold:

1. Observe participants' exploration of focal therapy planning;
2. Determine the participants' preferred method for creating treatment plans for focal therapy (manual, fully-automatic optimisation or interactive optimisation) and the reasons for their preference;
3. Investigate whether experience with an interactive optimisation tool will increase participant trust in focal therapy and in optimisation-based treatment planning for focal therapy;
4. Obtain feedback on the design of the prototype tool.

8.1 Study Design

Apparatus & Materials: We used the interactive optimisation prototype tool for this study after we rolled back the changes required to support whole gland rather than *focal therapy* and also integrated the improvements from the first study. We used the tool to prepare two automatically generated focal plans with different TCP values: **F2**: with TCP = 0.87 and **F4**: with TCP = 0.96.

Participants: Participants were recruited at a second presentation given to the brachytherapy team at the Alfred. This reported the findings from the first study, introduced focal therapy and explained the purpose of the second study. Participants from the first study were again asked to participate to ensure they were familiar with the tool and the project methodology and aims. One could not participate but two new clinical professionals were recruited and were provided with additional instruction in the tool (to compensate for their lack of experience of Study 1). This gave a total of 7 participants (one RO, three MPs and three RTs). As in the first study, because of the low number of participants we have also included the results from the pilot study with a member of our research team (an experienced RO).

Procedure: Our second study followed the same structure as the first:
1. *Introduction Activity:* We asked participants questions about their preferences in treatment planning methods (whole gland, focal) for prostate brachytherapy, and preference and trust in methods (manual, automatic, interactive) for creating a focal plan.
2. *Training Activity:* We presented our prototype tool and explained its operations. Participants were asked to briefly evaluate both TCD and

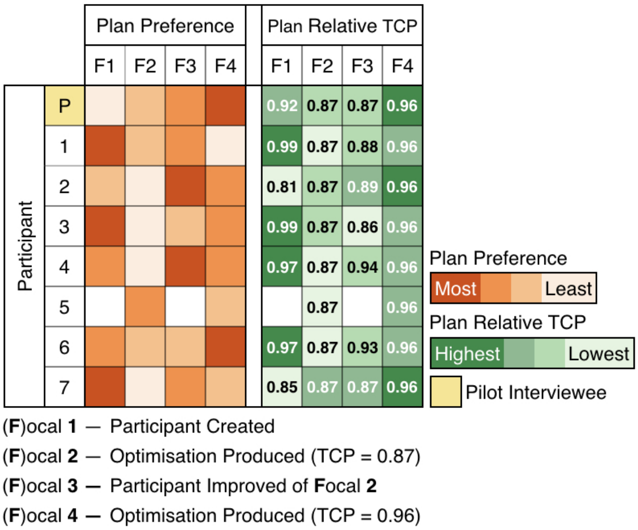

Fig. 8. The relative ranks of all four focal plans and their associated TCP scores and relative TCP ranks.

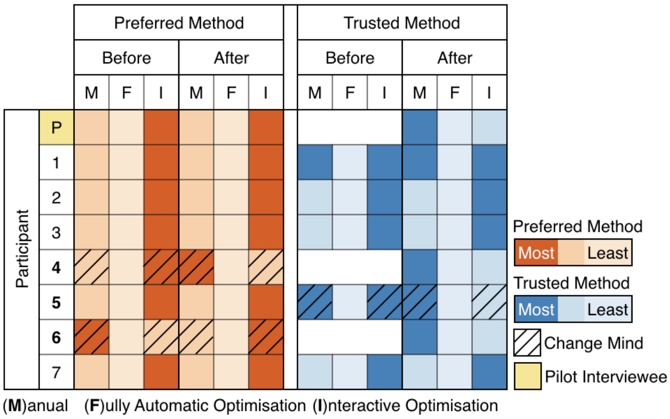

Fig. 9. Participant preferences and level of trust in different methods for creating a focal treatment plan including **M**anual, **F**ully automatic optimisation, and **I**nteractive optimisation. They were asked to rank the methods before and after experience with the tool.

TCP visualisations and provide comments.

3. *Planning Activity:* The main part of the study was to evaluate four focal treatment plans (one produced manually (**F1**), two produced fully automatically (**F2** and **F4**) and one produced using interactive optimisation (**F3**)):

(a) Participants were asked to manually create a focal plan **F1** with the tool and then score it. They were provided with the choice of two auto-seed-loading templates as the starting point, so as to reduce the time required for the study and to mirror the manual planning approach for the whole gland therapy approach they were familiar with.

(b) Next, focal plan **F2** was presented. Participants were asked to evaluate and then score it.

(c) Then participants were asked to improve focal plan **F2** using the tool and score the resulting focal plan **F3**.

(d) The final focal plan **F4** was presented and evaluated and scored by participants.

They were then asked to rank the four focal plans.

4. *Recap Activity:* We repeated the questions about participants' preferences of both treatment methods and approaches to create a focal plan. Suggestions for improving the prototype tool were solicited.

8.2 Results & Discussion

One participate did not wish to manually create or improve a focal plan because this participant thought it was outside their area of expertise. As a result, only focal plans **F2** and **F4** were included for this particular participant. We included the participant's other responses.

Aim 1 (Observation of participants' exploration of focal therapy planning) was based on the Planning Activity. To this end we asked participants to "think aloud" as they created a focal plan.

We observed they used different planning strategies. However all participants started with dose coverage of the prostate gland. Because of the unfamiliarity of focal therapy and TCP many participants were not sure about what a clinically acceptable focal plan should look like as they have never done any focal treatment before. They were unsure about the right TCP threshold and the interpretation of TCP contours.

One participant finished planning without using either TCP or TCD visualisations at all because of unfamiliarity. Another participant refined the focal plan by using the TCP contours "*as a second assessment*", whereas the other three radiotherapy team members fine-tuned plans based on the extra tumour information provided from TCD visualisations without looking at TCP contours at all. The remaining two participants adjusted their focal plans according to the TCD visualisation and finally double checked and refined plans by using TCP contours. Five of seven utilised the TCD visualisation to further adjust the seeds' and needles' positions to give a better coverage around the high tumour-risk areas. Most participants said the TCD visualisation was useful and that it did affect the way they do treatment planning, for example "*Having contours showing your [tumour] control probability is really good from a planning point of view.*" and "*I liked it (TCD visualisation).*" However, participants were curious and somewhat sceptical about the reliability of the data underlying the TCD calculation, for instance: "*I definitely think it (TCD visualisation) will be useful. If this information (TCD) is reliable, that will guide the treatment.*"

Participant ranking of the focal plans (see Fig. 8) was difficult to interpret. Focal plans **F1**, **F3** and **F4** received roughly equal ranks which indicated that focal plans produced by manual, fully automatic optimisation (with high TCP setting) and interactive optimisation are acceptable. However, the automatically produced plan with low TCP was not liked. It is also clear that overall TCP score is not the only quality that participants were using to evaluate the plans. Other factors, such as dose coverage, needle positions and patterns, were also important and considered in the evaluation. This provides support for interactive optimisation rather than automatic optimisation. One participant commented "*The optimisation does not take a lot of the clinical information you have and there's still some kind of knowledge that we have but the machine does not.*"

To address Aim 2 (User preferences for creating treatment plans for focal therapy) we asked participants to rank the methods (manual, fully automatic optimisation, interactive optimisation) in order of preference from most preferred (rank 1) to least preferred (rank 3) for creation of a focal therapy treatment plan and in terms of trust. They were asked at the beginning and the end of the interview so that we could see if their experience with the tool changed their response. The results are shown in Fig. 9.

Most participants (6 of 8) preferred interactive optimisation from the beginning to the end. Two changed their preferences. One changed from interactive optimisation to manual because the participant was not happy with the focal plan produced from optimisation (poor dose coverage and needle loading pattern, lack of symmetry) and felt that fine-tuning an optimisation produced plan cannot completely fix these problems or would take too long to do so. The other one preferred manual at the beginning but interactive optimisation in the end. After trying out the prototype tool they thought interactive optimisation has more potential in treatment planning because of the speed advantage from optimisation and the flexibility to make adjustment with interactions. The responses strongly support that interactive optimisation is the preferred method for focal therapy planning.

Aim 3 was to evaluate the effect of interactive optimisation on trust in planning method and treatment method. In the case of optimisation-

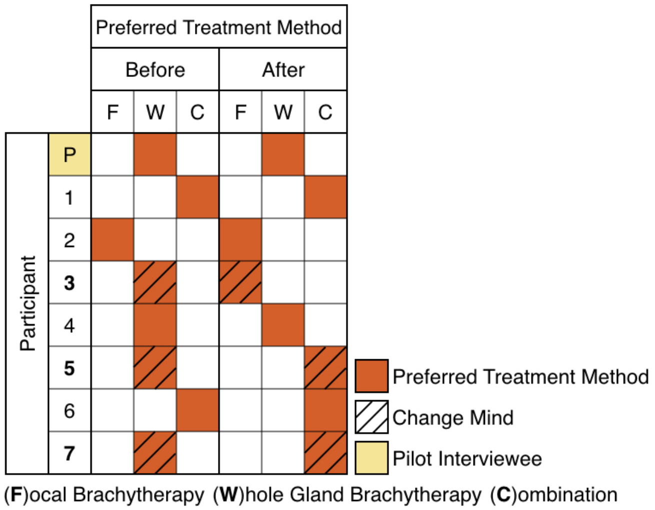

Fig. 10. Participant preferences for treatment methods in prostate brachytherapy, before and after experience with the tool.

based treatment planning half of the participants trusted interactive optimisation the most from the start to the end. There were 3 participants who did not trust any of the methods before trying and seeing each themselves. These cells were kept empty in the trust preference table (see Fig. 9). All 3 of them trusted manual planning the most at the end of the interview. Two of them were very sceptical about focal therapy during interviews. It's perhaps not surprising that they trusted the manual approach more in the end because they had a strong belief in whole gland therapy and manual treatment planning approach is the standard in whole gland therapy. One participant changed their mind from equally trusting both manual and interactive optimisation to trusting manual more than interactive optimisation. The main reason for this change was concern about prostate dose coverage and the belief that the coverage from both optimisation produced focal plans was not satisfying while using the manual approach could give better coverage to the prostate gland.

Overall, by the end of the study half of the participants trusted the manual approach and the other half trusted the interactive optimisation approach the most. What is clear is that the fully automatic optimisation approach is the least trusted, all 8 participants ranking it last. One stated "*Optimisation is like a black-box and I don't trust any black-box.*" Others also pointed out the importance of manual adjustment. We also heard many times that clinicians will very rarely accept a treatment plan from optimisation without any changes and more often than not they would like to make some manual adjustment to the plan.

In Study 1, experience with the tool for whole gland planning did not appear to increase or decrease participants' level of trust in interactive optimisation. However, it is a different story for focal therapy (see Fig. 10). Participants were asked 'If both focal brachytherapy and whole gland brachytherapy were available which would you prefer to use? Why?' at the very start and the very end of the interview. At the start of the study, 5 of 8 participants preferred whole gland therapy, another two preferred the combination of whole gland and focal therapy and only one preferred focal therapy. By the end of the study, 3 of the 5 who preferred whole gland therapy changed their minds: one preferred focal therapy and the other preferred the combination. The participants who preferred either the combination or focal therapy did not change their answers. One participant who changed their preference from whole gland therapy into focal therapy stated after using the tool that providing extra information about prostate tumour cells from TCD visualisation was really useful and she had become used to seeing the TCP contours. This is a strong indication that experience with the interactive planning tool and the planning exercises did increase participants' trust in focal therapy.

Aim 4 (Feedback on the design of the prototype interactive optimisation tool) was addressed in the Recap Activity and by observations of tool use in the Planning Activity.

There were few suggestions, suggesting they were now comfortable with the design of the tool and visualisations. Some participants suggested overlaying the TCP contours with the TCD visualisation, and the isodose contours with the TCD visualisation in order to better support the visual representation of a focal plan. We made the suggested changes and used them in the subsequent studies. When modifying plans they used *Add* (a seed), *Remove* (a seed) and *Steer* (a needle) but did not use *Lock & Re-optimise*. When queried about Lock & Re-optimise most responded it would be useful and some of them gave situations where it could be used such as in early stage of planning after loading seeds from templates to adjust the plan followed by manual fine-tuning using the other operations afterwards.

9 Conclusions

We have explored the relationship between visual analytics and interactive optimisation and developed a new theoretical framework for understanding the high-level user goals and tasks in interactive optimisation called the problem-solving loop that is modelled on the sense-making loop framework widely used in visual analytics.

Our other contribution was two studies providing an in-depth analysis of the potential use of interactive optimisation for treatment planning in whole-gland and focal LDR prostate brachytherapy. Our first study fed into the design of the problem-solving loop and also allowed us to refine the design of a prototype interactive optimisation tool for treatment planning.

The second study suggested that interactive optimisation did build trust in focal therapy and found that radiation oncology professionals overwhelmingly prefer to use interactive optimisation to create focal therapy treatment plans. These two studies, as well as the design and implementation of the prototype interactive optimisation tool we used in the studies, add significantly to our body of knowledge about the potential use of interactive optimisation in real-world applications and how to integrate interactive visualisation into such tools.

A limitation of the current research is that it is restricted to a single use-case of a visual analytics approach to interactive optimisation design and evaluation. This was unavoidable given that it was a deep study representing two years of close collaboration with domain experts. Further research is needed to verify applicability of the problem-solving loop in other application domains.

Another limitation of the study was that our prototype tool was not used by domain experts in actual clinical practice. Again this was unavoidable given that the tool and the focal treatment have not been clinically tested and health professionals are understandably conservative in their adoption of new tools and techniques. Future work will be to continue development of the tool with the aim to undertake clinical testing. We believe it is in precisely such high-consequence domains that visual analytics based interactive optimisation can have a significant impact by keeping the human experts intimately "in the loop".

Our research is only a first step in studying interactive optimisation from a visual analytics perspective. We believe this is a new and fruitful research direction that will allow interactive optimisation applications to benefit from visual analytics research into interactive visualisation and analytics and provide visual analytics with a new and important application field. This is an opportunity for visual analytics to broaden its scope and application domain to other aspects of decision making.

Acknowledgments

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References

[1] A. Agarwala, M. Dontcheva, M. Agrawala, S. Drucker, A. Colburn, B. Curless, D. Salesin, and M. Cohen. Interactive digital photomontage. In *ACM Transactions on Graphics (TOG)*, vol. 23, pp. 294–302. ACM, 2004.

[2] M. Ai-Chang, J. Bresina, L. Charest, A. Chase, J. C.-J. Hsu, A. Jonsson, B. Kanefsky, P. Morris, K. Rajan, J. Yglesias, et al. Mapgen: Mixed-initiative planning and scheduling for the Mars Exploration Rover mission. *Intelligent Systems, IEEE*, 19(1):8–12, 2004.

[3] M. Andersen, S. Kleindienst, L. Yi, J. Lee, M. Bodart, and B. Cutler. An intuitive daylighting performance analysis and optimization approach. *Building Research & Information*, 36(6):593–607, 2008.

[4] D. Anderson, E. Anderson, N. Lesh, J. Marks, B. Mirtich, D. Ratajczak, and K. Ryall. Human-guided simple search. In *AAAI/IAAI*, pp. 209–216, 2000.

[5] G. Bailly, A. Oulasvirta, T. Kötzing, and S. Hoppe. Menuoptimizer: Interactive optimization of menu systems. In *Proceedings of the 26th annual ACM symposium on User interface software and technology*, pp. 331–342. ACM, 2013.

[6] J. Bénabes, F. Bennis, E. Poirson, and Y. Ravaut. Interactive optimization strategies for layout problems. *International Journal on Interactive Design and Manufacturing (IJIDeM)*, 4(3):181–190, 2010.

[7] W. Berger, H. Piringer, P. Filzmoser, and E. Gröller. Uncertainty-aware exploration of continuous parameter spaces using multivariate prediction. In *Computer Graphics Forum*, vol. 30, pp. 911–920. Wiley Online Library, 2011.

[8] Y. Boykov and M.-P. Jolly. Interactive organ segmentation using graph cuts. In *Medical Image Computing and Computer-Assisted Intervention*, pp. 276–286. Springer, 2000.

[9] R. Brecheisen, B. Platel, A. Vilanova, and B. ter Haar Romeny. Parameter sensitivity visualization for DTI fiber tracking. *IEEE Transactions on Visualization and Computer Graphics*, 15(6):1441–1448, 2009.

[10] J. L. Bresina, A. K. Jónsson, P. H. Morris, and K. Rajan. Activity planning for the Mars Exploration Rovers. In *ICAPS*, pp. 40–49, 2005.

[11] A. M. Brintrup, J. Ramsden, and A. Tiwari. An interactive genetic algorithm-based framework for handling qualitative criteria in design optimization. *Computers in Industry*, 58(3):279–291, 2007.

[12] E. Brochu, T. Brochu, and N. de Freitas. A Bayesian interactive optimization approach to procedural animation design. In *Proceedings of the 2010 ACM SIGGRAPH/Eurographics Symposium on Computer Animation*, pp. 103–112. Eurographics Association, 2010.

[13] S. Bruckner and T. Moller. Result-driven exploration of simulation parameter spaces for visual effects design. *IEEE Transactions on Visualization and Computer Graphics*, 16(6):1468–1476, 2010.

[14] K. A. Butler, J. Zhang, C. Esposito, A. Bahrami, R. Hebron, and D. Kieras. Work-centered design: A case study of a mixed-initiative scheduler. In *Proceedings of the SIGCHI conference on Human factors in computing systems*, pp. 747–756. ACM, 2007.

[15] D. Coffey, C.-L. Lin, A. G. Erdman, and D. F. Keefe. Design by dragging: An interface for creative forward and inverse design with simulation ensembles. *IEEE transactions on visualization and computer graphics*, 19(12):2783–2791, 2013.

[16] K. A. Cook and J. J. Thomas. *Illuminating the Path: The Research and Development Agenda for Visual Analytics*. IEEE Computer Society, Los Alamitos, CA, 2005.

[17] D. Cosley, S. K. Lam, I. Albert, J. A. Konstan, and J. Riedl. Is seeing believing? How recommender system interfaces affect users' opinions. In *Proceedings of the SIGCHI conference on Human factors in computing systems*, pp. 585–592. ACM, 2003.

[18] M. L. Cummings, J. J. Marquez, and N. Roy. Human-automated path planning optimization and decision support. *International Journal of Human-Computer Studies*, 70(2):116–128, 2012.

[19] A. Diehl, L. Pelorosso, C. Delrieux, C. Saulo, J. Ruiz, M. E. Gröller, and S. Bruckner. Visual analysis of spatio-temporal data: Applications in weather forecasting. In *Computer Graphics Forum*, vol. 34, pp. 381–390. Wiley Online Library, 2015.

[20] A. Glass, D. L. McGuinness, and M. Wolverton. Toward establishing trust in adaptive agents. In *Proceedings of the 13th international conference on Intelligent user interfaces*, pp. 227–236. ACM, 2008.

[21] S. Goodwin, C. Mears, T. Dwyer, M. G. de la Banda, G. Tack, and M. Wallace. What do constraint programming users want to see? Exploring the role of visualisation in profiling of models and search. *IEEE Transactions on Visualization and Computer Graphics*, 23(1):281–290, 2017.

[22] J. L. Harman, J. O'Donovan, T. Abdelzaher, and C. Gonzalez. Dynamics of human trust in recommender systems. In *Proceedings of the 8th ACM Conference on Recommender systems*, pp. 305–308. ACM, 2014.

[23] A. Haworth, M. Ebert, D. Waterhouse, D. Joseph, and G. Duchesne. Prostate implant evaluation using tumour control probability — The effect of input parameters. *Physics in medicine and biology*, 49(16):3649, 2004.

[24] A. Haworth, C. Mears, J. M. Betts, H. M. Reynolds, G. Tack, K. Leo, S. Williams, and M. A. Ebert. A radiobiology-based inverse treatment planning method for optimisation of permanent I-125 prostate implants in focal brachytherapy. *Physics in medicine and biology*, 61(1):430, 2015.

[25] A. Haworth, S. Williams, H. Reynolds, D. Waterhouse, G. M. Duchesne, J. Bucci, D. Joseph, S. Bydder, and M. Ebert. Validation of a radiobiological model for low-dose-rate prostate boost focal therapy treatment planning. *Brachytherapy*, 12(6):628–636, 2013.

[26] C. V. Jones. Visualization and optimization. *ORSA Journal on Computing*, 6(3):221–257, 1994.

[27] A. Kapoor, B. Lee, D. Tan, and E. Horvitz. Interactive optimization for steering machine classification. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*, pp. 1343–1352. ACM, 2010.

[28] D. A. Keim, J. Kohlhammer, G. Ellis, and F. Mansmann. *Mastering the Information Age: Solving Problems with Visual Analytics*. Eurographics Association, 2010.

[29] J. B. Kollat and P. Reed. A framework for Visually Interactive Decision-making and Design using Evolutionary Multi-objective Optimization (VIDEO). *Environmental Modelling & Software*, 22(12):1691–1704, 2007.

[30] S. Langley, H. U. Ahmed, B. Al-Qaisieh, D. Bostwick, L. Dickinson, F. G. Veiga, P. Grimm, S. Machtens, F. Guedea, and M. Emberton. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. *BJU international*, 109(s1):7–16, 2012.

[31] D. Meignan, S. Knust, J.-M. Frayret, G. Pesant, and N. Gaud. A review and taxonomy of interactive optimization methods in operations research. *ACM Transactions on Interactive Intelligent Systems (TiiS)*, 5(3):17, 2015.

[32] K. Miettinen. Survey of methods to visualize alternatives in multiple criteria decision making problems. *OR spectrum*, 36(1):3–37, 2014.

[33] J. Nocedal and S. J. Wright. *Numerical Optimization*. Springer, New York, 1999.

[34] M. Nunes, B. Rowland, M. Schlachter, S. Ken, K. Matkovic, A. Laprie, and K. Bühler. An integrated visual analysis system for fusing MR spectroscopy and multi-modal radiology imaging. In *Visual Analytics Science and Technology (VAST), 2014 IEEE Conference on*, pp. 53–62. IEEE, 2014.

[35] J. Patten and H. Ishii. Mechanical constraints as computational constraints in tabletop tangible interfaces. In *Proceedings of the SIGCHI conference on Human factors in computing systems*, pp. 809–818. ACM, 2007.

[36] W. Pieters. Explanation and trust: What to tell the user in security and AI? *Ethics and information technology*, 13(1):53–64, 2011.

[37] R. G. Raidou, O. Casares-Magaz, L. P. Muren, U. A. Van der Heide, J. Rørvik, M. Breeuwer, and A. Vilanova. Visual analysis of tumor control models for prediction of radiotherapy response. In *Computer Graphics Forum*, vol. 35, pp. 231–240. Wiley Online Library, 2016.

[38] M. T. Ribeiro, S. Singh, and C. Guestrin. "Why should I trust you?": Explaining the predictions of any classifier. In *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, pp. 1135–1144. ACM, 2016.

[39] C. Rother, V. Kolmogorov, and A. Blake. Grabcut: Interactive foreground extraction using iterated graph cuts. In *ACM transactions on graphics (TOG)*, vol. 23, pp. 309–314. ACM, 2004.

[40] K. Savla, T. Temple, and E. Frazzoli. Human-in-the-loop vehicle routing policies for dynamic environments. In *Decision and Control, 2008. CDC 2008. 47th IEEE Conference on*, pp. 1145–1150. IEEE, 2008.

[41] S. D. Scott, N. Lesh, and G. W. Klau. Investigating human-computer optimization. In *Proceedings of the SIGCHI conference on Human factors in computing systems*, pp. 155–162. ACM, 2002.

[42] M. Sedlmair, C. Heinzl, S. Bruckner, H. Piringer, and T. Möller. Visual parameter space analysis: A conceptual framework. *IEEE Transactions on Visualization and Computer Graphics*, 20(12):2161–2170, 2014.

[43] M. Shibuya, H. Kita, and S. Kobayashi. Integration of multi-objective and interactive genetic algorithms and its application to animation design. In *Systems, Man, and Cybernetics, 1999. IEEE SMC'99 Conference Proceedings. 1999 IEEE International Conference on*, vol. 3, pp. 646–651. IEEE, 1999.

[44] H. Takagi. Interactive evolutionary computation: Fusion of the capabilities of EC optimization and human evaluation. *Proceedings of the IEEE*,

89(9):1275–1296, 2001.

[45] C. Thieke, K.-H. Küfer, M. Monz, A. Scherrer, F. Alonso, U. Oelfke, P. E. Huber, J. Debus, and T. Bortfeld. A new concept for interactive radiotherapy planning with multicriteria optimization: First clinical evaluation. *Radiotherapy and Oncology*, 85(2):292–298, 2007.

[46] T. Torsney-Weir, A. Saad, T. Moller, H.-C. Hege, B. Weber, J.-M. Verbavatz, and S. Bergner. Tuner: Principled parameter finding for image segmentation algorithms using visual response surface exploration. *IEEE Transactions on Visualization and Computer Graphics*, 17(12):1892–1901, 2011.

[47] A. Uğur and D. Aydin. An interactive simulation and analysis software for solving TSP using Ant Colony Optimization algorithms. *Advances in Engineering software*, 40(5):341–349, 2009.

[48] W. van Wezel and R. Jorna. Cognition, tasks and planning: Supporting the planning of shunting operations at the Netherlands Railways. *Cognition, Technology & Work*, 11(2):165–176, 2009.

[49] C. Zeidler, C. Lutteroth, W. Sturzlinger, and G. Weber. The Auckland Layout Editor: An improved GUI layout specification process. In *Proceedings of the 26th annual ACM symposium on User interface software and technology*, pp. 343–352. ACM, 2013.