UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VARIAN MEDICAL SYSTEMS, INC.,
Petitioners

v.

BEST MEDICAL INTERNATIONAL, INC.,
Patent Owner

Case IPR2020-0077
U.S. Patent No. 7,266,175
Issue Date: September 4, 2007

Title: PLANNING METHOD FOR RADIATION THERAPY

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,266,175

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List of Exhibits

Exhibit No.	Description of Document
1001	U.S. Patent No. 7,266,175 B1 to Merle Romesberg (filed July 9, 2004, issued September 4, 2007) ("'175" or "'175 patent")
1002	Declaration of Timothy Solberg, Ph.D.
1003	Spiridon V. Spirou, et al., *Smoothing Intensity-Modulated Beam Profiles to Improve the Efficiency of Delivery*, 28 Med. Phys. 2105 (2001) ("Spirou")
1004	Mark Langer, et al*., Improved Leaf Sequencing Reduces Segments or Monitor Units Needed to Deliver IMRT Using Multileaf Collimators*, 28 Med. Phys. 2450 (2001) ("Langer")
1005	*The Physics of Three-Dimensional Radiation Therapy: Conformal Radiotherapy, Radiosurgery and Treatment Planning*. (1993) ("Webb 1993")
1006	"Incorporating multi-leaf collimator leaf sequencing into iterative IMRT optimization," *American Association Physical Medicine* (June 2002) ("Siebers")
1007	Amendment and Response to Office Action Dated October 25, 2006 ("01/30/2007 Response")
1008	Amendment and Response to Office Action Dated May 3, 2006 filed in U.S. Appl. 10/887,966 dated August 7, 2006 ("08/07/2006 Response")
1009	Declaration of Mark P. Carol submitted re U.S. Appl. No. 10/887,966, dated January 2007 ("Carol Decl.")
1010	U.S. Patent 6,393,096 to Mark P. Carol et al. (filed May 27, 1999,

Exhibit No.	Description of Document
	issued May 21, 2002)
1011	Hall-Ellis Declaration
1012	U.S. Patent 6,038,283 to Mark P. Carol et al. (filed October 24, 1997, issued March 14, 2000) ("'283 Patent")
1013	"IMRT: Where We Are Today," *The Theory and Practice of Intensity Modulated Radiation Therapy* (1997) ("Carol Textbook")
1014	S. Webb, *Optimization of conformal radiotherapy dose distributions by simulated annealing: 2. Inclusion of scatter in the 2D technique* ("Webb 1991")
1015	William Que, *Comparison of Algorithms For Multileaf Collimator Field Segmentation*, 26 Med. Phys. 2390 ("Que")
1016	Notice of Allowability filed in U.S. Appl. 10/887,966 dated April 30, 2007
1017	S. Webb, *Intensity-Modulated Radiation Therapy*, (2001) ("Webb 2001")

Petitioner Varian Medical Systems, Inc. ("Petitioner") respectfully submits this Petition for Inter Partes Review of claims 13-16, 18, and 19 of U.S. Patent No. 7,266,175 **[Ex. 1001]** ("the '175 patent").

I. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(A)(1)

A. Real Party-In-Interest Under 37 C.F.R. §42.8.(b)(1)

In addition to Petitioner Varian Medical Systems, Inc., VMS International AG, VMS International Holdings, Inc., VMS Netherlands Holdings, Inc., and VMS Nederland BV are real parties-in-interest.

B. Related Matters Under 37 C.F.R. §42.8(b)(2)

The '175 patent is the subject of one pending litigation involving Petitioner: *Best Medical International, Inc. v. Varian Medical Systems, Inc.*, Case No. 1:18-cv-01599-UNA (D. Del. Oct. 16, 2018). Petitioner was served with a complaint in that action on October 18, 2018.

Petitioner filed a petition for *inter partes* review of the '175 patent on October 17, 2019 (IPR2020-00053).

C. Lead and Back-Up Counsel under 37 C.F.R. §42.8(b)(3)

Petitioner provides the following designation of counsel.

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D. Service Information

This Petition is being served by Federal Express to the attorney of record for the '175 patent, Best Medical International, Inc., Patent Counsel, 7643 Fullerton Road, Springfield, VA 22153. Petitioner consents to electronic service at the addresses provided above for lead and back-up counsel.

II. FEE PAYMENT

Petitioner requests review of twelve claims, with a $30,500 payment.

III. REQUIREMENTS UNDER 37 C.F.R. §§ 42.104 AND 42.108

A. Grounds for Standing

Petitioner certifies that the '175 patent is available for IPR and that Petitioner is not barred or otherwise estopped.

B. Identification of Challenge and Statement of Precise Relief Requested

The Petitioner requests institution of IPR based on:

Ground	Claims	Basis for Challenge under §103(a)
1	1, 4, 13-14, 18	Spirou (Ex. 1003)
2	1, 3-5, 8-9, 13-16, 18-19	Siebers (Ex. 1006), Langer (Ex. 1004), Spirou

Submitted with this Petition is the Declaration of Dr. Timothy Solberg (Ex.

1002), a qualified expert. (Solberg, ¶¶1-8, Ex. A.)

C. Considerations under §§ 325(d) and 314(a)

This Petition does not present a situation in which "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

Nor should the Board exercise its discretionary authority to decline to consider this Petition under §314(a) or *General Plastics*. On October 17, 2019 (one-day prior), the Petitioner filed an IPR petition (IPR2020-00053) challenging claims 13-16 and 19 of the '175 patent based on different grounds from the ones presented here. The grounds proposed in IPR2020-00053 rely on the primary reference Webb 2001 (Ex. 1017). Ground 1 in the present Petition relies instead on the primary reference Spirou. The references provide complementary theories for showing the obviousness of the challenged claims by meeting the key limitation of an "objective cost function" that includes a "dosimetric cost term" as well as a "delivery cost term" in different ways. Specifically, Webb 2001 teaches a claimed "delivery cost term" in the form of

$\boxed{w_3[w_1 S_+ - w_2 F_{\min}].}$, whereas the "delivery cost term" in

Spirou takes the form of $\boxed{\sum_{j \in \text{beams}} w_j(x_j' - x_j)^2,}$. As evident from their respective mathematical formulations, and shown below, they each operate to drive solutions with enhanced delivery efficiency in different ways.

During the prosecution of the ’175 patent, the Applicant placed much importance on the assertion that the ’175 patent was the first to include a delivery cost term together with a dosimetric cost term in a single cost function:

> The impetus for the [’175] patent was to propose for the first time the concept of giving the user the ability to control… the competing needs of conformality/avoidance (dosimetric fitness) and efficiency. Previously, cost functions… only considered dosimetry: that is how close the actual dose distribution, created by the optimization system, is to the desired dose distribution as entered by the user.”

(Ex. 1009, Carol Decl. at 4, paragraphs 6a3-6a4.) Given that the alleged inventiveness of the ’175 patent hinges on the inclusion of a delivery cost term in a cost function, Petitioner respectfully submits that both Webb and Spirou should be evaluated on their merits because together, they demonstrate that not only was the allegedly inventive concept already identified in the prior art, but in fact, different implementations had been independently developed. As the Federal Circuit has explained: “Independently made, simultaneous inventions, made within a comparatively short space of time, are persuasive evidence that the claimed apparatus was the product only of ordinary mechanical or engineering skill." *George RR Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010).

Moreover, the present Petition includes a second ground based on Siebers, Langer, and Spirou, which as shown below, provide yet additional evidence that the '175 patent contains no leap of inventiveness deserving of patentability.

Additionally, besides claims 13-16 and 19, this Petition challenges claims 1, 3-5, 8-9, and 18. The petition for IPR2020-00053 only challenges claims 13-16 and 19, which Plaintiff BMI asserted in its infringement contentions served on August 30, 2019 in the pending district court litigation. That is, the Petition presented here challenges 7 additional claims. "[D]iffering claim sets is a factor that weighs against exercise of [the Board's] discretion under § 314(a)." *3Shape A/S v. Align Tech.*, Case IPR2019-00160, Paper 9 at 39 (PTAB June 11, 2019). Petitioner is aware of no other IPR petitions with respect to the '175 patent. To the extent the Board grants only one of the two Petitions, Petitioner identifies the previously filed IPR2020-00053 as the preferred Petition for institution.

IV. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill as of July 2003 would be a medical physicist with a Ph.D. (or similar advanced degree) in physics, medical physics, or a related field, and two or more years of experience in radiation oncology physics treatment planning, treatment plan optimization related to radiation oncology applications, and computer programming associated with treatment plan optimization (or equivalent degree or experience). (Solberg, ¶13.)

V. TECHNOLOGY BACKGROUND

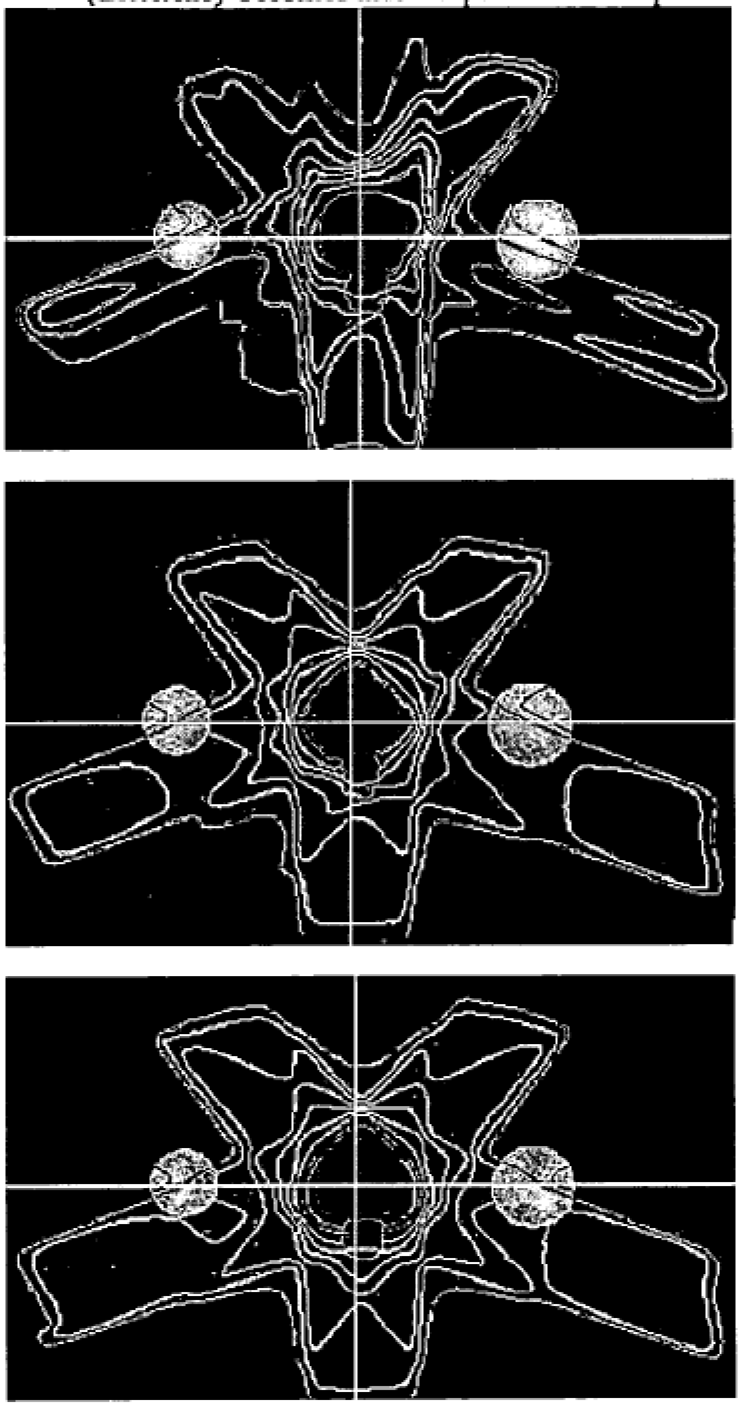
Dr. Solberg has provided an overview of the technology relevant to the ’175 patent. (Solberg, ¶¶24-32.)

VI. SUMMARY OF THE ’175 PATENT

The ’175 patent is entitled “Planning Method for Radiation Therapy,” and purports to provide a “[m]ethod and apparatus for controlling the correlation between the factors of treatment plan efficiency and dosimetric fitness” to optimize a radiotherapy plan. (’175, Abstract.)

The tradeoff between dosimetric fitness and delivery efficiency in treatment plans is illustrated in the “dose distribution intensity maps” shown in Figures 2A-2C and 4A-4C:

(Efficiency becomes more important from top to bottom):



Dosimetric Cost = 0.453
Segment Count = 97

FIG. 2A.

Dosimetric Cost = 0.653
Segment Count = 37

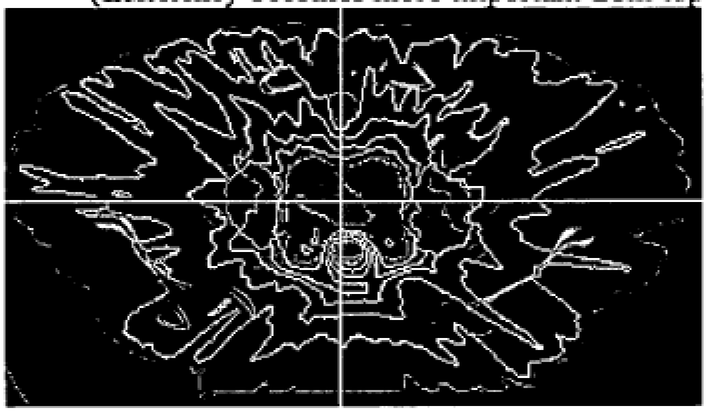
FIG. 2B.

Dosimetric Cost = 1.26
Segment Count = 5

FIG. 2C.

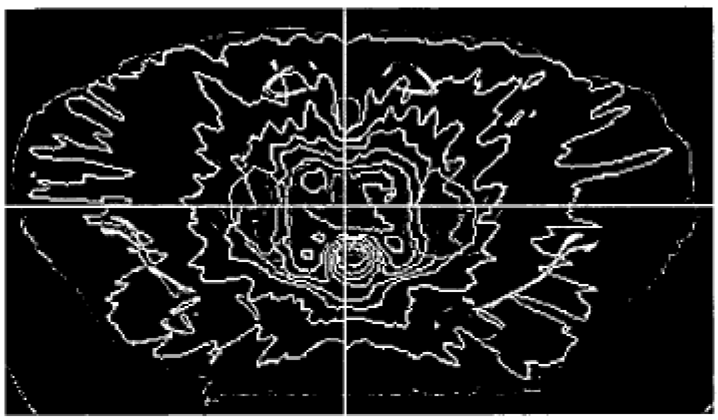
('175, Figs. 2A-2C; *see also id.*, 1:66-67 ("FIGS. 2A-2C are dose distribution intensity maps for three different radiotherapy plans;").)

(Efficiency becomes more important from top to bottom):



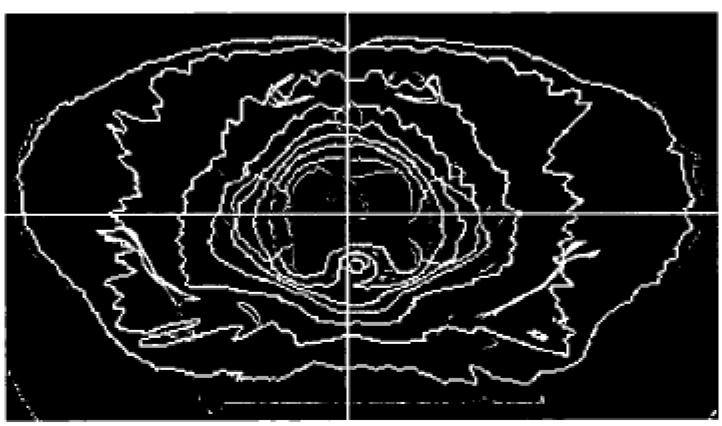
Dosimetric Cost = 0.132
Total Monitor Units = 22365

FIG. 4A.



Dosimetric Cost = 0.149
Total Monitor Units = 15624

FIG. 4B.



Dosimetric Cost = 1.94
Total Monitor Units = 6640

FIG. 4C.

(*Id.*, Figs. 4A-4C; *see also id.*, 2:3-4 ("FIGS. 4A-4C are dose distribution intensity maps for three different radiotherapy plans;").)

The '175 patent states that a user can control the tradeoff between dosimetric fitness and delivery efficiency, by controlling the number of MLC segments in a treatment plan and similarly, controlling the number of monitor units (MUs). ('175, 1:36-47.)[1] As noted in the '175 patent, the number of monitor units is proportional to the radiation "beam on" time. ('175, 2:28-35.)

VII. CLAIM CONSTRUCTION

For purposes of this Petition, Petitioner identifies the following terms. For claim terms not identified, Petitioner has applied the plain and ordinary meaning of those terms.

A. "optimizer"

The term "**optimizer**" appears in a number of claims of the '175 patent. For example, independent claim 11 recites "selecting <u>one of the plurality of algorithms</u> to be <u>the optimizer</u>." ('175, 5:64-65.) Consistent with how the term is used in claim 11, an "**optimizer**" would have been understood by persons of ordinary skill in the context of the '175 patent to refer to a form of an <u>**algorithm**</u> used for treatment planning. (Solberg, ¶40.)

The Applicant during prosecution further provided the following explanation on the operation of an "**optimizer**":

---

[1] All underlining, italics, and annotations has been added by Petitioner unless noted otherwise.

> [T]he delivery cost term is not a term quantified directly by the clinician to allow the clinician to determine how fast the plan can be delivered, but one used by *the optimizer* to evaluate each potential intensity pattern to thereby determine the optima (best value) of the objective function to determine a beam arrangement (between a continuum of dosimetric fitness and delivery efficiency) to be presented to the clinician during *the iterative optimization process*."

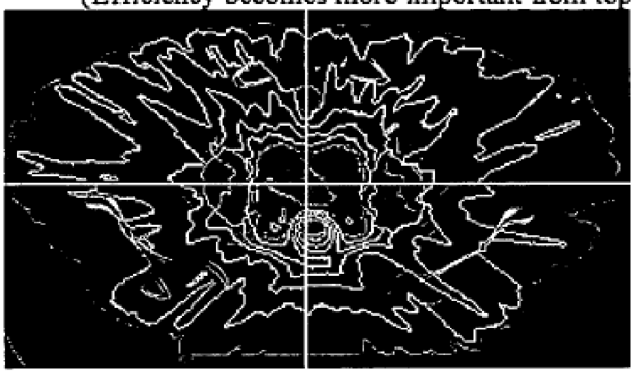
(Ex. 1007, 01/30/2007 Response, at 9; *see also* Ex. 1008, 08/07/2006 Response (similar), at 12; Ex. 1009, Carol Decl. at 4, ¶6a5 (similar).)

An "**optimizer**" is thus also an **iterative** process, as the above passage makes clear. The passage's description of an "**optimizer**" as involving the use of a "delivery cost term" and an "objective function" is consistent with the recitation of an "**optimizer**" in claims 13 and 19. Claim 13 recites "assigning a delivery cost term within an optimizer." Claim 19 likewise recites "evaluating an objective cost function within an optimizer." Accordingly, the term "**optimizer**" should be interpreted to mean an "**iterative optimization algorithm**."

B. "intensity map"

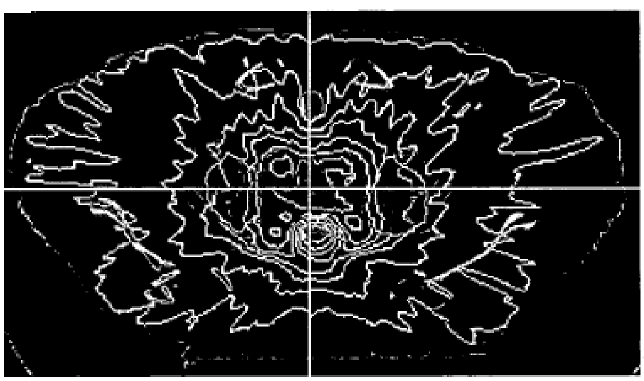
As explained by Dr. Solberg, the term "**intensity map**" in intensity modulated radiation therapy ("IMRT") typically refers to the intensity or "fluence" profile of a *single* radiation beam in a multi-beam arrangement. (Solberg, ¶¶44-45 (citing Ex. 1013).) In the traditional context, an intensity map is used to describe properties of a single beam, but obviously cannot provide information about the dosimetric fitness of the dose distribution of all beams. But the '175 patent uses "**intensity map**" in a different way. The '175 patent purports to show "dose distribution intensity maps" in Figures 2A-2C, 4A-4C, 7, and 8. ('175, 1:66-67, 2:3-4, 2:10-11, 2:11-12.) Some of these figures are reproduced below:

(Efficiency becomes more important from top to bottom):



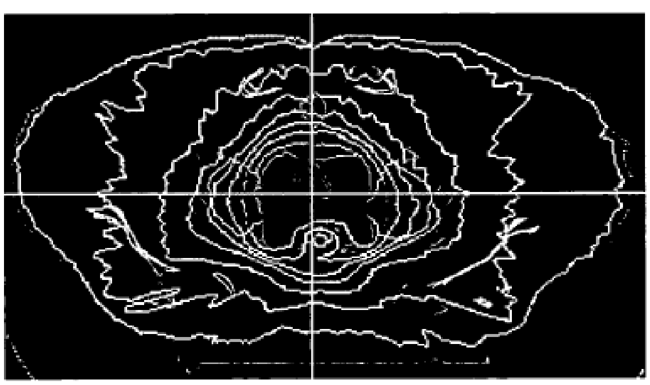
Dosimetric Cost = 0.132
Total Monitor Units = 22365

FIG. 4A.



Dosimetric Cost = 0.149
Total Monitor Units = 15624

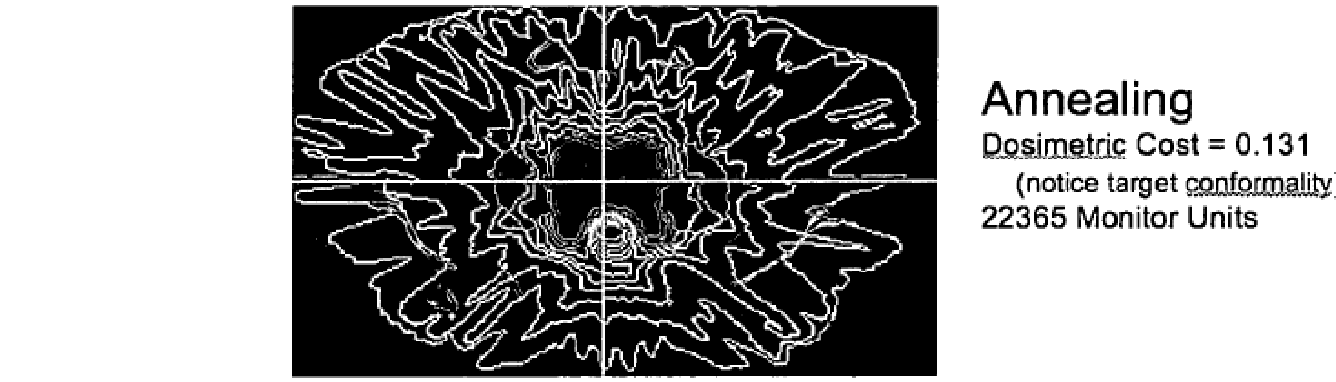
FIG. 4B.



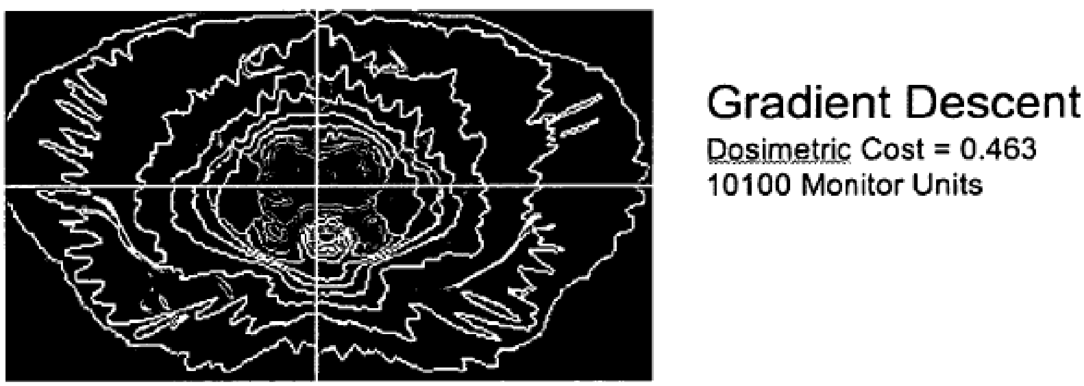
Dosimetric Cost = 1.94
Total Monitor Units = 6640

FIG. 4C.

('175, Figs. 4A-4C.)



('175, Fig. 7.)

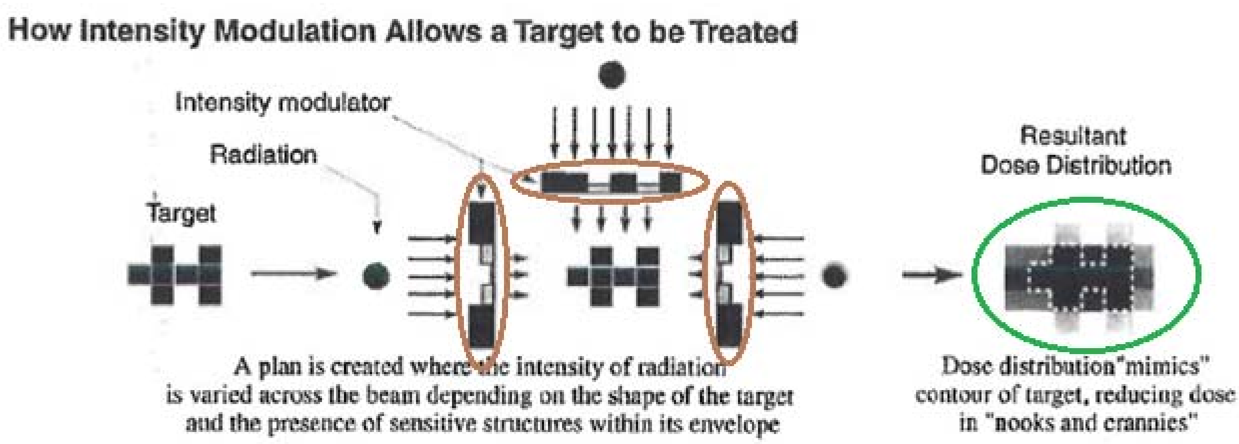


('175, Fig. 8.)[2]

Contrary to typical usage, in which an "**intensity map**" represents the *intensity profile* of a *single beam*, an "**intensity map**" as used in the '175 patent

[2] As explained by Dr. Solberg, the jagged lines shown are known as "isodose" lines, and each line traces through locations that all have the same dose, hence the term "iso" dose. (Solberg, ¶48 n.1.)

represents the resultant *dose distribution* created by *multiple beams* positioned around the target. (Solberg, ¶¶47-48.) This can be readily appreciated by comparing the above figures from the '175 patent to the figure below, taken from a textbook chapter written by Carol:



(Ex. 1013 at 19 (Fig. 1) (partial figure).)

Therefore, consistent with the figures showing "dose distribution intensity maps" provided in the '175 patent, and the detailed description of use of intensity maps to evaluate dosimetric fitness of a treatment plan, the term "**intensity map**" should be construed to mean a "**representation of dose distribution**." As the Federal Circuit has explained, "a claim term may be clearly redefined without an explicit statement of redefinition and even when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents." *Trustees of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1364

(Fed. Cir. 2016) (brackets, quotation marks and citation omitted). (Solberg, ¶¶49-55.)

Petitioner is mindful that the Board "need only construe the claims to the extent necessary to determine whether to institute *inter partes* review." *Abbott Vascular, Inc. v. FlexStent, LLC*, IPR2019-00882, Paper 11 at 5 (P.T.A.B. Oct. 7, 2019) (citing *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017)). The Board thus need not explicitly adopt Petitioner's construction to evaluate how the prior art has been applied to the claims, *see Oatey Co. v. IPS Corp*, 514 F.3d 1271, 1276 (Fed. Cir. 2008) – ***unless*** the Patent Owner attempts to distinguish the prior art by relying on an interpretation of "intensity map" (either express or implied) that reads out the construction proposed by Petitioner.

VIII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

This Petition presents two Grounds of obviousness. Ground 1 relies on Spirou. Ground 2 relies separately on Siebers, Langer, and Spirou.

A. Prior Art and Date Qualification for Ground 1

Ground 1 addresses claims 1, 4, 13-14, and 18 and as noted, relies on Spirou, briefly summarized below.

1. Spirou [Ex. 1003]

Spirou is an article entitled "Smoothing Intensity-Modulate Beam Profiles to Improve the Efficiency of Delivery" from the scientific journal *Medical Physics*.

Spirou qualifies as prior art under §102(b). (Ex. 1011, Declaration of Sylvia Hall-Ellis ("Hall-Ellis"), ¶¶42-47.)

Smoothing refers to "remov[ing] random (high spatial frequency) fluctuations" in a beam profile while "preserving the essential features of the profile (peaks, valleys, and gradients) that produce the optimum dose distribution." (Spirou, at 2106.) (Solberg ¶59.)

Spirou compares two algorithms for "smoothing" beam profiles. The second approach, called Method B and used in Petitioner's mapping, includes the "term within the algorithm's objective function that specifies the smoothness of the profiles as an optimization criterion." (Spirou, at 2105; Solberg, ¶60.) The objective function within the optimization process including the "beam profile smoothness" is defined by Spirou as Eq. (3):

$$F_{\mathrm{obj}} = \sum_{i \in \mathrm{targets}} w_i (d_i - d_p)^2 + \sum_{i \in \mathrm{organs}} w_i \zeta_i (d_i - d_c)^2 + \sum_{j \in \mathrm{beams}} w_j (x_j' - x_j)^2, \tag{3}$$

where x_j' is given by Eq. (1).

(Spirou, at 2107.) In this objective cost function, which includes cost terms for dosimetric fitness and delivery efficiency, "d_i and w_i are the dose and weight of the ith point, d_p is the prescription dose, d_c is the constraint dose, and ζ_i is a flag indicating whether the constraint is violated" and "x'_j is given by Eq. (1)." (Spirou, at 2106-2107.) "The first term is summed over the points in the targets, and the second over the points in the critical organs" and "the 'unsmoothness' of the profile negatively affects the cost function, so that its dosimetric effect is incorporated in the optimization process." (Spirou, at 2106.) Method B "allows multiple minimum-dose, maximum-dose as well as dose-volume constraints to be defined for any structure, each with varying penalty weights." (*Id.*; Solberg, ¶¶60-65.)

B. Ground 1: Claims 1, 4, 13-14, and 18 Over Spirou

1. Claim 1: "A method of determining a radiation beam arrangement, the method comprising the steps of:" (Claim 1[preamble])

To the extent the preamble of claim 1 is limiting, it is fully disclosed and rendered obvious by Spirou.

The '175 patent incorporates by reference U.S. Patent No. 6,038,283 (the "'283 Patent"), which explains that "an optimized treatment plan, or beam arrangement" "should be understood to include either the optimal beam positions around the treatment field, the optimal array of beam weights, or beam intensities, otherwise known as an intensity map or a fluence profile or both." ('283, 9:29-34.)

IMRT typically consists of at least two calculations: (1) development of a desired dosage map to target cancerous tissue in a patient with radiation beams without hitting non-cancerous surrounding tissue, and (2) determination of a leaf sequence on a multileaf collimator machine that is able to administer that desired dosage map on a patient.

Spirou's Method B defines a cost function that focuses on the first calculation. The "beam profiles" of Method B are desired dosage maps, and the algorithm "smooths" those beam profiles by "remov[ing] random (high spatial frequency) fluctuations" in a beam profile while "preserving the essential features of the profile (peaks, valleys, and gradients) that produce the optimum dose distribution." (Spirou 2106; Solberg, ¶78.) The smoothed beam profiles generated by Spirou's Method B provide "a final dose calculation" that can be administered to a patient. (Spirou, at 2105, 2107; Solberg, ¶78.)

The "**radiation beam arrangement**" of claim 1 are the smoothed "beam profiles" resulting from implementation of Spirou's Method B.

(a) "receiving prescription parameters for a patient target; and" (Claim 1[a])

The methods described by Spirou use "the treatment planning system developed at MSKCC."[3] (Spirou, at 2106.) Spirou details that "[t]he optimization algorithm used at MSKCC employs a dose-volume-based quadratic objective function" that evaluates the difference between the actual and prescribed dose for given points within the target and other organs. (Spirou, at 2106.) The algorithms

[3] MSKCC stands for Memorial Sloan Kettering Cancer Center.

described by Spirou require the use of a "prescription dose" for the target ("d_p" in the cost function) and a constraint dose ("d_c" for organs-at-risk such as the spinal cord). (Spirou 2106-2107.) These are "prescription parameters for a patient target." (Solberg, ¶80.)

(b) "evaluating a cost function for each of a set of a plurality of candidate intensity maps formed responsive to the prescription parameters to provide control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness, the cost function including a dosimetric cost term representing dosimetric cost and related to dosimetric fitness of the respective candidate intensity map and a delivery cost term representing delivery cost and related to delivery time to deliver radiation according to a beam arrangement represented by the respective candidate intensity map, the evaluation of the delivery cost term for each respective candidate intensity map having linear computational complexity with respect to the size of the respective candidate intensity map." (Claim 1[b])

"evaluating a cost function for each of a set of a plurality of candidate intensity maps formed responsive to the prescription parameters"

The cost function of Spirou Method B is the "dose-volume-based quadratic objective function" used within the iterative optimization process. (Spirou at 2106.) This objective function is:

$$F_{\mathrm{obj}} = \boxed{\sum_{i \in \mathrm{targets}} w_i (d_i - d_p)^2} + \boxed{\sum_{i \in \mathrm{organs}} w_i \zeta_i (d_i - d_c)^2}$$

$$+ \sum_{j \in \mathrm{beams}} w_j (x'_j - x_j)^2, \qquad (3)$$

where x'_j is given by Eq. (1).

(Spirou 2107.)

The "**prescription parameters**" correspond to d_p and d_c. The "**candidate intensity maps**," i.e., "representations of dose distributions" being evaluated at each iteration, correspond to the collection of d_i summed over all targets and organs.

The "dose-volume based quadratic objective function" of Spirou Method B incorporates the above two prescription parameters to evaluate how closely the dose distribution at each iteration of the optimization algorithm matches the prescribed dose for the target. (Solberg, ¶83.) Accordingly, the objective function is a "**cost function . . . formed responsive to the prescription parameters**."

Moreover, the cost function is "**evaluated . . . for each of a set of a plurality of candidate intensity maps**" in Method B as the dose distributions are evaluated with this cost function at each iteration of the optimization process. (Spirou 2105; Solberg, ¶84.) For example, Spirou explains that for "clinical cases[,] the termination condition was the standard used in routine planning: 100 iterations or a decrease in the value of the objective function of less than 1% in three successive iterations," thus requiring evaluating a minimum of three candidate intensity maps. (Spirou 2107; Solberg, ¶84.) In the phantom study disclosed in Spirou, "when method B was used, the optimization process terminated after [just] 18 iterations, since there was no further decrease in the value of objective function." (Spirou 2107.) In the study of a patient with paraspinal disease, the "optimization process [of Method B] concluded in only 26 iterations," in the study of a patient with cancer of the nasopharynx, "only 42 iterations were required," and in the study of a patient with cancer of the prostate, "only 25 iterations." (Spirou 2108, 2110; Solberg, ¶84.)

"to provide control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness, the cost function including . . . .

a dosimetric cost term representing dosimetric cost and related to dosimetric fitness of the respective candidate intensity map and . . .

a delivery cost term representing delivery cost and related to delivery time to deliver radiation according to a beam arrangement represented by the respective candidate intensity map, . . ."

In Spirou's Eq. (3), discussed above, Spirou's Method B involves evaluating, at each iteration of the optimization algorithm, both a dosimetric cost term and a delivery efficiency cost term:

$$F_{\mathrm{obj}} = \boxed{\sum_{i \in \mathrm{targets}} w_i (d_i - d_p)^2 + \sum_{i \in \mathrm{organs}} w_i \zeta_i (d_i - d_c)^2}$$
$$\boxed{+ \sum_{j \in \mathrm{beams}} w_j (x_j' - x_j)^2,} \qquad (3)$$

where x_j' is given by Eq. (1).

(Spirou at 2107; Solberg, ¶85.)

The "**dosimetric cost term**" in this objective cost function is boxed in red. As explained above and reproduced here: "d_i and w_i are the dose and weight of the *i*th point, d_p is the prescription dose, d_c is the constraint dose, and ζ_i is a flag indicating whether the constraint is violated." (Spirou at 2106; Solberg, ¶86.) This term is the sum of squared differences "over the points in the targets" and "over the points in the critical organs." (Spirou at 2106). The term thus evaluates how well the dose distribution generated at each iteration matches the desired dose distribution, d_p. The term in purple thus "**represent[s] dosimetric cost**" and is **"related to dosimetric fitness of the respective candidate intensity map."** (Solberg, ¶86.)

In this objection cost function, the **"delivery cost term"** is the smoothing term boxed in blue. The term is the sum of squared differences between the beam element and its value after smoothing. It is calculated according to Spirou Eq. (1):

$$x_j' = \sum_{k=-n_L}^{n_R} c_k \cdot x_{j+k},$$

"where x_j is the value of the *j*th beam element in the original profile, x_j' is the new value after smoothing, c_k is the weighting coefficient of each neighboring beam element, and n_L and n_R are the number of neighbors to the left and to the right to be included in the smoothing, respectively." (Spirou 2106; Solberg, ¶87.)

Spirou explains that smoothing decreases delivery cost and increases delivery efficiency. "The process of optimization is computationally complex and intensive" such that "it is inherently susceptible to noise and numerical artifacts, i.e. high-frequency spatial fluctuations," that "may manifest themselves as sharp peaks and valleys extending only a few millimeters." (Spirou 2105; Solberg, ¶88.) These fluctuations lead to several practical difficulties: "(a) the profiles may not be easy to generate due to limitations of the delivery system, (b) if the delivery technique is DMLC they often prolong the beam-on time, and (c) they are sensitive to treatment uncertainties." (Spirou 2105). Spirou teaches that smoothing is a "solution to this problem" because it "remove[s] random (high spatial frequency) fluctuations" in a beam profile while "preserving the essential features of the profile (peaks, valleys, and gradients) that produce the optimum dose distribution." (Spirou 2105-2106; Solberg, ¶88.) Spirou's empirical results further bear out that smoother beam profiles resulted in shorter beam-on time than less smooth beam profiles. (Spirou 2107-11; Solberg, ¶88.) Thus, the smoothing term boxed in blue in the cost function above is a "delivery cost term" "**representing delivery cost**."

Spirou explains that the smoothing term in Method B is "**related to delivery time to deliver radiation according to a beam arrangement represented by the respective candidate intensity map.**" "The <u>beam-on time</u> required for generating an IM beam profile as well as the accuracy of generating it, when factors such as scatter and leaf edge effects are taken into account, <u>depends upon the shape of the profile.</u>" (Spirou 2111; Solberg, ¶89.) "More highly modulated <u>profiles, with sharp gradients</u> in fluence, are more difficult to generate and <u>usually require a longer beam-on time</u>." (Spirou 2111.) Spirou exemplifies the improvement in beam-on time derived from incorporating smoothing into the objective function by comparing the beam profiles generated by Method B to the beam profiles generated without smoothing: Spirou's experimental results show that "at a dose rate of 240 MU/min [monitor units per minute]," Method B required "979 MU [monitor units]" compared to "2179 MU for the unsmoothed profiles." (Spirou 2111; Solberg, ¶89.)

The collection of beam profiles are "represented by the respective intensity map," i.e., the corresponding dose distribution at that iteration, because the dose distribution represents the dose collectively created by the combination of the corresponding beam profiles.

Spirou's Method B algorithm "**provide[s] control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness.**"

Every term in Spirou's algorithm includes a weighting coefficient, circled below.

$$F_{\text{obj}} = \sum_{i \in \text{targets}} w_i (d_i - d_p)^2 + \sum_{i \in \text{organs}} w_i \zeta_i (d_i - d_c)^2 + \sum_{j \in \text{beams}} w_j (x_j' - x_j)^2,$$

where x_i' is given by

$$x_j' = \sum_{k=-n_L}^{n_R} c_k \cdot x_{j+k},$$

w_i is the "weight of the *i*th point" for the dosimetric cost term, w_j is a weighting coefficient for the smoothing delivery cost term of the "jth beam element in the original profile," and c_k is the "weighting coefficient of each neighboring beam element" in the smoothing formula itself. (Spirou 2106-2107; Solberg, ¶91.) Hence, "the algorithm allows multiple minimum-dose, maximum-dose as well as dose-volume constraints to be defined for any structure, each with varying penalty weights." (Spirou 2106; Solberg, ¶91.) These weighting coefficients allow a user to prioritize dosimetric fitness (that is, fitting the prescribed doses) versus delivery efficiency (as represented by smoothing) by assigning values to the coefficients based on the tradeoff being calculated. (Solberg, ¶91.)

Spirou directly addresses such a tradeoff between dosimetric fitness and delivery efficiency. For example, Spirou explains that "[m]ore highly modulated [beam] profiles, with sharp gradients in fluence, are more difficult to generate and usually require a longer beam-on time." (Spirou at 2111.) Here, Spirou explains that the complexity of a beam profile directly correlates to delivery efficiency. (Solberg, ¶92.) Method B thus "**provide[s] control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness**" through use of a "dose-volume-based quadratic objective function" that includes a weighted dosimetric cost term and a weighted smoothing cost term.

Because this trade-off takes place at each step of the iterative optimization process in Spirou's Method B, it is "**within an optimizer**." Method B includes both a term for dosimetric cost and a "term <u>within</u> the algorithm's objective function that specifies the smoothness of the profiles as an optimization criterion." (Spirou 2105.)

The terms are both in the algorithm itself and the tradeoff between the two is evaluated at each iteration. (Solberg, ¶93.)

Assigning values to the weighting coefficients identified above requires a practitioner to make a trade-off based on the practitioner's preference between dosimetric fitness and delivery efficiency on a case-by-case basis:

> Is it preferable to smooth less aggressively and obtain a better plan that is, however, more difficult to accurately and efficiently deliver and is more susceptible to other factors, such as treatment uncertainties, or is it better to smooth more aggressively and obtain a worse plan that is, however, easier to generate? It is unlikely that one could give a simple answer to this question. Rather, it would have to be decided on a case-by-case basis, based on the particular patient, the tumor site and involved critical organs, the prognosis and possibility of disease recurrence, etc.

(Spirou at 2111.) Spirou teaches that the weighting coefficients within the cost function could and should be varied to modify the trade-off between dosimetric fitness and delivery efficiency on a case-by-case basis. (Solberg, ¶94.)

For instance, if the weighting coefficients for each beam's "neighbors" in the smoothing formula were set to 0, this would nullify the effect of the smoothing term within the cost function of Method B thereby resulting in a radiation treatment plan with a "substantially optimal dosimetric fitness" (because the only remaining consideration in the optimizer is the prescribed dose-volume information). (Solberg,

¶95.) Likewise, the weights for the dose-volume-based objective function could be set to 0, which would instead result in a radiation treatment plan that only optimizes for reduced complexity, which, as Spirou discloses and Petitioner explained at length, yields greater delivery efficiency. (Solberg, ¶95.) By using non-zero weights, Method B can be modified to achieve an intermediary result between these two extremes. (Solberg, ¶95.) Thus, the effect of implementing Spirou's Method B would be "**to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness**."

". . . the evaluation of the delivery cost term for each respective candidate intensity map having linear computational complexity with respect to the size of the respective candidate intensity map."

As discussed, the claimed "delivery cost term" in Spirou corresponds to the annotated term in Spirou's cost function reproduced below:

$$F_{\mathrm{obj}} = \sum_{i \in \mathrm{targets}} w_i (d_i - d_p)^2 + \sum_{i \in \mathrm{organs}} w_i \zeta_i (d_i - d_c)^2 + \boxed{\sum_{j \in \mathrm{beams}} w_j (x_j' - x_j)^2,}$$

(Spirou 2107.) "x_j is the value of the jth beam element in the original profile…." (Spirou 2106.)

As discussed, the claimed "**intensity map**" corresponds to the **representation**

of dose distribution computed at each iteration. The "size of the [] intensity map" corresponds to the number of beam elements as summed over all beams, because it is the total number of beam elements that would be required to create the desired dose distribution. (Spirou, e.g., 2107 ("To include beam profile smoothness in the optimization process, another term is introduced to the objective function…."), 2106 ("x_j is the value of the jth beam element in the original profile…."); Solberg, ¶98.) As the annotated cost term above makes clear, the computation $w_j(x_j' - x_j)^2$ is performed for each individual beam element of the beam profile. Thus, each additional beam element would require an additional computation of the term $w_j(x_j' - x_j)^2$. (Solberg, ¶98.)

Accordingly, a person of ordinary skill would have found it obvious that as size of the beam profile, i.e., the number of beam elements, increases, the computational complexity of the overall cost term, $\sum_{j \in \text{beams}} w_j(x_j' - x_j)^2$, would increase in linear proportion. (Solberg, ¶99.) Evaluating the cost term of Spirou thus has "**linear computational complexity with respect to the size of the respective candidate intensity map**," as claimed. Spirou also explicitly refers to this term as a "linear filter." (Spirou at 2106.)

2. Claim 4: "A method as defined in claim 1, wherein the step of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness within an optimizer includes the step of assigning a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan based upon complexity of each respective dose intensity map."

Spirou's Method B "provid[es] control of a trade-off between treatment plan delivery efficiency and dosimetric fitness within an optimizer" through its use of a combined objective function that incorporates dose-volume goals with a cost term for each dose distribution's complexity. (Solberg, ¶101.) The portion of the objective function that assesses complexity—as measured by smoothness—corresponds to the "delivery cost term." This delivery cost term is dose distribution at each iteration because it evaluates all of the corresponding beam elements used to create that dose distribution. And multiple dose distributions, i.e., "**a plurality of dose intensity maps**," are evaluated iteratively, one dose distribution ("intensity map") at each iteration, until an optimized dose distribution is computed. (Solberg, ¶101.)

Spirou's Method B thus "assign[s] a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan based upon complexity of each respective dose intensity map."

3. Claim 13: "A method of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness to optimize a radiation treatment plan within a continuum between delivery efficiency and dosimetric fitness, the method comprising the steps of:" (Claim 13 [preamble])

To the extent the preamble of claim 13 is limiting, it is fully disclosed and rendered obvious by Spirou. It is also identical in language to elements of claim 1[b].

(a) "assigning a delivery cost term within an optimizer to each of a plurality of intensity maps representing a potential radiation beam arrangement, the assignment based on complexity of each respective intensity map; and" (Claim 13[a])

As described in claim 1, Spirou's Method B involves incorporating a delivery cost term (the smoothing term) for the complexity of the intensity map resulting from the potential radiation beam arrangement at each iteration of and within the optimization algorithm. (Solberg, ¶104.) Also, explained above, each iteration generates a new dose distribution corresponding to the set of beam profiles generated at that iteration, and thus the algorithm generates multiple dose distributions, i.e., "a plurality of intensity maps" over multiple iterations, one "intensity map" at each iteration. (Solberg, ¶104.) One of skill in the art would understand that the disclosures in Spirou relied upon in Petitioner's analysis in claim 1 correspond to "assigning a delivery cost term within an optimizer to each of a plurality of intensity maps representing a potential radiation beam arrangement, the assignment based on complexity of each respective intensity map."

(b) "evaluating an objective cost function for each of the plurality of intensity maps, the objective function including a dosimetric cost term and the delivery cost term, the dosimetric cost term representing dosimetric fitness of the respective intensity map and the delivery cost term representing delivery efficiency." (Claim 13[b])

As explained in Petitioner's analysis in claim 1, at each iteration of the optimization algorithm, Spirou's Method B evaluates an objective function that is a combination of: (1) a dose-volume-based objective function that provides a "dosimetric cost term representing dosimetric fitness of the respective intensity map" for that iteration, and (2) a "delivery cost term representing delivery efficiency" for that iteration as measured by the smoothing formula. Thus, Spirou discloses or renders obvious each element of claim 13. (Solberg, ¶105.)

4. Claim 14: "A method as defined in claim 13, wherein the delivery cost term is a function of delivery time required to deliver radiation according to a beam arrangement represented by the respective intensity map."

As for the additional limitation of claim 14, it is similar to language describing the "delivery cost term" in claim element 1[b]. The main difference is the term "*function* of delivery time," rather than "related to delivery time." The delivery cost term in Spirou's Method B is a measure of beam profile complexity that, as explained by Spirou, is a function of delivery time: "More highly modulated profiles, with sharp gradients in fluence, are more difficult to generate and usually require a longer beam-on time." (Spirou at 2111; Solberg, ¶109.) That more complex beam profiles used to deliver the corresponding dose distribution result in longer beam-on times is consistent with the understanding of one of skill in the art at the time, (*see, e.g.,* Solberg ¶109) ("[U]sually the dominant factor for total treatment time is the number of segments, but the total monitor units delivered could also have an effect on the treatment time, as well as on the background dose. The total monitor units is roughly proportional to the relative fluence[.]"); *see also* Langer 2450, *infra*)*,* and thus Spirou's measure of complexity would be understood as a function of, and proxy for, delivery time. (Solberg, ¶109.) Based on Spirou's specific disclosure and a skilled artisan's general knowledge of the relationship between complexity and delivery time, one of skill in the art would understand that Method B's delivery cost term would be higher for plans that would take longer to deliver, and lower for plans that would take less time to deliver—i.e., Spirou's delivery cost term (its measure of complexity/smoothness) is "a function of delivery time required to deliver radiation according to a beam arrangement represented by the respective intensity map." (Solberg, ¶109.)

C. Prior Art and Date Qualification for Ground 2

Ground 2 addresses claims 1, 3-5, 8-9, 13-16, and 18-19 and as noted relies on Siebers and Langer, briefly summarized below, in addition to the aforementioned Spirou.

1. Siebers [Ex. 1006]

Siebers is an article entitled "Incorporating Multi-leaf Collimator Leaf Sequencing into Iterative IMRT Optimization" from the scientific journal *Medical Physics*. Siebers qualifies as prior art under §102(b). (Hall-Ellis, ¶¶54-59.)

Siebers "propose[s] a simple method to incorporate beam delivery constraints into the IMRT optimization process." (Siebers, 953 (right column).) This optimization process is shown in Figure 2:

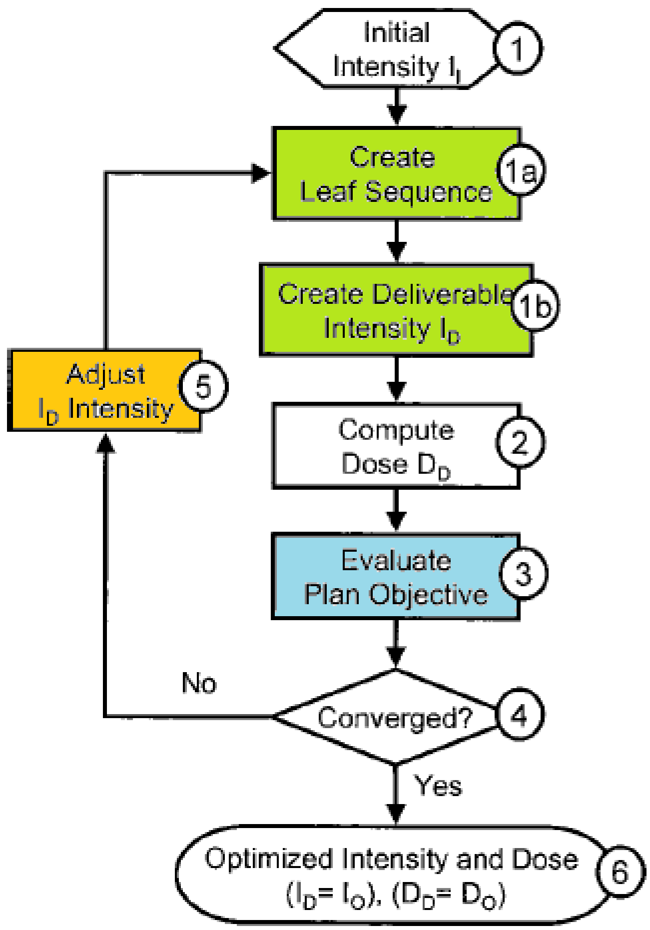


FIG. 2. Flow diagram for the deliverable-based optimization method. Intensities are converted to MLC leaf sequences and deliverable intensities inside of the iterative IMRT optimization loop. The same leaf sequencer is used as in traditional optimization.

(*Id.* (right column) (Fig. 2).) At the beginning of each new iteration, as shown in color annotation above, the optimization algorithm directly creates a leaf sequence based on the input intensity pattern for that iteration.

2. Langer [Ex. 1004]

Langer is an article entitled "Improved Leaf sequencing reduces segments or monitor units needed to deliver IMRT using multileaf collimators" published in the scientific journal *Medical Physics*. Langer qualifies as prior art under §102(b). (Hall-Ellis, ¶¶48-53.)

Langer describes an algorithm to generate an IMRT sequence "with the fewest possible segments when the minimum number of monitor units are used." (Langer 2450.) Langer identifies "two important measures of sequence efficiency": "One is the total number of monitor units needed to generate the map and the other is the number of segments, or setups of the leaves." (Langer 2450.) Langer explains why these two parameters are "important measure of sequence efficiency":

> <u>More monitor units</u> unfavorably affect treatment delivery by increasing the component of machine leakage and lengthening each treatment session. A lengthened treatment session worsens machine throughput and leads to inaccuracies in patient positioning, while machine leakage is a source of discrepancy between the planned and delivered dose distribution. <u>More segments</u> also lengthen the treatment session because of the time needed to switch the beam on and off and to move the leaves. <u>An efficient sequence of leaf movements should take the fewest possible segments to generate a map with the number of monitor units that it uses. It should also use the minimum number of monitor units for the number of segments it takes</u>.

(Langer 2450.)

Langer's proposed algorithm defines an equation for the total number of monitor units used in a given leaf sequence. (Langer 2452.) Langer uses this equation for the total monitor units as an objective function to be minimized by the optimization algorithm for leaf sequences. (Langer 2452.) This objective function is evaluated for each proposed leaf sequence subject to satisfying a series of inequalities that incorporate a term *T* representing "an upper bound on the number of monitor units that can be required." (Langer 2451-52.) Additionally, Langer notes that its algorithm could be modified to optimize for other objective functions, such as to "minimize a *weighted combination* of the numbers of monitor units and segments, or minimize the number of segments for different settings of the allowed number of monitor units." (Langer at 2457.)

D. Ground 2: Claims 1, 3-5, 8-9, 13-16, and 18-19 Over Siebers, Langer, and Spirou

Independent claims 1, 13, and 19 and dependent claims 3, 4, 5, 8, 9, 14, 15, 16, and 18 would have been obvious to one of skill in the art reading Siebers, Langer, and Spirou together.

Siebers teaches a method to incorporate the leaf sequencing step into the algorithm that generates intensity maps and evaluates them iteratively to generate an optimized intensity and dose, depicted in Siebers Figure 2 below:

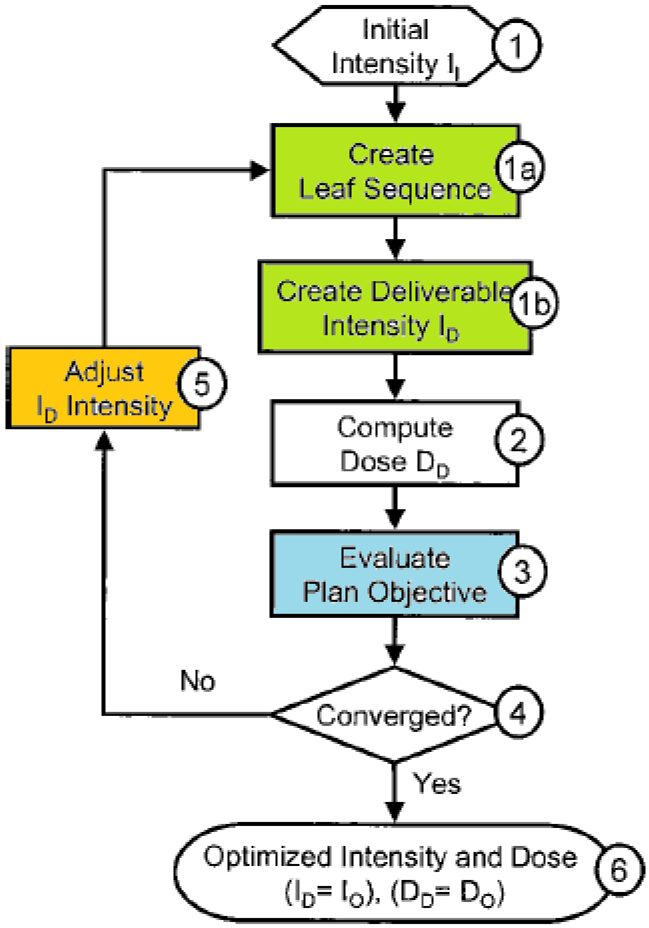


FIG. 2. Flow diagram for the deliverable-based optimization method. Intensities are converted to MLC leaf sequences and deliverable intensities inside of the iterative IMRT optimization loop. The same leaf sequencer is used as in traditional optimization.

(Siebers, 953 (color annotation added).) Siebers' proposed method "unifies the IMRT optimization and IMRT multi-leaf collimator (MLC) leaf sequencing tasks, resulting in deliverable beam intensity profiles and dynamic MLC instructions at the completion of the optimization sequence." (Siebers 952.) Deliverability constraints are incorporated and assessed in moving from Siebers' box 1a to Siebers' box 1b, which generates a proposed leaf sequence and assesses that leaf sequence for whether it satisfies the deliverability constraints: "The deliverable intensities (box 1b, Fig. 2) are derived from the MLC trajectories (box 1a, Fig. 2). They include all restrictions of the MLC delivery . . . ." (Siebers 955.) Dosimetric fitness is evaluated in Siebers' box 3, which "evaluate[s] the plan objective function (box 3, Fig. 2), hence, the plan quality score." (Siebers 955; Solberg, ¶111.)

Siebers demonstrates the added efficiency of inserting the leaf sequencing step within the overall cost function by developing alternative treatment plans for 17 IMRT patients and comparing, as one measure of efficiency, the total number of monitor units required to deliver the deliverable treatment plans versus the (non-deliverable) optimized treatment plans. (Siebers 955–957; Solberg, ¶112.) Use of Siebers' deliverable-based optimization algorithm resulted in, on average, 57–68% fewer number of MUs to deliver the patient plan in all 17 cases. (Siebers 957.) Siebers explains that "[t]he reduction in MUs is apparently due to the intensity filtering and smoothing present in the leaf-sequencing algorithm that is repeatedly applied during deliverable-based optimization. (Solberg, ¶112.) Since the [deliverable-based optimization] plan requires more deliverable-based optimization iterations for convergence, the filtering process is applied more often; hence, fewer MUs are required. In both cases [traditional optimization combined with deliverable-based optimization and deliverable-based optimization alone], the resultant plans from deliverable-based optimization result in improved treatment plan quality in terms of dose distribution and treatment delivery efficiency [compared to traditional optimization alone]." (Siebers 957; Solberg, ¶112.)

Langer discloses an optimizing cost function that addresses an efficiency problem at the leaf sequencing step: "total number of monitor units needed to generate the map" and "number of segments, or setups of the leaves." (Langer 2450.) Langer explains why these two parameters are "important measure of sequence efficiency":

> <u>More monitor units</u> unfavorably affect treatment delivery by increasing the component of machine leakage and lengthening each treatment session. A lengthened treatment session worsens machine throughput and leads to inaccuracies in patient positioning, while machine leakage is a source of discrepancy between the planned and delivered dose distribution. <u>More segments</u> also lengthen the treatment session because of the time needed to switch the beam on and off and to move the leaves. <u>An efficient sequence of leaf movements should take the fewest possible segments to generate a map with the number of monitor units that it uses. It should also use the minimum number of monitor units for the number of segments it takes</u>.

(Langer 2450.) Langer introduces an algorithm that reduces first monitor units and then number of segments needed to deliver the IMRT profiles generated by algorithms such as Spirou Method B. (Solberg, ¶113.) Langer provides evidence of its algorithm improving efficiency. (Langer 2454-2456). Specifically:

> Results were compared to sequences given by the routine of Bortfeld that minimizes monitor units by treating each row independently, and the areal or reducing routines that use fewer segments at the price of more monitor units. The Bortfeld algorithm used on average 58% more segments than provided by the integer algorithm with bidirectional motion and 32% more segments than did an integer algorithm admitting only unidirectional sequences. The areal algorithm used 48% more monitor units and the reducing algorithm used 23% more monitor units than did the bidirectional integer algorithm, while the areal and reducing algorithms used 23% more segments than did the integer algorithm [admitting only unidirectional sequences].

(Langer 2450 (underlining added).)

One of skill in the art would have found it obvious to employ the combined leaf sequencing-dose optimization framework of Siebers with the specific leaf sequence approach of Langer, and to further combine Siebers' dose-based objective function and Langer's efficiency-based objective function into a single objective function for use in Siebers' framework. (Solberg, ¶114.) The feasibility and desirability of using such a combined objective function is described in Spirou. As explained in detail for Ground 1 above, Spirou provides an optimizing cost function that includes both a dosimetric cost term and a delivery cost term. (Spirou 2107-2111; Solberg, ¶114.)

<u>Rationale and Motivation to Combine:</u> There are multiple reasons why a skilled artisan would be motivated to combine Siebers, Langer, and Spirou in this way. **First**, as detailed above, all three demonstrate that their modifications to IMRT optimization lead to increased delivery efficiency, and specifically to increased delivery efficiency as measured by MUs. (Solberg, ¶115.) **Second**, Siebers specifically teaches insertion of leaf sequencing requirements (such as those of Langer) within an IMRT optimization routine that otherwise resembles standard IMRT optimization. (Solberg, ¶115.) Siebers does not provide specific deliverability (i.e., leaf sequencing) constraints nor objective function equations, instead providing a framework into which one of skill of the art could insert IMRT optimization and leaf sequencing algorithms known in the art—such as those of Langer and Spirou, to which one of skill in the art would look for implementation details. (Solberg, ¶115.) Siebers additionally includes data that traditional optimization algorithms combined with its deliverable-based optimization algorithm resulted in more efficient leaf sequencing distributions than use of its algorithm alone, effectively teaching that Siebers' algorithm can successfully be combined with elements taken from other optimization methods. (Siebers at 957.) **Third**, all three references measure delivery efficiency in more or less the same manner: Spirou uses "smoothing" as a proxy for "beam-on time;" Langer uses "number of segments" and "total number of monitor units;" and Siebers uses "reduction in [monitor units]." (Solberg, ¶115.) Siebers explains what was generally understood by those of skill in the art at the time—that all of these terms were correlated measures of delivery efficiency—when stating that "<u>reduction in MUs</u> is apparently due to the intensity filtering and <u>smoothing</u> present in the leaf-sequencing algorithm that is repeatedly applied during deliverable-based optimization." (Siebers 957.) Because all three measure delivery efficiency similarly, each demonstrates that its algorithm improves delivery efficiency, and because Siebers teaches that combining such algorithms can improve delivery efficiency, a skilled artisan would have found it obvious to combine Siebers, Langer, and Spirou and have been motivated to do so with a reasonable expectation of success. (Solberg, ¶115.)

The resulting combined algorithm is depicted below:

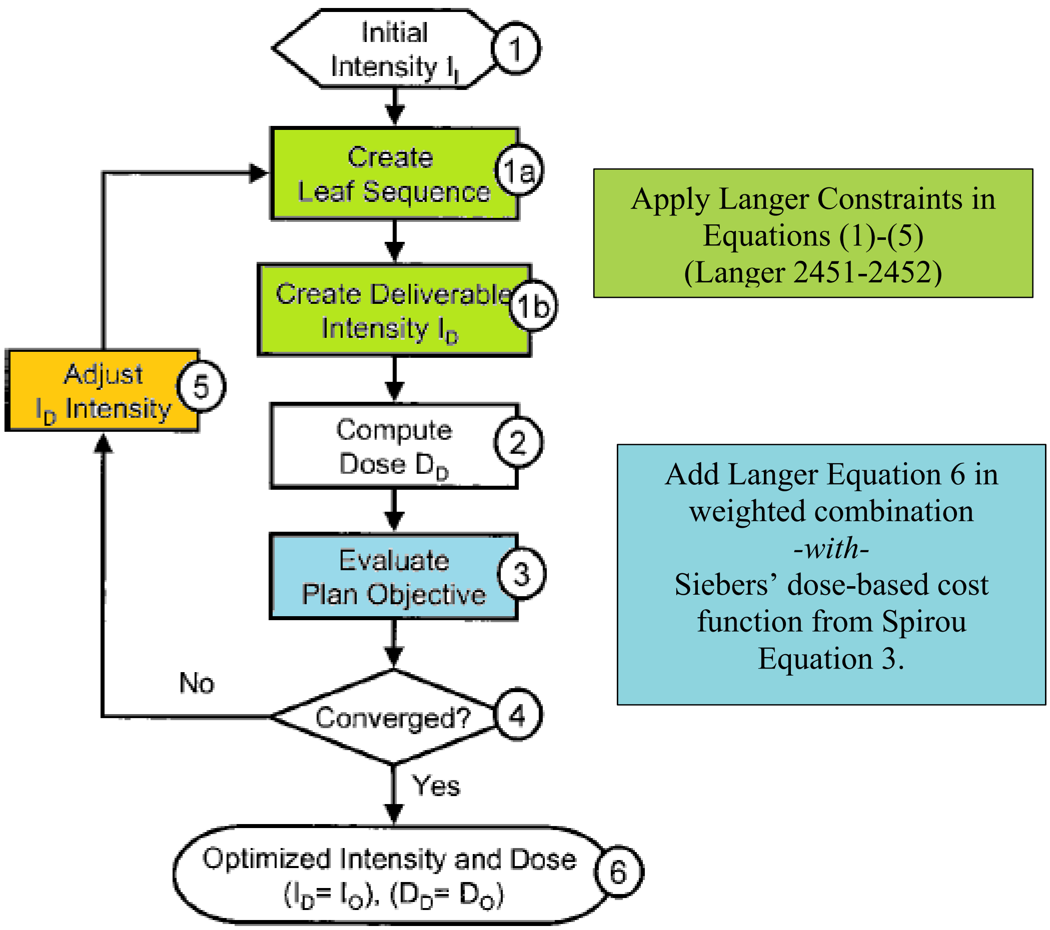


FIG. 2. Flow diagram for the deliverable-based optimization method. Intensities are converted to MLC leaf sequences and deliverable intensities inside of the iterative IMRT optimization loop. The same leaf sequencer is used as in traditional optimization.

1. The resulting objective cost function is depicted below:

$$F_{\mathrm{obj}} = \boxed{\sum_{i \in \text{targets}} w_i (d_i - d_p)^2} + \boxed{\sum_{i \in \text{organs}} w_i \zeta_i (d_i - d_c)^2}$$

$+$

$$\sum_{t}^{T} z^t = Z.$$

Siebers Fig. 2 (Siebers 953) modified with Spirou Eq.3 (Spirou 2107) and Langer 2451-2452. The resulting cost function used in Siebers Step 3 thus has both a dosimetric cost term as disclosed in Spirou with Langer delivery cost term to minimize the total monitor units. (Solberg, ¶117.)

2. Claim 1: "A method of determining a radiation beam arrangement, the method comprising the steps of:" (Claim 1[preamble])

To the extent the preamble of claim 1 is limiting, it is fully disclosed and rendered obvious by Siebers.

Siebers addresses both elements of IMRT. Siebers boxes 1a and 1b determine a leaf sequence and verify that it is administrable: "The deliverable intensities (box 1b, Fig. 2) are derived from the MLC trajectories (box 1a, Fig. 2). They include all restrictions of the MLC delivery . . . ." (Siebers 955.) Siebers boxes 2 and 3 then calculate and evaluate the proposed dose of radiation beams corresponding to the deliverable leaf sequence in order to develop an optimal dose distribution: "These deliverable intensities are used to compute the deliverable dose distributes (D_D, box 2, Fig. 2), which are used in turn to evaluate the plan objective function (box 3, Fig. 2), hence, the plan quality score." (Siebers 955; Solberg, ¶120.)

The aim of Siebers' algorithm is thus to "**determin[e] a radiation beam arrangement**": as Siebers explains, it "result[s] in deliverable beam intensity profiles and dynamic MLC instructions at the completion of the optimization sequence." (Siebers 952; Solberg, ¶121.)

(a) "receiving prescription parameters for a patient target; and" (Claim 1[a])

Siebers discloses use of a "plan objective function" corresponding to "the plan quality score." (Siebers 955.) This "plan objective function" is designed to find a plan that "best meet[s] the specified treatment objectives," in other words, that best meets a set of desired prescription parameters. (Siebers 958.) Receiving dose prescriptions and converting those prescriptions into objective functions was well-known in the art at the time. (Solberg, ¶122.)

For example, a specific example of a set of prescription parameters that could be selected as Siebers' "plan objective function" is provided in Spirou. As described in Ground 1, Spirou uses "the treatment planning system developed at MSKCC," and in particular its "dose-volume-based quadratic objective function" that evaluates the difference between the actual and prescribed dose for given points within the target and other organs. (Spirou at 2106.) The algorithms described by Spirou require the use of a "prescription dose" for the target ("d_p" in the cost function) and a constraint dose ("d_c" for organs-at-risk such as the spinal cord). (Spirou 2106-2107.) These are "**prescription parameters for a patient target**." (Solberg, ¶123.)

(b) "evaluating a cost function for each of a set of a plurality of candidate intensity maps formed responsive to the prescription parameters to provide control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness, the cost function including a dosimetric cost term representing dosimetric cost and related to dosimetric fitness of the respective candidate intensity map and a delivery cost term representing delivery cost and related to delivery time to deliver radiation according to a beam arrangement represented by the respective candidate intensity map, the evaluation of the delivery cost term for each respective candidate intensity map having linear computational complexity with respect to the size of the respective candidate intensity map." (Claim 1[b])

Siebers recites two primary benefits to its algorithmic framework: "best meet[ing] the specified treatment objectives" and "more efficient beam delivery requiring fewer monitor units." (Siebers 958.) Given Siebers' explicit reference to reducing monitor units as the efficiency measure of interest, Langer's approach to leaf sequencing, and in particular Langer's approach to minimizing monitor units within leaf sequencing, makes Langer's use of monitor units an obvious selection for the type of leaf sequencing to incorporate into Siebers' framework. (Solberg, ¶124.)

Langer's algorithm for minimizing the total number of monitor units involves two sets of formulae: (1) a series of inequalities (i.e., constraints) that, when satisfied, provide the monitor units at each beam element used by a leaf sequence to deliver a set intensity distribution (Equations (1)-(5)); and (2) an objective function to minimize the sum of the total number of monitor units (Equation (6)). (Langer 2451-2452.) Langer's inequalities for determining the monitor units associated with a leaf sequence incorporate a term "T" where "T is an upper bound on the number of monitor units that can be required." (Langer 2452.) Monitor units are evaluated in units of time t extending from t=1 (the first unit of time) through t=T (the last unit of time, equal to the upper bound on monitor units), thus implying a constraint that the monitor units per time unit output of the machine is constant. (Langer 2451-2452.)

Langer's first set of formulae are recited in Equations (1)-(5). These equations enforce various physical limitations of the MLC delivery device and calculate the number of monitor units used by a given leaf sequence. (Solberg, ¶126.) Specifically, equation (1) enforces "the condition that the leaves in any row cannot override each other, meaning that a beam element cannot be covered at the same time by both a left leaf and a right leaf," and relates this condition to whether or not any radiation is allowed to pass through a given beam element. (Langer 2451 and Equation (1); Solberg, ¶126.) Equations (2) and (3) enforce the rule that "[i]f a leaf covers a beam element, then every element between it and the side of the collimator to which the leaf is connected is also covered." (Langer 2451 and Equations (2)-(3); Solberg, ¶126.) Equation (4) requires "the sum d^t_{ij}" of the monitor units delivered to each beam element *ij* to equal "the intensity assigned to beam element *ij*" in the intensity map for which a leaf sequence is sought. (Langer 2451-52 and Equation (4); Solberg, ¶126.) Finally, "[t]he total number of monitor units expended is tallied" as a new variable z^t based on the beam element monitor units d^t_{ij} by satisfying the inequality detailed in Equation (5):

$$\sum_{i}^{I} \sum_{j}^{J} d_{ij}^{t} \leqslant z^{t} IJ$$

(Langer 2452 and Equation (5); Solberg, ¶126.)

In other words, because Langer's Equations (1)-(5) enforce various physical and other deliverability requirements of the leaf sequence, these equations define a set of constraints corresponding to the Siebers' "delivery constraints," which are applied in the transition from Siebers' box 1a to box 1b. (Siebers 955.) As explained by Siebers, the "delivery constraints" "include all restrictions of the MLC delivery and incorporate best available approximations related to the transmission and scattering characteristics of the MLC." (Siebers 955.) Because Langer's Equations (1)-(5) relate to restrictions on MLC delivery, it would have been obvious to one of skill in the art to use the inequalities described by Langer in Equations (1)-(5) as "delivery constraints" in Siebers' framework. (Solberg, ¶127.)

Langer's second formula is an objective function. In Siebers' framework, the objective function is evaluated in box 3. (*See* Siebers Fig. 2; *see also* Siebers 955.) One of skill in the art would have readily appreciated that this objective function step would be an appropriate step in Siebers' framework to evaluate Langer's objective function. In order to find a dose distribution that "best meet[s] the specified treatment objectives," Siebers' algorithm contemplates a dose-based objective function, whereas Langer's objective function in geared towards improving delivery efficiency as measured in terms of total monitor units. One of skill in the art would have appreciated that Siebers' dose-based objective function and Langer's delivery-efficiency-based objective function could be combined together as a weighted sum of the two separate objective functions, in order to simultaneously optimize both for dosimetric fitness and delivery efficiency. (Solberg, ¶128.)

That a dose-based objective function and a delivery-efficiency-based objective function could be combined as a weighted sum in a single objective function was known in the art—Spirou's Method B provided a clear example of how to combine these two types of objective functions into a single equation, as described in Ground 1. (Solberg, ¶129.)

"evaluating a cost function for each of a set of a plurality of candidate intensity maps formed responsive to the prescription parameters"

The combination of Siebers, Langer, and Spirou thus results in a single objective function that incorporates: (1) a term to improve the dosimetric fitness of the beam arrangement and (2) a term to improve delivery efficiency, as measured by monitor units. The first term, which aims to "best meet the specified treatment objectives," is "**formed responsive to the prescription parameters.**" (Solberg, ¶130.)

For example, the "dose-volume-based quadratic objective function" of Spirou Method B can be modified to form the weighed combination. (Spirou at 2106.) The objective function specified by Spirou is:

$$F_{\text{obj}} = \boxed{\sum_{i \in \text{targets}} w_i (d_i - d_p)^2} + \boxed{\sum_{i \in \text{organs}} w_i \zeta_i (d_i - d_c)^2} + \boxed{\sum_{j \in \text{beams}} w_j (x_j' - x_j)^2}, \qquad (3)$$

where x_j' is given by Eq. (1).

(Spirou 2107.)

Boxed in green is the term for the prescription dose. The values are "summed over [] points in the targets" to determine how well the smoothed beam profile being evaluated at a particular iteration in Method B hits the targeted cancerous tissue. (Solberg, ¶132.)

Boxed in purple is the term for the constraint dose. The values are "summed . . . over points in the critical organs." (Spirou 2106; Solberg, ¶133.)

Boxed in red is the delivery efficiency term used by Spirou. (Solberg, ¶134.) In order to instead form a weighted combination of a dose-based objective function with *Langer*'s delivery efficiency term, the portion of Spirou Equation (3) boxed in red would instead be replaced by Langer's Equation (6):

$$\min \sum_{t}^{T} z^t = Z. \qquad (6)$$

As described for Ground 1, the "dose-volume based quadratic objective function" of Spirou Method B incorporates prescription parameters (boxed in green and purple) to evaluate how closely the dose distribution at each iteration of the optimization algorithm matches the prescribed dose for the target. (Solberg, ¶135.) Accordingly, the objective function is a "**cost function . . . formed responsive to the prescription parameters**."

Moreover, the combined cost function is "**evaluated . . . for each of a set of a plurality of candidate intensity maps.**" Siebers explains that the objective function is evaluated in box 3 at each iteration of the algorithm. (Siebers Fig. 2; Siebers 955.) This iterative loop, which includes evaluating the objective function for each successive proposed dose distribution ("intensity map"), continues until "convergence or termination." (Siebers 954.) Siebers defines "convergence" in terms of "the relative difference between sequential plan quality scores," which necessarily requires evaluating multiple proposed dose distributions. (Solberg, ¶136.)

"to provide control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness, the cost function including . . . .

a dosimetric cost term representing dosimetric cost and related to dosimetric fitness of the respective candidate intensity map and . . .

a delivery cost term representing delivery cost and related to delivery time to deliver radiation according to a beam arrangement represented by the respective candidate intensity map, . . ."

The combination of Siebers, Langer, and Spirou would result in an objective function with both a dosimetric cost term and a delivery efficiency cost term, as described above.

The "**dosimetric cost term**" in this combined objective cost function is Siebers' objective function representing a "plan quality score," such as, for example, what is boxed in green and purple in Spirou's Equation 3 above. As explained above and reproduced here, in Spirou's Equation 3: "d_i and w_i are the dose and weight of the *i*th point, d_p is the prescription dose, d_c is the constraint dose, and ζ_i is a flag indicating whether the constraint is violated." (Spirou at 2106.) This term is the sum of squared differences "over the points in the targets" and "over the points in the critical organs." (Spirou at 2106). The term evaluates how well the dose distribution that would be created by the beam profiles match to the prescribed dosing parameters and hence "**represent[s] dosimetric cost"** and is **"related to dosimetric fitness of the respective candidate intensity map."** (Solberg, ¶138.)

In the combined objective cost function of Siebers, Langer, and Spirou, the **"delivery cost term"** is Langer's Equation 6. The term is the sum of total monitor units:

$$\min \sum_{t}^{T} z^{t} = Z. \tag{6}$$

(Langer 2452.) By incorporating the sum of total monitor units in the objective function, the algorithm will seek to minimize monitor units in addition to minimizing deviations from the prescribed radiation dose. (Solberg, ¶139.) The total number of monitor units is a "**delivery cost**" wherein "more efficient beam delivery" requires "fewer monitor units." (Siebers 958.)

Furthermore, because Langer uses a constant rate of monitor units per unit of time and explicitly measures monitor units in terms of time (*see* Langer 2451-2452), Langer's Equation 6 is a delivery cost term "**related to delivery time to deliver radiation according to a beam arrangement represented by the respective**

candidate intensity map."

Furthermore, the combination of Siebers, Langer, and Spirou "**provide[s] control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness within an optimizer to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness.**"

Every term in Spirou's objective function includes a weighting coefficient, circled below.

$$F_{\mathrm{obj}} = \sum_{i \in \mathrm{targets}} w_i (d_i - d_p)^2 + \sum_{i \in \mathrm{organs}} w_i \zeta_i (d_i - d_c)^2 + \sum_{j \in \mathrm{beams}} w_j (x_j' - x_j)^2,$$

where x_i' is given by

$$x_j' = \sum_{k=-n_L}^{n_R} c_k \cdot x_{j+k},$$

(Spirou 2106-2107; Solberg, ¶142.) Hence, "the algorithm allows multiple minimum-dose, maximum-dose as well as dose-volume constraints to be defined for any structure, each with varying penalty weights." (Spirou 2106.)

Substituting Langer's Equation (6) as the delivery cost term would preserve the use of weighting coefficients—in fact, Langer explicitly contemplates that its cost term for monitor units can be used as part of "a weighted combination." (Langer 2457.) These weighting coefficients allow a user to prioritize dosimetric fitness (that is, fitting the prescribed doses) versus delivery efficiency (as represented by (as represented by total monitor units via Langer Equation 6)) by assigning values to the coefficients based on the tradeoff being calculated. (Solberg, ¶143.) Thus, the combination "**provide[s] control of a tradeoff between treatment plan delivery efficiency and dosimetric fitness**" through use of a "dose-volume-based quadratic objective function" that includes a weighted dosimetric cost term and a weighted smoothing cost term. (Solberg, ¶143.)

Because this trade-off takes place at each iteration within Siebers' optimization process as box 3 of Siebers' Figure 2, it is "**within an optimizer**." (Solberg, ¶144.)

As explained in Ground 1, assigning values to the weighting coefficients Petitioner identified above requires a practitioner to make a trade-off based on the practitioner's preference between dosimetric fitness and delivery efficiency on a case-by-case basis—this trade-off is no less true when monitor units are explicitly minimized. (Solberg, ¶145.) In this case, if the weighting coefficient for total monitor units were set to 0 (or the weighting coefficients for the dose-based cost terms were set very high), this would nullify the effect of the use of total monitor units within the cost function thereby resulting in a radiation treatment plan with a "substantially optimal dosimetric fitness" (because effectively the only remaining consideration in the optimizer is the prescribed dose-volume information). (Solberg, ¶145.) Likewise, the weights for the dose-volume-based objective function could be set to 0, which would instead result in a radiation treatment plan that only optimizes for reduced monitor units and hence improved delivery efficiency. (Solberg, ¶145.) By using non-zero weights, the combined cost function can be modified to achieve an intermediary result between these two extremes. Thus, the effect would be "**to optimize a radiation treatment plan within a continuum between substantially optimal dosimetric fitness and enhanced delivery efficiency at an expense of dosimetric fitness**."

". . . the evaluation of the delivery cost term for each respective candidate intensity map having linear computational complexity with respect to the size of the respective candidate intensity map."

As discussed, the claimed "delivery cost term" in the combination is Langer's Equation 6:

$$\min \sum_{t}^{T} z^{t} = Z. \qquad (6)$$

As discussed, the claimed "**intensity map**" corresponds to the representation of dose distribution created at each iteration. The size of the intensity map, as explained, corresponds to the total number of beam elements across the set of beams that would be used to create the desired dose distribution. Tallying the total number of monitor units for Langer's Equation 6 requires making an assessment of the monitor units at each beam element at each unit of time from t=1 to t=T, where T is a fixed upper bound. (Langer 2451-52.) Each addition of 1 beam element to the beam profile corresponds to an increase of T required calculations to determine the delivery cost term. (Solberg, ¶148.)

Accordingly, a person of ordinary skill would have found it obvious that as size of the intensity map, i.e., the total number of beam elements, increases, the computational complexity of the overall delivery cost term would increase in linear proportion. Evaluating the delivery cost term thus has "**linear computational complexity with respect to the size of the respective candidate intensity map**," as claimed. (Solberg, ¶149.)

3. Claim 3: "A method as defined in claim 1, wherein the delivery cost term is a function of a number of intensity changes across the respective intensity map."

Langer's delivery cost term is a "**function of a number of intensity changes across the respective intensity map**" because each desired intensity change requires changing the setup of the beam leaf positions and Langer teaches that "[w]hen the leaves are moved in discrete steps with the beam off from one setup of positions to the next," the "total number of monitor units needed to generate the map" changes. (Langer 2450.) "An efficient sequence of leaf movements" corresponding to intensity changes across an intensity map "should take the fewest possible segments to generate a map" with the "minimum number of monitor units" required. (Langer 2450.) One of skill in the art would understand that this minimum number would generally be positively correlated with the number of intensity changes (more changes means more monitor units required and vice versa). (Solberg, ¶151.)

4. Claim 4: "A method as defined in claim 1, wherein the step of providing control of a trade-off between the treatment plan delivery efficiency and dosimetric fitness within an optimizer includes the step of assigning a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan based upon complexity of each respective dose intensity map."

The weighting coefficients used in Spirou and preserved by substituting Langer's Equation (6) provide "**control of a trade-off between treatment plan delivery and dosimetric fitness**." Langer explicitly contemplates that its cost term for monitor units can be used as part of "a weighted combination." (Langer 2457.) These weighting coefficients allow a user to prioritize dosimetric fitness (that is, fitting the prescribed doses) versus delivery efficiency (as represented by total monitor units via Langer Equation 6) by assigning values to the coefficients based on the tradeoff being calculated. (Solberg, ¶153.)

Because this trade-off takes place at each iteration within Siebers' optimization process as box 3 of Siebers' Figure 2, it is "**within an optimizer**."

The combination "**includes the step of assigning a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan based on upon complexity of each . . . map.**" As discussed, the claimed "delivery cost term" in the combination is Langer's Equation 6:

$$\min \sum_{t}^{T} z^t = Z. \qquad (6)$$

The claimed "**intensity map**," as explained, corresponds to the representation of dose distribution evaluated at each iteration. The maps are representative of "**dosage for a proposed radiation therapy treatment plan**" as disclosed by Siebers, Langer, and Spirou. Langer 2454 ("A summary of the segment and monitor unit numbers totaled over the entire <u>treatment</u> for the examples studied is shown in Table I."), 2456 (Table I's caption reads "Treatment delivery maps generated for contours of prostate case"); Spirou 2106 ("In this article, we discuss implementations of the two smoothing methods using the <u>treatment</u> planning system developed at MSKCC."), 2107-2110 (running its algorithm on patient intensity profiles for various types of cancer). And, Langer's algorithm assigns this delivery cost term "**based up on the complexity of each respective dose intensity map**." Both intensity changes and size changes are a measure of the complexity of intensity maps, and as explained at length in claim 1[b] and claim 3 above that the delivery cost term calculated in Langer is a function of size and intensity changes in each map. (Solberg, ¶155.)

5. Claim 5: "A method as defined in claim 4,"

(a) "wherein the delivery cost term is a function of a number of intensity changes across the respective dose intensity map; and" (Claim 5[a])

As explained for the nearly identical language in Claim 3 above, Langer's delivery cost term is a "**function of a number of intensity changes across the respective dose intensity map**" ("dose" is the only extra word). The "**delivery cost term**" is total number of monitor units. Each desired intensity change in an intensity map requires changing the setup of the beam leaf positions. Langer teaches that "[w]hen the leaves are moved in discrete steps with the beam off from one setup of positions to the next," the "total number of monitor units needed to generate the map" and "the number of segments, or <u>setup of the leaves</u>" changes. (Langer 2450.) "An efficient sequence of leaf movements" corresponding to intensity changes across an intensity map "should take the fewest possible segments to generate a map" with the "minimum number of monitor units" required. (Langer 2450.) Thus, one of skill in the art would understand that the more intensity changes in a map, the higher the number of monitor units required, thus rendering the delivery cost term a function of a number of intensity changes across the dose intensity map in that iteration of the overall combined algorithm. (Solberg, ¶158.)

(b) "wherein the method further includes the step of rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value." (Claim 5[b])

The "**delivery cost term**" in this proposed combination is total number of monitor units.

One of the deliverability constraints incorporated into the Langer inequalities used in Siebers boxes 1a and 1b is T where "T is an upper bound on the number of monitor units that can be required."

$$\sum_{t=1}^{T} d_{ij}^{t} = I_{ij}\,, \tag{4}$$

(Langer 2451.) This equation represents desired intensity for an beam element *ij*, as assigned to a matrix with rows and columns (represented by *i* and *j*) for all elements up to the *T*th element. (Solberg, ¶160.)

T is incorporated into the delivery cost function of Langer:

$$\min \sum_{t}^{T} z^{t} = Z. \tag{6}$$

(Langer 2452.) This delivery cost function runs from *t*th monitor unit to a T maximum number of monitor units. Thus, one of skill in the art would understand that the total number of monitor units (which is the delivery cost term) cannot exceed the preselected threshold T. (Solberg, ¶161.)

Any intensity map resulting in the total number of monitor units exceeding *T* will necessarily be rejected, because it will not correspond to an allowable leaf sequence at Siebers' boxes 1a and 1b, and thus will never be calculated in Langer's delivery cost function at Siebers' box 3. (Solberg, ¶162.)

Further, Langer also teaches that its "integer model can be generalized to include other goals that have been considered for leaf sequencing routines. (Langer 2457.) For example, the model "can . . . minimize the number of segments for different settings of the allowed number of monitor units." (Langer 2457.) The model can also "be extended to consider more complicated expressions of leaf movement that may track wear and tear or overall delivery time." (Langer 2457.)

One of skill in the art reading Langer would understand that a variety of thresholds for "the allowable number of monitor units" (Langer 2457) can be set for rejecting a does distribution for which the total number of Mus needed for delivery would be too high. (Solberg, ¶164.) As a result, it would have been obvious to one of skill in the art that Spirou's objective function, substituted with Langer's cost term for total monitor units, and with Langer's constraints inserted into 1a and 1b of the algorithmic diagram taught by Siebers, "**includes the step of rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value**." (*Id.*)

6. Claim 8: "A method as defined in claim 1, wherein delivery efficiency is represented by total monitor units to deliver the radiation treatment plan; and wherein the step of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness within an optimizer includes the step of limiting inflation of total monitor units from initially simple and efficient beam arrangements to more complex beam arrangements."

Langer discloses a delivery cost term that is an explicit measure of total monitor units, identifying it as an "important measure[] of sequence efficiency" and disclosing an algorithm to "generate a sequence with . . . the minimum number of monitor units." (Langer 2450.) Delivery efficiency with Langer's delivery cost term is thus "**represented by total monitor units to deliver the radiation treatment plan.**" (Solberg, ¶167.)

Including Langer's delivery cost term for total monitor units in the objective function at Siebers' box 3 will seek to minimize the overall objective function—including the tally of total monitor units—by progressively selecting treatment plans that reduce the objective function. (Solberg, ¶168.) The combined objective function creates a beam profile with a reduced number of monitor units. As such, the combination of Siebers, Langer, and Spirou has the effect "**of limiting inflation of total monitor units from initially simple and efficient beam arrangements to more complex beam arrangements.**"

Further, each of the intensity maps generated by the combined algorithm is evaluated against Langer's delivery cost term of total monitor units in each iteration of the algorithm (since Langer's leaf sequencing algorithm, including its cost term for total monitor units, is computed within the iterative optimization loop, as taught by Siebers). (Solberg, ¶169.) Langer's algorithm contains a constraint that imposes a maximum number of number units, *T*; that upper threshold of monitor units will prevent inflation of total monitor units beyond the threshold. (*See* Langer 2452; Solberg, ¶169.) Accordingly, one of skill in the art would understand that combination of Siebers, Langer, and Spirou "**includes the step of limiting inflation of total monitor units from initially simple and efficient beam arrangements to more complex beam arrangements**."

7. Claim 9: "A method as defined in claim 1,"

(a) "wherein delivery efficiency is represented by total monitor units to deliver the radiation treatment plan;" (Claim 9[a])

Langer's delivery cost term is a measure of total monitors to deliver a radiation treatment plan, as represented by:

$$\min \sum_{t}^{T} z^{t} = Z. \qquad (6)$$

(Langer 2452.) By incorporating the sum of total monitor units in the objective function, the algorithm will seek to minimize monitor units, and "more efficient beam delivery" requires "fewer monitor units." (Siebers 958; Solberg, ¶172.) Thus, Langer's delivery cost term is a measure of "**delivery efficiency [] represented by total monitor units to deliver a radiation treatment plan**."

(b) "wherein the step of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness within an optimizer includes the step of assigning a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan, the delivery cost term indicating total monitor units associated with each respective intensity map; and" (Claim 9[b])

When Spirou and Langer are combined by replacing the delivery cost term (the smoothing term) in Spirou's Method B with the equation for total monitor units from Langer, the effect is to calculate the new delivery cost term representing total monitor units at each iteration in the optimization algorithm. This results in "assigning a delivery cost term to each of a plurality of dose intensity maps for each proposed radiation therapy treatment plan, the delivery cost term indicating total monitor units associated with each respective intensity map." ('175, 5:34-41).

As described for a similar limitation in claim 1 above, a trade-off between delivery efficiency (as represented by total monitor units) and dosimetric fitness can be accomplished through weighting coefficients. Such coefficients are already a part of Spirou's original objective function for the dosimetric cost term and its original delivery cost term. (Solberg, ¶174.) When the delivery cost term is replaced by

Langer's delivery cost term, a similar weighting coefficient can be applied, as disclosed by Langer. (Langer 2457.) Use of such coefficients would have been obvious to a skilled artisan. (Solberg, ¶174.)

(c) "wherein the method further includes the step of rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value." (Claim 9[c])

It would have been obvious to one of skill in the art that Langer's constraint limiting the total number of monitor units *T* discloses this claim limitation. All leaf sequences with a total number of monitor units exceeding preselected threshold value *T* would be rejected. As identified in claim 5[b], it would have been obvious to a skilled artisan to apply the multiple other possible "threshold values" of delivery cost suggested by Langer to reject inefficient intensity maps. (Langer 2457; Solberg, ¶175.)

8. Claim 13: "A method of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness to optimize a radiation treatment plan within a continuum between delivery efficiency and dosimetric fitness, the method comprising the steps of:" (Claim 13[preamble])

Petitioner's analysis of the preamble of claim 13 is identical to claim 1[b].

(a) "assigning a delivery cost term within an optimizer to each of a plurality of intensity maps, representing a potential radiation beam arrangement, the assignment based on complexity of each respective intensity map; and" (Claim 13[a])

The combination of Spirou with Langer in view of Siebers incorporates a "**delivery cost term**" of total number of monitor units that depends on the complexity of the dose distribution resulting from the potential radiation beam arrangement at each iteration of and within the optimization algorithm. Petitioner's analysis in claims 1[b], 3, and 4 apply here. Briefly, each iteration of combined algorithm generates a new dose distribution, and thus the algorithm generates "**a plurality of intensity maps**" over multiple iterations. The assignment of the delivery cost term is based on the complexity of each dose distribution, in that factors such as the total number of elements and intensity changes will affect the monitor unit count. Larger maps (increase in size, as recited in element 1[b]) and more intensity changes (as recited in claim 3) will increase the monitor count, and vice versa. (Solberg, ¶178.) Thus, one of skill in the art would understand that the resulting algorithm from combing Siebers, Langer, and Spirou "**assign[s] a delivery cost term within an optimizer to each of a plurality of intensity maps representing a potential radiation beam arrangement, the assignment based on complexity of each respective intensity map**."

(b) "evaluating an objective cost function for each of the plurality of intensity maps, the objective function including a dosimetric cost term and the delivery cost term, the dosimetric cost term representing dosimetric fitness of the respective intensity map and the delivery cost term representing delivery efficiency." (Claim 13[b])

Petitioner's analysis of claim 13[b] is similar to claim 1[b]. To summarize briefly, the "**evaluated objective cost function**" in this combination corresponds to Spirou's algorithm substituted with Langer's delivery cost term, as sequenced in Siebers' iterative loop. The function is evaluated "**for each of the plurality of intensity maps**" generated at the end of each loop. The "**dosimetric cost term**" is the same as that used by Spirou in Ground 1 and represents dosimetric fitness for the same reasons described above for claim 1 (in both Grounds). (Solberg, ¶179.) The "**delivery cost term"** is provided by Langer Equation (6), which minimizes total monitor units, and represents "**delivery efficiency**" because "more efficient beam delivery" requires "fewer monitor units." (Siebers 958, Solberg, ¶179.)

9. Claim 14: "A method as defined in claim 13, wherein the delivery cost term is a function of delivery time required to deliver radiation according to a beam arrangement represented by the respective intensity map."

The total number of monitor units represents delivery cost: "[t]he studies [comparing Langer's 2-step integer algorithm to two other algorithms] measure the costs, in . . . the number of monitor units, of introducing the leaf movement constraints." (Langer 2451.) Leaf movement/sequencing is the manner in which IMRT is "delivered," hence monitor units represent "**delivery cost**." (Langer 2450; Solberg, ¶181.)

Langer establishes that the total number of monitor units in its algorithm is a function of delivery time to deliver radiation according to a beam arrangement represented by the . . . intensity map:

> <u>Intensity maps were related to the beam times</u> assigned to each leaf position according to established rules for the construction of leaf sequencing algorithms. <u>The rules take the fluence of a beam element to be proportional to its cumulative exposure measured in monitor units</u>.

(Langer 2451 (underlining added).) This is consistent with the background understanding of one of skill in the art that monitor units are a function of delivery time: the higher the number of units, the higher the delivery time (and vice versa). (Solberg, ¶182.)

In fact, Langer explicitly measures monitor units in terms of time. Time "*t*" is a variable in the calculation of Langer's delivery cost term itself. (Langer 2451-2452.) Langer uses a rate of monitor units per unit of time t extending from t=1 (the first unit of time) through $t=T$ (the last unit of time, equal to the upper bound on monitor units), thus implying a constraint that the monitor units per time unit output of the machine is constant. (Langer 2451-2452.) Because Langer uses a constant rate of monitor units per unit of time and explicitly measures monitor units in terms of time, Langer's Equation 6 is a delivery cost term that is a "**function of delivery time required to deliver radiation according to a beam arrangement represented by the respective intensity map.**" (Solberg, ¶183.)

10. Claim 15: "A method as defined in claim 13, wherein the delivery cost term represents at least one of the following: a segment count and an amount of total monitor units, to deliver radiation according to a beam arrangement represented by the respective intensity map."

The delivery cost term in Petitioner's combination is Langer's Equation 6 measuring "the total number of monitor units needed to complete the intensity map." (Langer 2452; Solberg, ¶186.)

11. Claim 16: "A method as defined in claim 13, wherein the delivery cost term is a function of a number of intensity changes across the respective does intensity map; and wherein the method further includes the step of rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value."

As articulated for claim 3 above, Langer's Equation 6 delivery cost term is a "**function of a number of intensity changes across the respective dose intensity map**" because each desired intensity change requires changing the setup of the beam leaf positions and Langer teaches that "[w]hen the leaves are moved in discrete steps with the beam off from one setup of positions to the next," the "total number of monitor units needed to generate the map" changes. (Langer 2450.) "An efficient sequence of leaf movements" corresponding to intensity changes across an intensity map "should take the fewest possible segments to generate a map" with the "minimum number of monitor units" required. (Langer 2450.) One of skill in the art would understand that this minimum number would generally be positively correlated with the number of intensity changes (more changes means more monitor units required and vice versa). (Solberg, ¶189.)

And the proposed combination "further includes the step of rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value" for the same reasons articulated for claim 5[b] and summarized for claim element 9[c]. It would have been obvious to one of skill in the art that Langer's constraint limiting the total number of monitor units *T* discloses this claim limitation. (Solberg, ¶190.) All values exceeding preselected threshold value *T* would be rejected. Also, as shown in claim 5[b], it would have been obvious to a skilled artisan to apply the multiple other possible "threshold values" of delivery cost suggested by Langer to reject inefficient intensity maps. (Langer 2457.)

12. Claim 18: "A method as defined in claim 13, wherein the delivery cost term represents a segment count; and wherein simulated annealing is utilized to form the radiation therapy plan having a delivery cost not exceeding a predetermined segment count and having a minimal dosimetric cost."

Langer's cost term includes "**total monitor units to deliver the radiation treatment plan**." (Langer 2450, 2451-2452.) In addition, Siebers discloses that its optimization method of putting a leaf-sequencing algorithm inside the optimization loop "results in more efficient beam delivery requiring fewer monitor units." (Siebers 958.)

As explained above in claim 8, in the combined objective function depicted above, each of the intensity maps generated is evaluated against Langer's delivery cost term of total monitor units in each iteration of the loop (since Langer's leaf sequencing function is computed within the loop, as taught by Siebers). Langer's algorithm additionally contains a constraint that imposes a threshold on the maximum number of monitor units; that constraint alone will also prevent "**inflation of total monitor units**." (Solberg, ¶194.)

13. Claim 19

(a) "A method of providing control of a trade-off between treatment plan delivery efficiency and dosimetric fitness to optimize a radiation treatment plan within a continuum between delivery efficiency and dosimetric fitness, the method comprising the steps of:" (Claim 19[preamble])

The preamble of claim 19 is identical to that of claim 13, and thus satisfied by Siebers, Spirou, and Langer for the same reasons.

(b) "evaluating an objective cost function within an optimizer for each of a plurality of intensity maps, the objective function including a dosimetric cost term and the delivery cost term, the delivery cost term representing total monitor units to deliver radiation according to a beam arrangement represented by the respective intensity map; and" (Claim 19[a])

"*evaluating an objective cost function within an optimizer for each of a plurality of intensity maps*": The mapping of the prior art to this limitation is the same as the mapping provided for claim 13[b]'s recitation of "evaluating an objective cost function for each of the plurality of intensity maps." The claimed "**optimizer**" in claim 19[a] corresponds to the same iterative optimization algorithm described in claim1[b]. The "**objective cost function**" corresponds to the same function as described in claim element 1[b]. (Solberg, ¶198.)

"***the objective function including a dosimetric cost term and the delivery cost term*"**: As explained for claim 1[b], the "**dosimetric cost term**" in this combined objective cost function is Siebers' objective function representing a "plan quality score," such as, for example, what is boxed in green and purple in Spirou's Equation 3 below:

$$F_{\text{obj}} = \boxed{\sum_{i \in \text{targets}} w_i (d_i - d_p)^2} + \boxed{\sum_{i \in \text{organs}} w_i \zeta_i (d_i - d_c)^2}$$
$$+ \boxed{\sum_{j \in \text{beams}} w_j (x_j' - x_j)^2}, \qquad (3)$$

where x_j' is given by Eq. (1).

(Spirou 2107.) In the combined objection cost function of Siebers, Langer, and Spirou, the **"delivery cost term"** is Langer's Equation 6. The term is the sum of total monitor units:

$$\min \sum_{t}^{T} z^t = Z. \qquad (6)$$

(Langer 2452.) By incorporating the sum of total monitor units in the objective function, the algorithm will seek to minimize monitor units in addition to minimizing deviations from the prescribed radiation dose. (Solberg, ¶199.)

"***the delivery cost term representing total monitor units to deliver radiation according to a beam arrangement represented by the respective intensity map***": The delivery cost term from Langer Equation 6 is a measure of total monitor units to deliver radiation according to a beam arrangement represented by an intensity map. This term is calculated for each iteration of the Siebers loop in the proposed combination, and thus is done for each "respective intensity map." (Solberg, ¶200.)

(c) "rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value." (Claim 19[b])

The proposed combination renders obvious the step of "rejecting each intensity map resulting in the delivery cost term exceeding a preselected threshold value" for the same reasons articulated for claim 5[b]. (Solberg, ¶201.) It would have been obvious to one of skill in the art that Langer's constraint limiting the total number of monitor units *T* discloses this claim limitation. All values exceeding preselected threshold value *T* would be rejected. (Solberg, ¶201.) Also, it would have been obvious to a skilled artisan to apply the multiple other possible "threshold values" of delivery cost suggested by Langer to reject inefficient intensity maps. (Langer 2457.)

IX. CONCLUSION

Petitioner respectfully requests institution of review on the challenged claims.

Dated: October 18, 2019

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) because it contains 13960 words, according to the word-processing system used to prepare this petition, excluding the parts of this petition that are exempted by 37 C.F.R. § 42.24(a) (including the table of contents, a table of authorities, mandatory notices, a certificate of service or this certificate word count, appendix of exhibits, and claim listings).

DATED: October 18, 2019

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. Sections 42.6 and 42.105, that a complete copy of the attached **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,266,175,** including all exhibits (**Nos. 1001-1015**) and related documents, are being served via Federal Express on the 18th day of October, 2019, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon Patent Owner by serving the correspondence address of record with the USPTO as follows:

Best Medical International, Inc.
Patent Counsel
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And, via Federal Express upon counsel of record for Patent Owner in the litigation pending before the U.S. District Court for the District of Delaware entitled *Best Medical Int'l, Inc. v. Varian Medical Systems, Inc.*, Case No. 1:18-cv-01599-UNA as follows:

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