OPTIMIZATION AND INVERSE PLANNING TOOLS IN ONCENTRA GYN

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Abbreviations

Abbreviation	Definition
SDP	Source Dwell Position
ASDP	Active Source Dwell Position
PTV	Planning Target Volume
CTV	Clinical Target Volume
GTV	Gross Tumor Volume
HIPO	Hybrid Inverse Planning and Optimization
OAR	Organ At Risk
VOI	Volume Of Interest
HR-CTV	High Risk CTV
IR-CTV	Intermediate Risk CTV

Part A: Optimization Tools in Oncentra GYN

Optimization assumes that the applicator is placed (virtual or live applicator/catheters) and that the patient relevant anatomy is defined (PTV, CTVs, GTVs, OARs). Furthermore the appropriate region of source stepping within each catheter is defined. This defines the source dwell positions (SDPs), the active ones (ASDPs), out of all possibilities within each catheter, that have to be considered by the Optimization Engine. This is normally done either automatically by using the ***Autoactivation***[1] tool or manually using the corresponding graphical tools in Oncentra GYN (SDP Selection).

Optimization is defined as the technology that **adapts** the dwell times and dwell weights at the corresponding dwell positions within each of the available applicators/catheters to achieve the desired dose distribution.

Oncentra GYN offers four Optimization tools:

Manual adjustment
Graphical optimization
Geometrical optimization
Inverse optimization

In order to have a uniform terminology among different treatment sites, Oncentra GYN has been developed taking into account the GYN GEC ESTRO recommendations for brachytherapy of cervix cancer [15,16]. The aim of these recommendations is to achieve uniform recording and reporting of cervix cancer brachytherapy treatments. Oncentra GYN supports the evaluation of treatment plans according to these guidelines. Furthermore it can be used for prospective treatment planning using the GYN GEC ESTRO concept also for prescribing.

The **PTV**, further used in this document and in Oncentra GYN, is the **CTV** which is used for prescribing, which is either the HR-CTV or IR-CTV. CTV is then either the IR-CTV, or the HR-CTV depending on the selection for PTV or any additional sub target structures of clinical interest. **GTV** can be used additionally as a boost region.

In Oncentra GYN the term **applicator** is used for intracavitary applicators as tandem/ring or tandem/ovoids, while catheter can be every device where sources can be placed, e.g. interstitial needles guided through template holes in the ring or ovoids [17].

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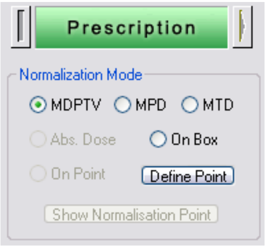
[1] Terms in ***Bold Italic*** can be found in the graphical user interface.

1. Manual Adjustment

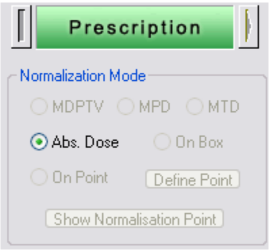
Using this tool, the user is able to manually define or adjust the dwell weights or dwell times of the corresponding source dwell positions.

Several tools available in Oncentra GYN can be incorporated for identifying the most appropriate source dwell position for adjusting its weight or time (e.g. ***Dose Verification to a Point*** in ***Dose Evaluation*** module).



● MDPTV ○ MPD ○ MTD
○ Abs. Dose ○ On Box
○ On Point

When the ***Normalization Mode*** is relative (not absolute dose) and using the manually ***Dwell Weights*** adjustment it has to be kept in mind, that the influence of the changes of the weights on the dose distribution are significantly influenced by the normalization procedure. To achieve more localized effects to the dose distribution, the editing of ***Dwell Times*** is more appropriate.



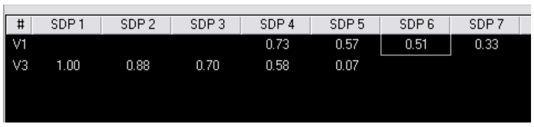
○ MDPTV ○ MPD ○ MTD
● Abs. Dose ○ On Box
○ On Point

When the user edits the ***Dwell Times*** directly, and applies the changes, then the ***Normalization Mode*** is automatically switched to **"absolute dose"** (***Abs. Mode***).

Optimization of dose distribution using the manual adjustment is a trial and error procedure:

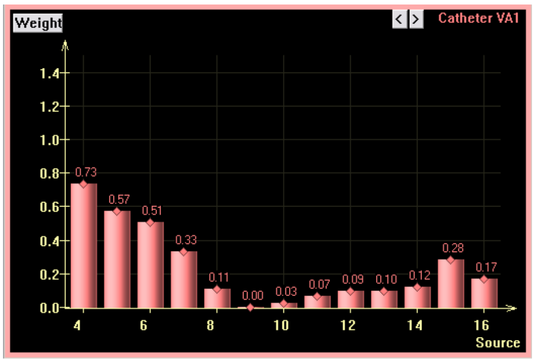
change dwell weights / times → *evaluate resulted dose distribution* → *adjust dwell weights / times* and so on.

Two ***Special*** tools are available for the simplification and speed up the process of manual dwell weights/times adaptation: ***Table Drag & Drop*** and ***Bar Graph***.



#	SDP 1	SDP 2	SDP 3	SDP 4	SDP 5	SDP 6	SDP 7
V1				0.73	0.57	0.51	0.33
V3	1.00	0.88	0.70	0.58	0.07		

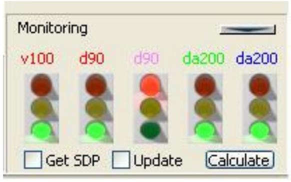
In the lower part of the screen, where the information about the catheters is displayed, one option is to show the dwell times/weights for each ASDP. Using the ***Table Drag & Drop*** tool, the user can simply drag and drop the dwell weight/time value of any ASDP to any other in the table.



The ***Bar Graph*** option represents the dwell times or weights as bars which can be interactively changed by dragging & dropping the corresponding control point with the mouse.

Furthermore, instead of moving each bar, the user can just draw a continuous line (see the green line in the figure) by moving the mouse with the right button pressed. Then, the position of each control point is adapted to the position of the line.

1.1 Monitoring (Traffic lights)



Oncentra GYN is offering an easy to understand tool for immediate evaluation of the main dose-volume parameter values as selected by the user.

The ***Monitoring*** can be used to evaluate up to 5 DVH-based parameter values always during creating the treatment plan. It practically incorporates a dose-volume-constraint tool for up to 5 most important from user point of view DVH-based parameters. It can be activated on selecting  (arrow button) in the lower part of each module. Re-clicking the arrow button hides the monitoring display.

The monitoring parameters including their ranges and a tolerance level are defined in the preferences (***Protocol → Constraints/Protocol/Monitoring***). The tolerance level is used to define the classification of an occurred value of a monitoring parameter to green, yellow or red color. Green means that the observed monitoring parameter value e.g. D_{90} for the target is within the user-defined range (high and low constraint value in the protocol folder in preferences). Yellow means that the concrete parameter value is outside the user defined range but within the tolerance level as defined in the preferences. Finally red color means that the value of the specific parameter is deviating more than the tolerance level form the user-defined constraint values.

Each parameter listed in the monitoring field is represented by its name, colored according the VOI color, and a traffic light. Monitoring is available for all optimization methods.

2. Graphical Optimization

This method can be explained as an automatic adaptation of the dwell weights / times of specific source dwell positions based on the user defined change in the shape of an isodose line.

Thus user defines the shift / change of the isodose line (by dragging the line with the mouse) and the Graphical Optimization Engine calculates the required changes in the dwell weights / times of some of the source dwell positions. The ***Global / Local*** regulator defines the degree of locality for these adjustments. In other words it defines if only very close neighboring dwell positions or also far neighboring dwell positions to the location of the changed isodose line have to be considered.

The ***Normalized*** option defines that the system should follow the user-defined normalization scheme. Thus as in the case of manually changing dwell weights, the effect of these changes is filtered through the normalization procedure. If the user wishes that the system should follow exactly these changes in the isodose shape / line, then the ***Absolute*** mode has to be selected (similar to editing / adjusting the dwell times directly, e.g. using ***Manual Adjustment***).

The buttons ***Undo***, ***Undo All*** and ***Redo*** ensure that any change(s) of the pan will be reversible.

Furthermore, the monitoring functionality (as described in 1.1) is also available for this method.

The implementation of this method in Oncentra GYN is same as in Oncentra Prostate as well as PLATO BPS v14.x planning system.

3. Geometrical Optimization

This is a catheter orientated optimization that generally adjusts the dwell weights at the source dwell positions according to the density of the neighborhood of each dwell position.

If for the optimization of an ASDP all the other ASDPs are to be considered the ***On Distance*** mode can be used. In the case where the ASDPs belonging to the same catheter with the ASDP to be optimized are not to be considered there is the ***On Volume*** mode.

This optimization method does not need anatomical information. Its goal is to homogenize the dose distribution around catheters. Assuming that the catheters are inserted in such a way that their geometrical distribution fits to the geometry of the PTV, the resulted dose distribution is expected to fit more or less to the anatomy.

On Volume mode is adequate when trying to avoid cold areas in between catheters. When a small number of catheters are used or catheter geometry is highly irregular, the resulted dose distribution has to be evaluated carefully. In these cases high volumes of very high doses may exist around catheters. In such cases ***On Distance*** mode is expected to result in more homogeneous dose distributions.

Furthermore, the monitoring functionality (as described in 1.1) is also available for this method.

The implementation of Geometrical Optimization in Oncentra GYN is identical to that of Oncentra Prostate and PLATO BPS v14.x planning system [1], [2].

Geometrical Optimization method results to relative dwell weights that are then transferred to dwell times based on **(a)** the normalization mode, **(b)** the dose prescription: the F-Factor and the prescribed dose (PD), and **(c)** the current strength of the used source.

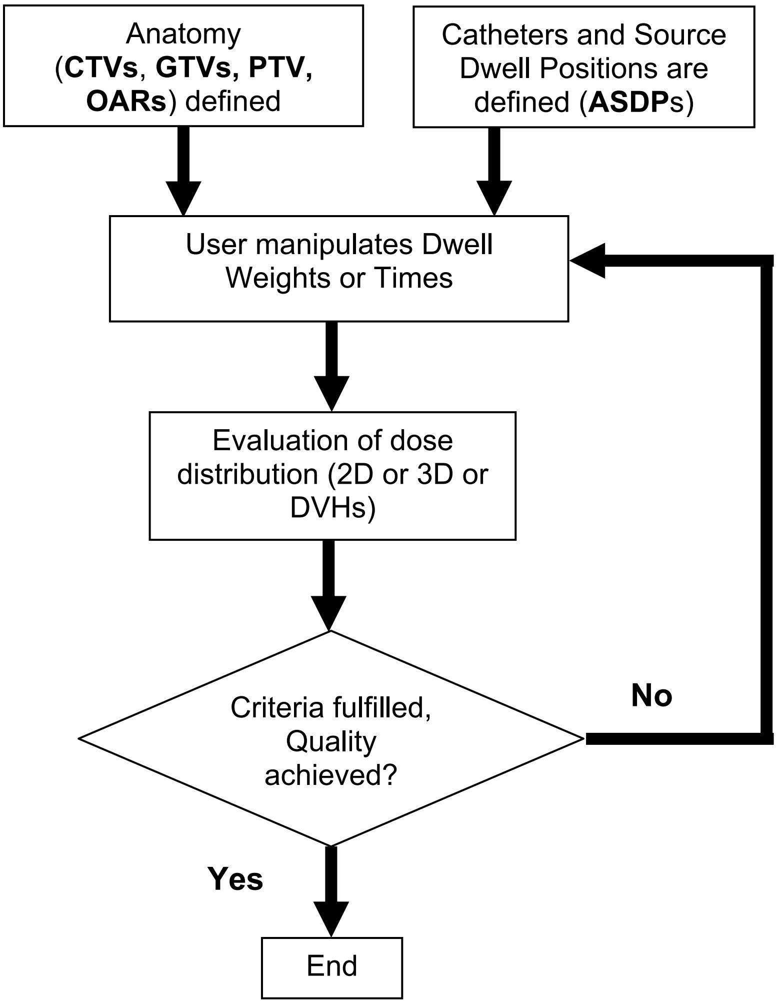
4. Inverse Optimization

4.1 A short introduction to inverse optimization

In all three methods described previously, the user tries to achieve a dose distribution which fulfils the dosimetric criteria by manipulating the dwell weights or times. This family of optimization methods is called **forward optimization**.

As can be seen in the following workflow, forward optimization incorporates a large and time consuming number of iterations of user actions.

Forward optimization diagram



The term **forward** (also known as **simulation** or **modelization**) means, that the user is trying to predict the dosimetric result by setting the values of the dwell times or weights and then evaluates the results of the estimation by calculating the dose distribution. Obviously this is a difficult and complicated task, given that the dosimetric result is a combination of the dwell times / weights and the anatomy/geometry.

A more advanced family of optimization methods is the so called **inverse optimization methods**. The term **inverse** means that user defines the actual result he wishes to achieve,

(i.e., the desired or *ideal dose distribution*) to infer the values of the dwell times or weights, which are the parameters of the dosimetric system.
Here, the user is requested to define/select the criteria defining the quality of the dose distribution as well as the penalty mechanism that has to be applied when these criteria are not met or are violated.

When the quality of the dose distribution is expressed on the basis of the 3D dose distribution in relation to the anatomy (CTVs, GTVs, PTV, OARs) then the terminology **Anatomy Based Optimization** (ABO) is used. In the following discussion the anatomy based inverse optimization is considered.

Generally speaking, the user defines the required or ideal 3D dose distribution and the optimization engine estimates the values of dwell weights / times of the sources (**x**) within the available catheters so that the required dose distribution is achieved - or at least be as close as possible to the required distribution as possible - .

A natural measure quantifying the similarity of a dose distribution at N sampling points with dose values d_i to the corresponding optimal dose values d_i* is a distance measure. A common measure is the L_α norm [3][4]:

$$L_\alpha = \left(\sum_{i=1}^{N} (d_i - d_i^*)^\alpha \right)^{\frac{1}{\alpha}} \tag{1}$$

The differences between various dosimetric based objective functions are concerning a) the norm used (i.e. the value of α) for defining the distance between the ideal and actual dose distribution b) the penalization method for the case of violation and c) the dose normalization applied.

For $\alpha = 2$ (i.e. L_2) we have the Euclidean distance or variance-based objective functions, where the dose values above or below the whished dose value are penalized quadraticaly. For $\alpha = 1$ is penalized linearly while for $\alpha = 0$ the penalization is independent of the dose value.

Thus, Equation (1) describes mathematically the deviation of the actual dose distribution $\{d_i\}$ from the ideal one $\{d_i^*\}$ as a distance measure. L_α can be considered as the **objective function** of the optimization problem and the objective of the optimization process itself is then to minimize the value of this objective function. By minimizing L_α we get dose distributions more similar to the ideal one. The best possible dose distribution is the one that results to the minimum value of the distance-based objective function L_α. L_α as well as d_i are functions of the dwell weights/times vector **x**: $L_\alpha = L_\alpha(\mathbf{x})$ and $d_i = d_i(\mathbf{x})$.

Unfortunately in practice it is not possible or not feasible to define the complete desired 3D dose distribution. The alternative is that user defines a range $[D_L, D_H]$ within which the dose value at any sampling point d_i has to lie. This is equivalent to $D_L \le d_i \le D_H$, for i=1,…,N.

This way, the single objective function of Equation (1) is replaced by the following pair, $f_L(\mathbf{x})$ and $f_H(\mathbf{x})$ [3],[4],[5]:

$$f_L(\mathbf{x}) = \frac{1}{N} \sum_{i=1}^{N} \Theta(D_L - d_i(\mathbf{x}))(D_L - d_i(\mathbf{x}))^\alpha \tag{2}$$

$$f_H(\mathbf{x}) = \frac{1}{N}\sum_{i=1}^{N}\Theta(d_i(\mathbf{x}) - D_H)(d_i(\mathbf{x}) - D_H)^{\alpha} \quad (3)$$

where Θ(x) is the step function defined as:

$$\Theta(x) = \begin{cases} 1 & x > 0 \\ 1/2 & x = 0 \\ 0 & x < 0 \end{cases} \quad (4)$$

For $\alpha = 2$ we obtain the quadratic type (variance) of objectives, where for $\alpha = 1$ a linear form.

Generally speaking the pair objective functions $f_L(\mathbf{x})$ and $f_H(\mathbf{x})$ are defined for any volume of interest, VOI, CTVs, GTVs, PTV and OARs.

Both, low and high, objective functions are applicable in the case of CTVs, GTVs and PTV to define the range of dose required for these targets. For OARs only the high objective function, $f_H(\mathbf{x})$, is considered, which protects the specific OAR from an overdosage. The aim of the low objective is to ensure a minimum level of dose and is obviously not applicable to the case of OARs.

The role of high objective function $f_H(\mathbf{x})$ for CTVs, GTVs and PTV is to avoid (similarly to OARs) volumes of high dose values in these VOIs. In this case, we can consider this objective function to express the homogeneity of the dose distribution within CTVs, GTVs and PTV.

In fact when we try to optimize the dose distribution with respect to CTVs, GTVs, PTV and OARs we have to optimize (minimize) several objectives. This is per definition a **multiobjective (MO) optimization problem**.

We have competing objectives: Increasing the dose in the PTV will result in an increase of the dose outside the PTV and onto other OARs. A trade-off between the objectives exists and –in most of the times- we don't have a situation in which all the objectives can be satisfied in a best possible way simultaneously.

One way for tackling a MO optimization problem (used also in current IMRT planning systems) is by combining the objective functions $f_i(\mathbf{x})$ using weight factors w_i, i=1,…,M also called penalties or **importance factors**. A single, total objective function f, is compiled as a weighted aggregation (i.e. a weighted sum):

$$f(\mathbf{x}) = \sum_{i=1}^{M} w_i f_i(\mathbf{x}) \quad (5)$$

where M is the total number of objectives (i.e., objective functions)

The importance factor of an objective is considered as a measure of the significance of this objective in the optimization process. In fact (based on results from MO optimization theory) it is enough to consider only normalized weights, $\sum_{i=1}^{M} w_i = 1, w_i \geq 0, \forall i$.

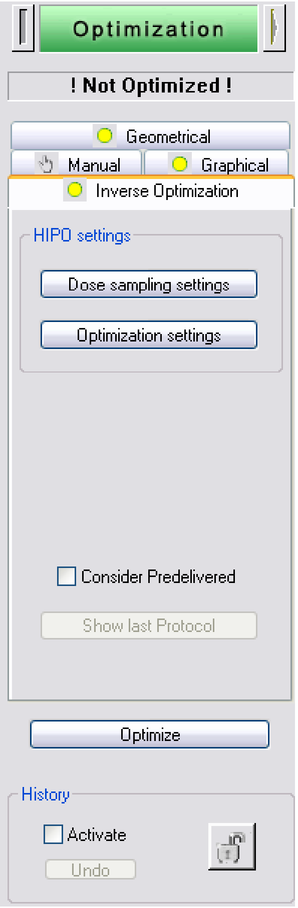
One could consider this method as an *a priori* multiobjective optimization. To get a good result with this method some knowledge of the importance factors and their influence on the results is required. Even if the solution obtained is a global optimal solution, *i.e.* the best possible, for the aggregate single objective function (5), it is possible that by using another set of importance factors, another, better solutions can be obtained.

This is often a try-error procedure that requires repeating optimizations with different sets of importance factors until the treatment planner considers that the optimization result is acceptable. If the result for some of the objectives is not satisfactory then the corresponding importance factor is increased. As this has an effect on the other weights the result for another objective(s) will, most probably, deteriorate.

Oncentra GYN is installed with default values for the importance factors of each objective. These values can be considered as good starting point for the optimization process using the aggregate single objective function as described in Equation (5). Most of the times, this set of default values is delivering a plan of acceptable quality, although the user is encouraged to try many different settings until gathering enough experience on the way that the optimizer works.

4.2 Inverse optimization with HIPO

The **H**ybrid **I**nverse **P**lanning and **O**ptimization (**HIPO**) tool has two main functionalities, as mentioned by its name: inverse planning and inverse optimization. In this paragraph the second functionality will be analyzed.



HIPO inverse optimization method is based on the low and high objective functions as described by Equation (2) and Equation (3) for α = 1. The user defines in general the acceptable range of the dose values within the specific VOI [D_L, D_H], with D_L the low and D_H the high dose limit for that VOI.

PTV related Objective Functions

With $D_{L,PTV}$ and $D_{H,PTV}$ the low and high dose limits for the PTV, the pair objective functions for PTV are given by:

$$f_{L,PTV}(\mathbf{x}) = \frac{1}{N_{PTV}} \sum_{i=1}^{N_{PTV}} \Theta(D_{L,PTV} - d_i^{PTV})(D_{L,PTV} - d_i^{PTV}) \qquad (6)$$

$$f_{H,PTV}(x) = \frac{1}{N_{PTV}} \sum_{i=1}^{N_{PTV}} \Theta(d_i^{PTV} - D_{H,PTV})(d_i^{PTV} - D_{H,PTV}) \qquad (7)$$

N_{PTV} is the total number of dose sampling points in PTV and PTV surface.

Commonly $D_{L,PTV}$ = 100% or equivalently equal to the prescribed dose PD. Currently there exists no straightforward concept to define the value for $D_{H,PTV}$. In general the maximum dose around the intrauterine sources has been very high for a typical intracavitary dose distribution, while it should be limited at the vaginal wall, and the parametrial tissue outside the uterus. A dedicated concept to achieve this also for intracavitary/interstitial approaches will be described later. The value for $D_{H,PTV}$ should be according to each institutional standard, e.g. 300%.

Both PTV related objectives are mandatory for HIPO.

OARs Objective

When OARs have to be considered in the optimization, only the high objective function as described in Equation (3), with α = 1.0 is utilized. This is due to the fact, that only the use of a high dose limit $D_{H,OAR}$ makes sense for the case of organs at risk. The OAR objective function, f_{OAR}, for each of the OARs considered is then given by[3][4]

$$f_{H,OAR}(\mathbf{x}) = \frac{1}{N_{OAR}} \sum_{i=1}^{N_{OAR}} \Theta(d_i^{OAR} - D_{H,OAR})(d_i^{OAR} - D_{H,OAR}) \qquad (8)$$

N_{OAR} is the total number of dose sampling points in the corresponding OAR.

The high dose limits for the OARs are naturally related to the maximum acceptable values to these OARs or more appropriate DVH values as D_{2cc} and/or $D_{0.1cc}$ for those organs. The experience for optimization of prostate plans shows an advantage to use somehow lower values for the $D_{H,OAR}$ than those allowed for the maximum doses. This is in line to use the dose constraint of D_{2cc} for $D_{H,OAR}$ which is only ~60 to ~80% of the maximum dose.

Normal Tissue (NT) Objective

In order that the optimization takes also care of those regions outside the PTV where no OARs are defined, Oncentra GYN offers the possibility that user considers for those regions an additional high objective, the so-called ***Normal Tissue*** (NT) objective:

$$f_{H,NT}(\mathbf{x}) = \frac{1}{N_{NT}} \sum_{i=1}^{N_{NT}} \Theta(d_i^{NT} - D_{H,NT})(d_i^{NT} - D_{H,NT}) \qquad (9)$$

N_{NT} is the total number of dose sampling points in the NT, which are produced within a shell of a specific thickness around the PTV, avoiding any OAR that could be there.

In intracavitary brachytherapy it is appropriate to have a $D_{H,NT}$ significantly higher than the prescribed dose PD, e.g 200% of the PD. This allows maintaining a typical pear shaped isodose shape. In contrast to the case of prostate the dose distribution can be expanded outside CTV, especially in cranial direction inside the uterus if no OAR constraint is violated.

The NT objective is mandatory for HIPO.

Gross Tumor Volume (GTV) Objective

Here similarly to PTV the two dose limits for GTV, $D_{L,GTV}$ and $D_{H,GTV}$, for the GTV (Boost volume) are considered and the corresponding pair objective functions (as for the case of PTV) are given by:

$$f_{L,GTV}(\mathbf{x}) = \frac{1}{N_{GTV}} \sum_{i=1}^{N_{GTV}} \Theta(D_{L,GTV} - d_i^{GTV})(D_{L,GTV} - d_i^{GTV}) \tag{10}$$

$$f_{H,GTV}(\mathbf{x}) = \frac{1}{N_{GTV}} \sum_{i=1}^{N_{GTV}} \Theta(d_i^{GTV} - D_{H,GTV})(d_i^{GTV} - D_{H,GTV}) \tag{11}$$

N_{GTV} is the total number of dose sampling points in the GTV.

It makes sense to use a low dose limit for GTV that is higher than that for PTV, $D_{L,PTV}$ = 100%. Similarly the high dose limit for GTV could be higher than that for PTV. Multiple GTVs can be defined and considered by HIPO optimization engine.

Clinical Target Volume (CTV) Objective

In case where a CTV have to be defined by the planer this can also be considered in the optimization process.

Here similarly to PTV the two dose limits for CTV, $D_{L,CTV}$ and $D_{H,CTV}$, for the CTV are considered and the corresponding pair objective functions (as for the case of PTV) are given by:

$$f_{L,CTV}(\mathbf{x}) = \frac{1}{N_{CTV}} \sum_{i=1}^{N_{CTV}} \Theta(D_{L,CTV} - d_i^{CTV})(D_{L,CTV} - d_i^{CTV}) \tag{12}$$

$$f_{H,CTV}(\mathbf{x}) = \frac{1}{N_{CTV}} \sum_{i=1}^{N_{CTV}} \Theta(d_i^{CTV} - D_{H,CTV})(d_i^{CTV} - D_{H,CTV}) \tag{13}$$

N_{CTV} is the total number of dose sampling points in the CTV.

The definition of a CTV depends on the planer. It can include, be included, be completely independent or intersecting with the PTV. Multiple CTVs can be defined and considered by HIPO optimization engine. In other words, HIPO supports optimization of multiple, independent targets.

The Aggregate Objective Function

Then the total objective function f using Equations (6) to (13) is given by:

$$f(\mathbf{x}) = \sum_{i=1}^{M} w_i f_i(\mathbf{x}) =$$

$$
\begin{aligned}
&= w_{L,PTV} \cdot f_{L,PTV}(x) + w_{H,PTV} \cdot f_{H,PTV}(x) + \\
&\sum_{i=1}^{M_{GTV}} \left[w_{L,GTV_i} \cdot f_{L,GTV_i}(x) + w_{H,GTV_i} \cdot f_{H,GTV_i}(x) \right] + \\
&\sum_{i=1}^{M_{CTV}} \left[w_{L,CTV_i} \cdot f_{L,CTV_i}(x) + w_{H,CTV_i} \cdot f_{H,CTV_i}(x) \right] + \\
&w_{H,NT} \cdot f_{H,NT}(x) + \sum_{i=1}^{M_{OAR}} \left[w_{H,OAR_i} \cdot f_{H,OAR_i}(x) \right]
\end{aligned}
\tag{14}
$$

with

$$
w_{L,PTV} + w_{H,PTV} + \sum_{i=1}^{M_{GTV}} \left[w_{L,GTV_i} + w_{H,GTV_i} \right] + \sum_{i=1}^{M_{CTV}} \left[w_{L,CTV_i} + w_{H,CTV_i} \right] + w_{H,NT} + \sum_{i=1}^{M_{OAR}} w_{H,OAR_i} = 1.0
$$

and M_{CTV} ,M_{GTV} and M_{OAR} are the total number of CTVs, GTVs and OARs respectively considered in the optimization.

Settings regarding the dose sampling points

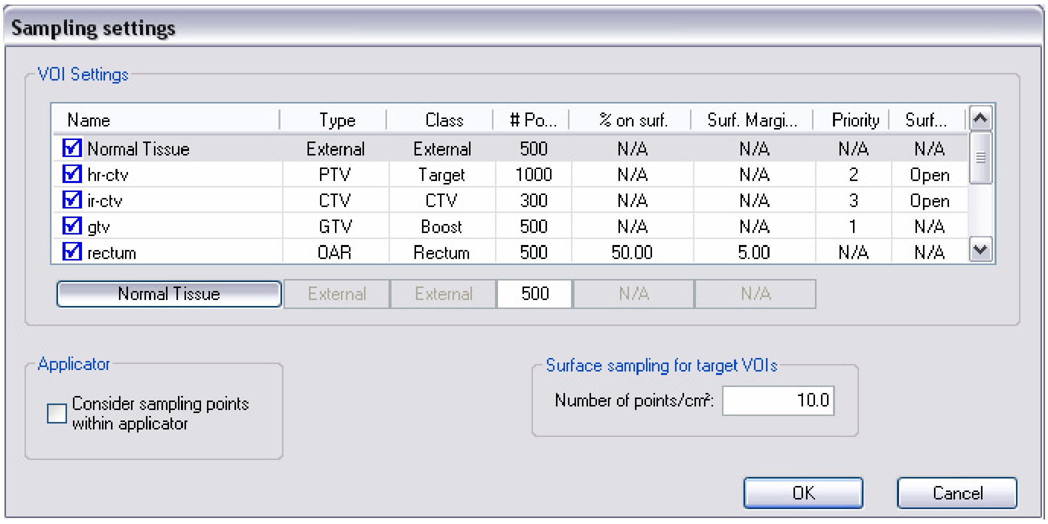
As described in Equations (6) to (13), the calculation of the objective functions for all the volumes of interest (VOIs) is based on the dose values at a specific number of dose sampling points generated on the surface and in the volume of these VOIs.

It is essential to note that Oncentra GYN can take care, if wished by the user, that these dose sampling points are not within the physical catheters and applicator and thus to ensure that the corresponding dose values represent dose to real patient anatomy. The methods and the settings used to achieve this are independent of the optimization method selected. On the other hand, many systems available in the market and many studies are considering sampling points in the applicator and catheters, so an option is available for the user to ***consider sampling points within the applicator***.

The method of effectively generating uniformly distributed dose sampling points on 3D surfaces (not only on contours) and in volumes is described in [7].

It is important to keep the density of sampling points on PTV surface nearly 10.0 points per cm², since this has be shown to result to an adequate estimation of all important statistical parameters for the dose distribution on PTV surface such as dose minimum, maximum, mean and variance [7].

The system allows the user to define the percentage of the sampling points dedicated to an OAR which will be created/sampled on the surface of the organ. This is to increase efficacy for sampling the maximal doses in the OARs, assuming that the dose is distributed from source dwell positions lying outside the OARs (that is always the case). In addition the user can define margin (***Surface Margin*** in mm) to focus production of dose sampling points not only on the surface of the OAR but also in the neighborhood of the PTV. The degree of this neighborhood is defined via the surface margin value. This again increases the efficacy of sampling points where the maximum dose to that OAR is achieved.



Sampling settings

VOI Settings

Name	Type	Class	# Po...	% on surf.	Surf. Margi...	Priority	Surf...
☑ Normal Tissue	External	External	500	N/A	N/A	N/A	N/A
☑ hr-ctv	PTV	Target	1000	N/A	N/A	2	Open
☑ ir-ctv	CTV	CTV	300	N/A	N/A	3	Open
☑ gtv	GTV	Boost	500	N/A	N/A	1	N/A
☑ rectum	OAR	Rectum	500	50.00	5.00	N/A	N/A
Normal Tissue	External	External	500	N/A	N/A		

Applicator

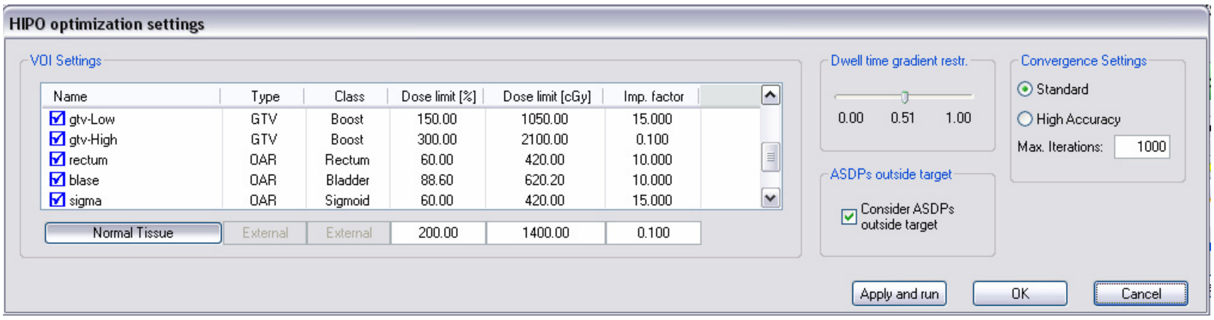
☐ Consider sampling points within applicator

Surface sampling for target VOIs

Number of points/cm²: 10.0

Optimization Settings

In ***Optimization Settings*** all related parameters for HIPO are defined. Based on the defined VOIs and the preset values, several objectives regarding PTV, CTVs, GTVs, NT and OARs can be activated or deactivated and the corresponding low and high dose limit values and their importance factors can be accepted or changed (see figure bellow).



HIPO optimization settings

VOI Settings

Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ gtv-Low	GTV	Boost	150.00	1050.00	15.000
☑ gtv-High	GTV	Boost	300.00	2100.00	0.100
☑ rectum	OAR	Rectum	60.00	420.00	10.000
☑ blase	OAR	Bladder	88.60	620.20	10.000
☑ sigma	OAR	Sigmoid	60.00	420.00	15.000
Normal Tissue	External	External	200.00	1400.00	0.100

Dwell time gradient restr.: 0.00 0.51 1.00

ASDPs outside target

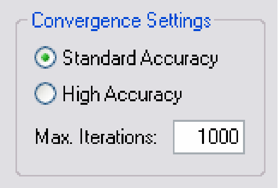
☑ Consider ASDPs outside target

Convergence Settings

● Standard

○ High Accuracy

Max. Iterations: 1000



Convergence Settings

● Standard Accuracy

○ High Accuracy

Max. Iterations: 1000

In ***Convergence Settings***, algorithmic specific settings are listed. In the majority of the cases the ***Standard*** accuracy is adequate for the convergence of the algorithm. ***High Accuracy*** will increase the number of iterations needed and thus the execution time and in extreme case will improve the objective function by some few percents. <u>Thus for clinical use the Standard Accuracy is recommended.</u> The maximum number of iterations (***Max. Iterations***) defines the upper limit of iterations that the algorithm is allowed to run. In most of the plans, 200 to 500 iterations are enough to ensure convergence. So, for clinical use 1000 as a maximum for the iterations number is enough.

HIPO is providing a set of additional unique functionalities including

Dwell time gradient restriction

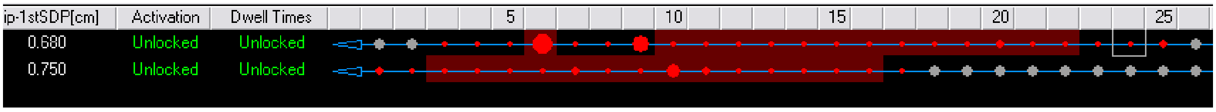
Optimization on part of the implant (lock of dwell times)

Optimization considering pre-delivered dose which are improving the efficiency of the optimizer and the quality of the plan.

Dwell time gradient restriction

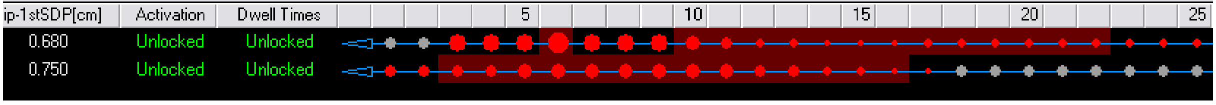
The dwell time gradient restriction (***Dwell time gradient restr.***) parameter considers - in addition to all other anatomy based dosimetric objectives - the gradient of the dwell weights or times of the source within the separate catheters and acts as a weight for the corresponding objective function. This parameter takes values in the range [0, 1]. A value of 0 will get the system to ignore this (no restriction for dwell time gradient), where a value of 1 results to the maximum consideration of it.

In other words, high values of this parameter are expected to produce solutions with smooth changes of dwell times/weights along each catheter and prevent solutions with dominating ASDPs. As an example we are giving the optimization results using the minimum (Fig. a) and maximum (Fig. b) values of the gradient restriction. The dwell time gradient restriction acts practically as a dose modulation restriction filter.



ip-1stSDP[cm]	Activation	Dwell Times
0.680	Unlocked	Unlocked
0.750	Unlocked	Unlocked

Figure (a)



ip-1stSDP[cm]	Activation	Dwell Times
0.680	Unlocked	Unlocked
0.750	Unlocked	Unlocked

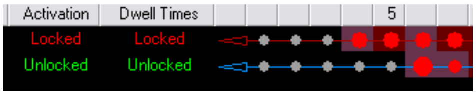
Figure (b)

Optimization on part of the implant (locking the dwell times)

In many cases, the planner is getting close to an acceptable plan at least in a part of the implant. For example, an applicator (tandem & ring and catheters) is inserted and the corresponding dwell times are defined using HIPO or any other optimization method. The result can be generally seen as good, giving as an example the wished standard peer shaped 3D dose distribution but the planner identifies some specific areas, where a better coverage of the target(s) is necessary. The planner could for example plan some extra catheters in those areas where extra dose achievement is needed.

For such cases HIPO offers a functionality that allows locking the dwell times at ASDPs within specific applicators and or some of the available catheters. In this way it is ensured that the contribution of the locked catheters to the total dose distribution is now frozen. Then user can run HIPO now for the unlocked catheters (unlocked dwell times for all ASDPs within those catheters). HIPO will adjust the dwell times for the unlock dwell positions (in our example within the additional catheters/needles) in order to improve the existing dose distribution according to the user-defined objectives.

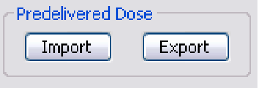
Such a stepwise procedure supports also different optimization settings for different catheter types, in particular intracavitary and interstitial applicators. The dose distribution, especially for high dose values, can then be optimized according to experiences from conservative manual loading.



Activation	Dwell Times
Locked	Locked
Unlocked	Unlocked

The user can lock/unlock the dwell times of all ASDPs within a catheter by simply clicking in the column ***Dwell Times*** at the corresponding row, in the catheters table.

Predelivered dose



HIPO is able to perform inverse optimization considering dose already delivered (e.g. from another fraction). Any calculated 3D dose distribution can be exported / imported from the ***File Operations*** mode and considered as delivered. Then the user can define a new (higher) prescribed dose and ask HIPO to optimize the objectives in order to achieve the prescribed dose, given the predelivered dose. This is done by ticking the option ***Consider Predelivered*** in HIPO settings tab.

After the optimization, the user has the option to display the predelivered (imported) dose distribution, the current dose distribution (output of HIPO optimization) or the sum of both of them. This option is given in ***Dose Settings*** mode.

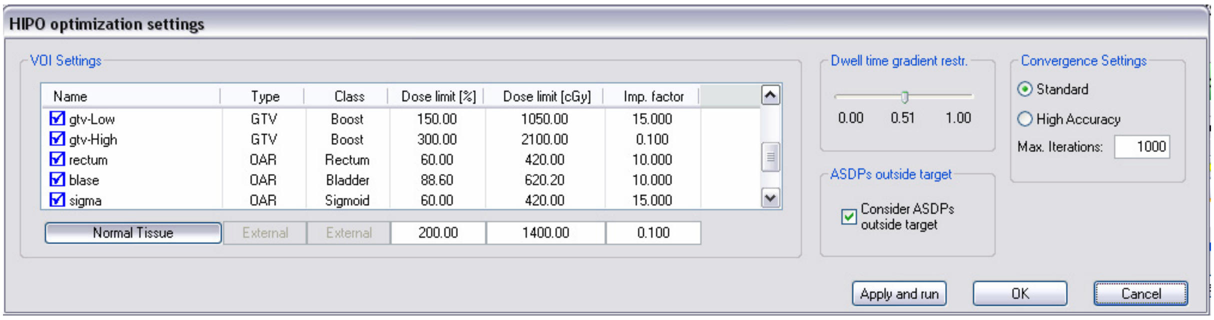
This functionality can help for the case that something is going wrong with the delivery of the dose in a fraction. An example could be the case of miss-connection of 2 catheters, After identification of this error at the end of the treatment, user can reconstruct this miss-connection in Oncentra GYN and export the dose distribution resulted by this. Then for the second fraction given by the same implant, this dose is imported as predelivered and user runs the optimization procedure with HIPO considering the pre-delivered dose. It is obvious that in such a case the prescribed dose and the corresponding dose limits for all relevant VOIs for the 2nd fraction have to be defined as the total of two fractions. The results will demonstrate if it is possible and how to adjust the delivery of the second fraction, in such a way that the deviations acquired during the 1st fraction are counterbalanced.

Another term proposed for this type of optimization is "*topographic optimization*", meaning that the inverse dose optimization is performed taking into account not only the anatomy and the objectives but also the "topography" of an existing dose distribution.

Exampes of clinical scenarios

In the clinical practice different scenarios can be implemented. In the following, two representative cases are addressed and the corresponding settings and workflow are presented.

Case A: A standard applicator from the applicator configuration list is used. Optimization Settings for such a case can be as in the following two figures.



HIPO optimization settings

VOI Settings

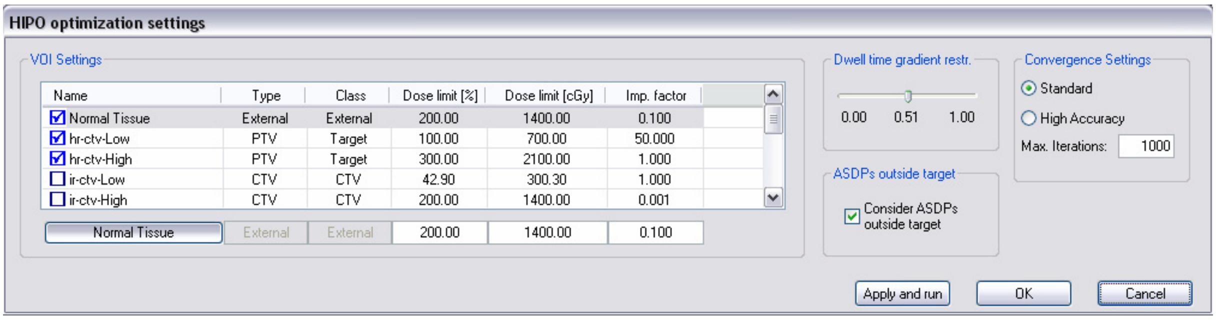
Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ gtv-Low	GTV	Boost	150.00	1050.00	15.000
☑ gtv-High	GTV	Boost	300.00	2100.00	0.100
☑ rectum	OAR	Rectum	60.00	420.00	10.000
☑ blase	OAR	Bladder	88.60	620.20	10.000
☑ sigma	OAR	Sigmoid	60.00	420.00	15.000
Normal Tissue	External	External	200.00	1400.00	0.100

Dwell time gradient restr.: 0.00 0.51 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000



HIPO optimization settings

VOI Settings

Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ Normal Tissue	External	External	200.00	1400.00	0.100
☑ hr-ctv-Low	PTV	Target	100.00	700.00	50.000
☑ hr-ctv-High	PTV	Target	300.00	2100.00	1.000
☐ ir-ctv-Low	CTV	CTV	42.90	300.30	1.000
☐ ir-ctv-High	CTV	CTV	200.00	1400.00	0.001
Normal Tissue	External	External	200.00	1400.00	0.100

Dwell time gradient restr.: 0.00 0.51 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000

Case B: Additional catheters/needles are to be placed through the available holes in the applicator, as it is the case for the Vienna applicator.

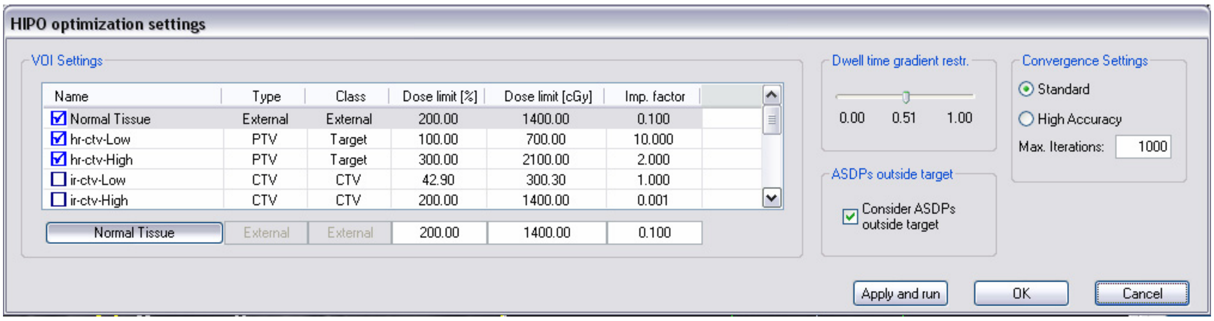
For this case the availability (defined in the Preferences) of two different optimization settings could be useful and are recommended. The aim is obviously to achieve an adequate coverage of PTV. At the same time, user wishes to maintain the “typical” intracavitary dose distribution. In this case, most of the dose contribution to the target(s) results from the source dwell positions within the intracavitary applicator. Additional interstitial needles are then placed to fine tune the dose distribution - mostly at the lateral extensions of the CTVs, where there is not adequate coverage from the applicator -. Such an approach can protect from the existence of high dose regions outside the uterus, where structures as nerves, vessels and connective tissue are present without explicit contours.

This is from workflow point of view an iterative procedure:

a) Load the 1st set of optimization settings defined in the presets especially to be applied to the applicator and optimize the dwell times for ASDPs within the applicator
b) Apply any further adjustment of the dose distribution using any of the tools in Oncentra GYN (e.g. graphical optimization) if wished
c) Lock now the dwell times within the catheters of the applicator
d) Load the 2nd set of optimization settings especially defined in the presets and run HIPO for the additional interstitial needles considering the dose contribution from the frozen dwell times within the applicator
e) Check if the result is the desired. If yes, then stop adjustments

f) If not, lock the dwell times of the ASDPs within the additional interstitial catheters
g) Unlock dwell times within applicator and go to step (a)

1st set (Applicator only)



HIPO optimization settings

VOI Settings

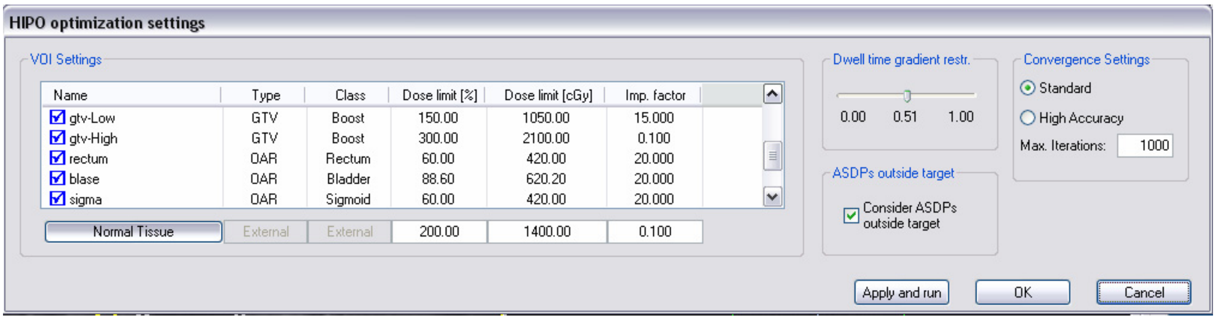
Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ Normal Tissue	External	External	200.00	1400.00	0.100
☑ hr-ctv-Low	PTV	Target	100.00	700.00	10.000
☑ hr-ctv-High	PTV	Target	300.00	2100.00	2.000
☐ ir-ctv-Low	CTV	CTV	42.90	300.30	1.000
☐ ir-ctv-High	CTV	CTV	200.00	1400.00	0.001
Normal Tissue	External	External	200.00	1400.00	0.100

Dwell time gradient restr.: 0.00 0.51 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000



HIPO optimization settings

VOI Settings

Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ gtv-Low	GTV	Boost	150.00	1050.00	15.000
☑ gtv-High	GTV	Boost	300.00	2100.00	0.100
☑ rectum	OAR	Rectum	60.00	420.00	20.000
☑ blase	OAR	Bladder	88.60	620.20	20.000
☑ sigma	OAR	Sigmoid	60.00	420.00	20.000
Normal Tissue	External	External	200.00	1400.00	0.100

Dwell time gradient restr.: 0.00 0.51 1.00

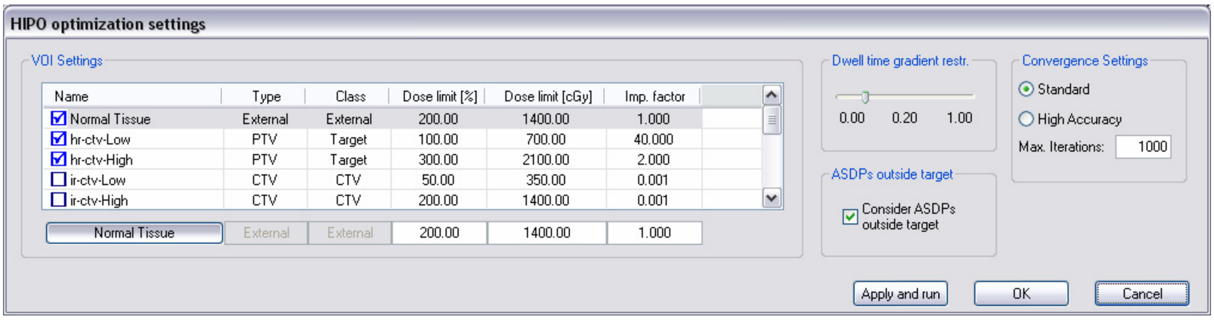
ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000

This set should mainly spare OARs, while target coverage will be achieved with the additional needles using the 2nd set.

2nd set (Additional catheters only)



HIPO optimization settings

VOI Settings

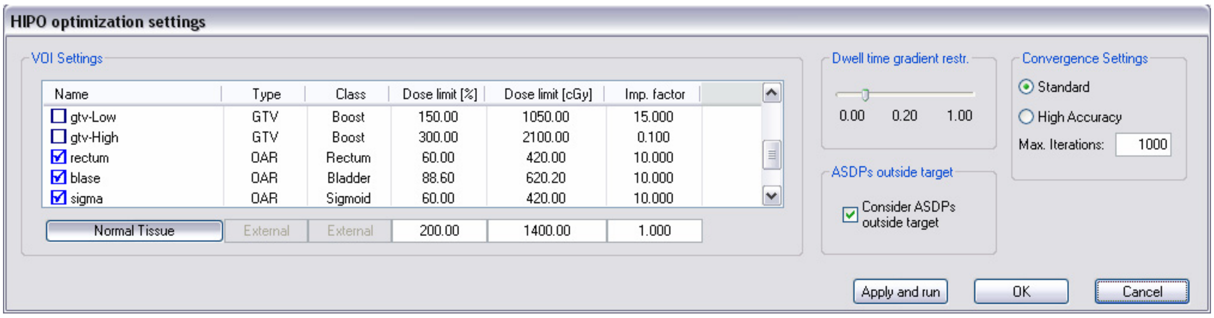
Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ Normal Tissue	External	External	200.00	1400.00	1.000
☑ hr-ctv-Low	PTV	Target	100.00	700.00	40.000
☑ hr-ctv-High	PTV	Target	300.00	2100.00	2.000
☐ ir-ctv-Low	CTV	CTV	50.00	350.00	0.001
☐ ir-ctv-High	CTV	CTV	200.00	1400.00	0.001
Normal Tissue	External	External	200.00	1400.00	1.000

Dwell time gradient restr.: 0.00 0.20 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000



HIPO optimization settings

VOI Settings

Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☐ gtv-Low	GTV	Boost	150.00	1050.00	15.000
☐ gtv-High	GTV	Boost	300.00	2100.00	0.100
☑ rectum	OAR	Rectum	60.00	420.00	10.000
☑ blase	OAR	Bladder	88.60	620.20	10.000
☑ sigma	OAR	Sigmoid	60.00	420.00	10.000
Normal Tissue	External	External	200.00	1400.00	1.000

Dwell time gradient restr.: 0.00 0.20 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

Convergence Settings: ● Standard ○ High Accuracy

Max. Iterations: 1000

Comments on HIPO algorithm

HIPO incorporates objective functions similar to those of IPSA method [5], but makes use of a considerably faster optimization engine that enables interactive (try-error) optimization using HIPO engine in Oncentra GYN. A typical time for inverse optimization with HIPO in Oncentra GYN is ~5 sec.

In addition HIPO offers the extra functionalities of dwell time gradient restriction, optimization on a predelivered dose distribution and optimization with some dwell times “locked”. All these functionalities are not available with IPSA or any other commercially available optimization engines.

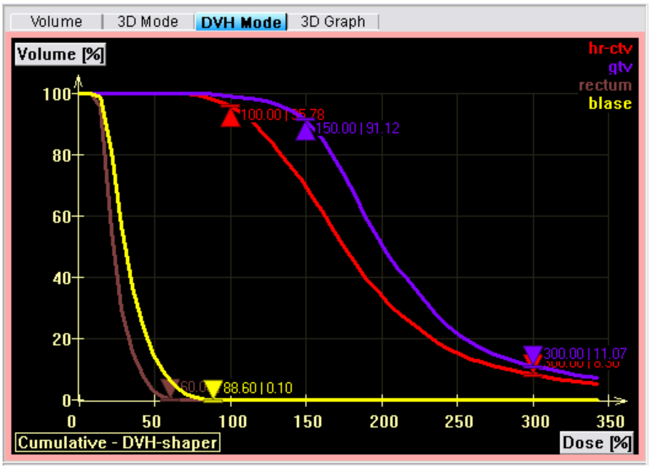
Depending on the implant and anatomy geometries and the user defined penalization, very high values Dosimetric parameters V_{100} and D_{min} for the PTV can be achieved. This is possible due to the ability of HIPO to expand the dose distribution, within some limits related to the NT objective, also outside to PTV.

Note that HIPO works always in the absolute dose (***Abs. Dose***) normalization mode.

Furthermore, the monitoring functionality (as described in 1.1) is also available for HIPO.

4.3 DVH-Shaper

After an inverse optimization using HIPO, by opening the ***DVH Mode***, the ***DVH-Shaper*** tool is available. This is recognized by the label at the lower left corner in the DVH view window and the special markers (triangles, Up or Down oriented) available on the DVH curves.



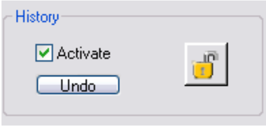
What is the DVH-Shaper?

It is a graphical, interactive tool, enabling user to adjust the optimization parameters graphically, on the DVH, and in a native way avoiding numbers and penalization inputs. The system displays a control point for each of the considered objectives on the corresponding DVH, which is marked by a triangle in the color of the DVH curve. Up triangle (▲) stands for low objective and low dose limit, where down triangle (▼) stands for high objective and high dose limit.

Oncentra GYN shows always after the optimization the DVH values at these control points; Dose values and histogram values are separated by a bar (|). The DVH-Shaper is available only in the Cumulative DVH mode.

How does DVH-Shaper work?

General



After a specific optimization is finished and before start working with ***DVH-Shaper***, it is recommended to activate the ***History*** and Lock this optimization and its result. Oncentra GYN offers this unique possibility at the lower part of the GUI for the optimization. By activating the ***History*** and locking the current result, user can always, by pressing the ***Undo*** button, return to the original situation, independently of how many efforts have been done in between. It is important that user evaluates the changes resulted by his action on that specific control point for all the DVH curves shown, for all other objectives considered. If the result is appropriate, user can deactivate the History and thus keep the current optimization result.

After an optimization using the HIPO method has been done, the DVHs for the selected VOIs are shown with the following control points representing each of the objective functions considered in the optimization.

(A) PTV

One control point is shown for the low objective (see Equation 6) with an Up triangle ▲ is shown at the PTV DVH curve at the low dose limit position, $D_{L,PTV}$.

The second control point is shown for the high objective (see Equation 7) and it is marked by a Down triangle ▼. This control point is placed at the DVH curve for PTV at the corresponding user-defined high dose limit, $D_{H,PTV}$.

It has to be mentioned here that both control points are always present due to the fact that both PTV related objectives are mandatory for HIPO.

(B) GTV (Boost volume)
In the HIPO method the GTV VOIs are handled similarly to PTV and thus two objectives, the low and the high, can be considered for the optimization (see Equations 10 and 11). For these objectives there will be two control points, ▲ and ▼, placed as described for the case of PTV at the user-defined low, $D_{L,GTV}$, and high, $D_{H,GTV}$, dose limits respectively. Since both of these objectives are optional, only the control point of the selected GTV-objective(s) will be available (none, one or both).

(C) CTV
CTV VOIs are also handled similarly to PTV & GTV, thus two objectives, the low and the high, can be considered for the optimization (see Equations 12 and 13). For these objectives there will be two control points, ▲ and ▼, placed as described for the case of PTV at the user-defined low, $D_{L,CTV}$, and high, $D_{H,CTV}$, dose limits respectively. Since both of these objectives are optional, only the control point of the selected CTV-objective(s) will be available (none, one or both).

(D) NT (Normal Tissue)
Although the NT objective as described by Equation (9) is always used in HIPO, there is no control point available for that objective. This is mainly due to the fact that NT it is an artificial VOI surrounding the PTV and the aim of the corresponding objective is to prevent the expansion of the dose distribution at regions outside the PTV. Thus there is no DVH available for VOI and as a consequence there is no control point available for NT in the DVH-Shaper tool.

(E) OARs
For each OAR considered, HIPO offers a corresponding high objective that is based on the user defined high dose limit for that OAR, $D_{H,OAR}$, (see also Equation 8). In this case a Down triangle ▼ marks the corresponding control point that is placed on the DVH curve for that OAR at the dose level $D_{H,OAR}$.

User can then drive the HIPO optimization engine to improve the dosimetric results by manipulating one of the available control points.

Rules

There are a few simple rules regarding the successful use of the DVH shaper functionality. The principle is that the user can, using the left mouse button, drag the control point and move it towards the Up or Down direction as defined by the corresponding control triangles. A horizontal bar drawn at the edge of the triangle notes the sensitive area for manipulating this control point. After dropping the control point, HIPO runs automatically and the resulted DVHs are shown together with the original (e.g. the locked) ones.

The current DVHs are shown as thick light colored curves, where the locked ones as thin dark curves. During the shifting of the control point, the system shows in the GUI the name of the corresponding objective of HIPO method. User should carefully manipulate the control points, waiting for the result and evaluating the sensitivity of the achieved result on the changes of that control point. In any case the start situation can be restored by pressing ***Undo***.

Oncentra GYN DVH-Shaper offers the user the possibility to change/adapt the corresponding dose limits for every objective selected for optimization. This can be done by keeping the control button pressed and clicking with the left mouse button on the corresponding control point. Then the shape of the triangle is changed form vertically aligned to horizontally aligned and the dose value that corresponds to the current mouse position is displayed. While in this mode, the user can shift the control point only horizontally. After dropping the control point, HIPO runs and optimize the plan with the new dose limits and displays automatically the resulted DVHs.

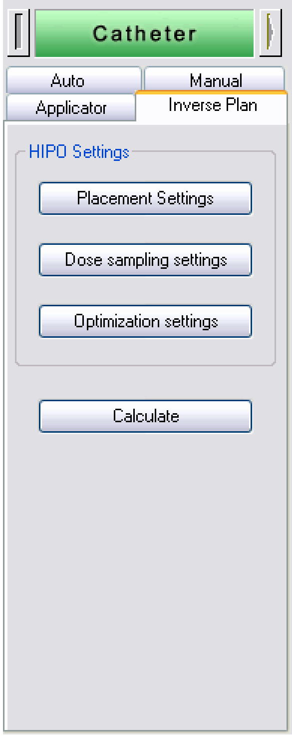
User should also make such manipulations /adaptations very carefully, observing and evaluating the changes achieved in the DVHs, which demonstrate graphically the intercorrelations existing between the different objectives.

When the optimization is locked, DVH-Shaper shows always the DVHs of the originally locked optimization and the DVHs resulted from the current user operation. If user wishes to see only the changes resulted from the last two sequential operations, then he should unlock the optimization by clicking on the lock icon (***History*** GUI area, down right). If the current result is the expected one, user can accept and keep the current optimization by deactivating the ***History*** option of the DVH-Shaper tool.

Limitation

It has to be mentioned, that for vertical manipulations of the control points, DVH-Shaper will attempt to shift the corresponding DVH curve at that direction. The user operation defines the direction of shifting but this will probably not result to shifting the DVH at exactly that user defined point/position.

Part B: Inverse Planning in Oncentra GYN



As mentioned previously, optimization assumes that catheters (virtual or live catheters) are placed, the corresponding appropriate source dwell positions (ASDPs) are selected and that the patient relevant anatomy is previously defined (CTVs, GTVs, PTV, OARs). Optimization then **adapts** the dwell times (or weights) at the corresponding dwell positions of the source within each of the available catheters so that the desired dose distribution results.

Inverse planning begins one step before and is the technology that **adapts (a)** the catheter placement, **(b)** the corresponding source dwell positions (ASDPs) and **(c)** the dwell times (or weights) of the source at these positions within each of these catheters so that the desired dose distribution results.

The inverse planning engine assumes that the user has already defined the patient relevant anatomy (CTVs, GTVs, PTV, OARs), as it is the case for the inverse optimization, and also the number of catheters to be used.

The term **inverse** means here that the user uses the actual result he wishes to achieve, namely a) the number of catheters he likes to insert and b) the desired or ideal dose distribution he likes to achieve in order to infer a) the exact placement (positions) of these catheters, b) the adequate source dwell positions (ASDPs) within these catheters and c) the corresponding values of the dwell times or weights, that all are the parameters of the dosimetric system.

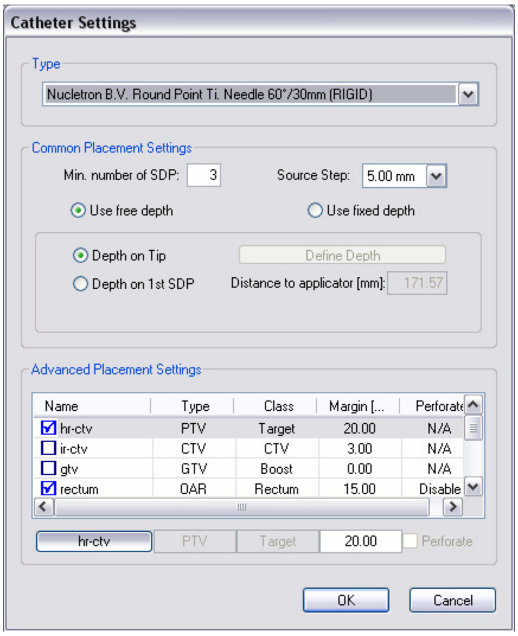
1. Hybrid Inverse Planning and Optimization (HIPO)

HIPO is the inverse planning engine available in Oncentra GYN. As explained earlier, HIPO has two functionalities: inverse planning and inverse optimization. The second one was presented in paragraph 4.2. The first one, which will be described in this paragraph, is available in ***Catheter Placement*** module.

This system utilizes topology related features and a stochastic algorithm for adjusting and adapting the catheter/needle configuration and an inverse optimization engine for the adjustment of dwell times of the source dwell positions within the catheters.

The main difference in the GUI when compared to that of pure inverse optimization, is that in the case of inverse planning the user has to define the catheter placement rules, available under the ***Placement Settings*** menu.

Settings regarding the catheter placement



Catheter Settings

Type: Nucletron B.V. Round Point Ti. Needle 60°/30mm (RIGID)

Common Placement Settings

Min. number of SDP: 3
Source Step: 5.00 mm
● Use free depth
○ Use fixed depth
● Depth on Tip
○ Depth on 1st SDP
Distance to applicator [mm]: 171.57

Advanced Placement Settings

Name	Type	Class	Margin [...	Perforate
☑ hr-ctv	PTV	Target	20.00	N/A
☐ ir-ctv	CTV	CTV	3.00	N/A
☐ gtv	GTV	Boost	0.00	N/A
☑ rectum	OAR	Rectum	15.00	Disable

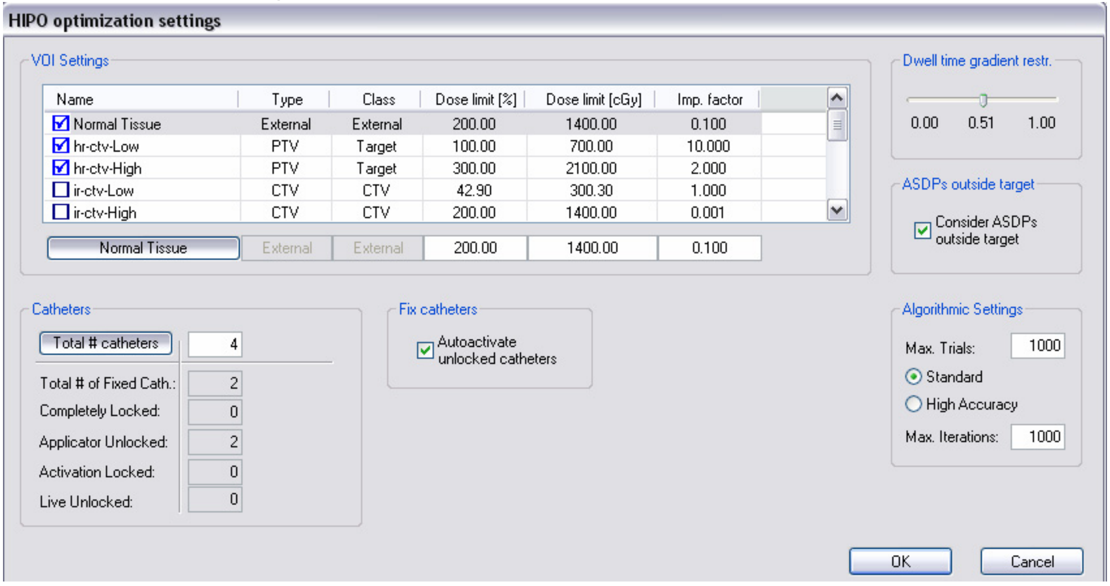
hr-ctv | PTV | Target | 20.00 | ☐ Perforate

These are identical with the catheter settings for the ***Auto*** and ***Manual*** catheter placement in ***Catheter Placement*** module. All catheters that can be placed according to these settings will be considered by HIPO. Out of all these possible catheters HIPO will then search out the most appropriate ones, according to the user selected objectives and importance factors. It has to be mentioned that user can preset all these parameters according to his own experience in the corresponding **Preferences / Protocol** in the **Placement** tab.

Settings regarding the dose sampling points

These are exactly the same as in the HIPO for inverse optimization and have been described in the corresponding section.

Optimization Settings



HIPO optimization settings

VOI Settings

Name	Type	Class	Dose limit [%]	Dose limit [cGy]	Imp. factor
☑ Normal Tissue	External	External	200.00	1400.00	0.100
☑ hr-ctv-Low	PTV	Target	100.00	700.00	10.000
☑ hr-ctv-High	PTV	Target	300.00	2100.00	2.000
☐ ir-ctv-Low	CTV	CTV	42.90	300.30	1.000
☐ ir-ctv-High	CTV	CTV	200.00	1400.00	0.001

Normal Tissue | External | External | 200.00 | 1400.00 | 0.100

Dwell time gradient restr.: 0.00 0.51 1.00

ASDPs outside target: ☑ Consider ASDPs outside target

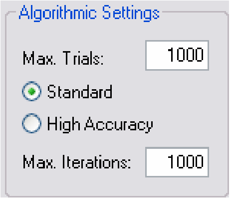
Catheters

Total # catheters: 4
Total # of Fixed Cath.: 2
Completely Locked: 0
Applicator Unlocked: 2
Activation Locked: 0
Live Unlocked: 0

Fix catheters: ☑ Autoactivate unlocked catheters

Algorithmic Settings

Max. Trials: 1000
● Standard
○ High Accuracy
Max. Iterations: 1000

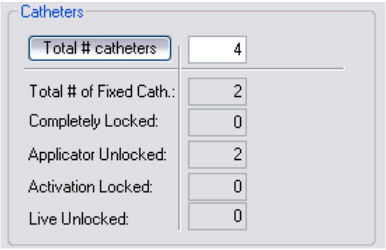


Algorithmic Settings

Max. Trials: 1000
● Standard
○ High Accuracy
Max. Iterations: 1000

The optimization settings for the inverse planning part of HIPO are (as expected) similar to these of the inverse optimization functionality. The ***VOI Settings***, the ***Dwell time gradient restr*** and a part of the ***Algorithmic Settings*** are identical and explained in previous paragraphs. The only new setting is the ***Max. Trials*** number, defining the maximum number of set-ups (plans) that HIPO will try before it stops. Normally, 1000 is covering full search of every possible position for each catheter.

It has to be mentioned that all optimization and dose sampling settings are common for both HIPO functionalities. This means that when the value of a setting or an option is changed in one functionality, it automatically changes for the other too.



Catheters

Total # catheters: 4

Total # of Fixed Cath.: 2

Completely Locked: 0

Applicator Unlocked: 2

Activation Locked: 0

Live Unlocked: 0

In the **Catheters** information block, the user defines the number of catheters that HIPO has to place automatically so that the objectives will be fulfilled in the best possible way (obviously under consideration of the user-defined penalties/ importance factors).

The user must take care that the number of catheter requested to be placed is higher than the total number of “fixed” catheters. By the term “fixed” catheters are described all those catheters that are either already placed and obviously cannot be moved by HIPO or catheters having locked status. Such kind of catheters can be divided into four categories:

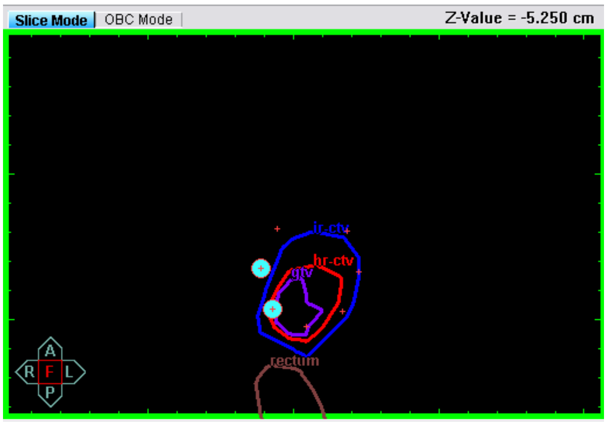
- Catheters that are embedded in the applicator
- Live catheters
- Catheters with locked dwell times (completely locked)
- Catheters with locked activation status (ie, SDPs cannot be activated/deactivated)

We have to explain here that the lock status of the ASDPs within catheters has two levels: lock of dwell times at the ASDPs or onely lock of their activation status (ASDP). The lock of activation has the meaning that no changes are allowed in the activation status (i.e., activating / de-activating) of the SDPs belonging to this catheter.

Execution of the HIPO inverse planning

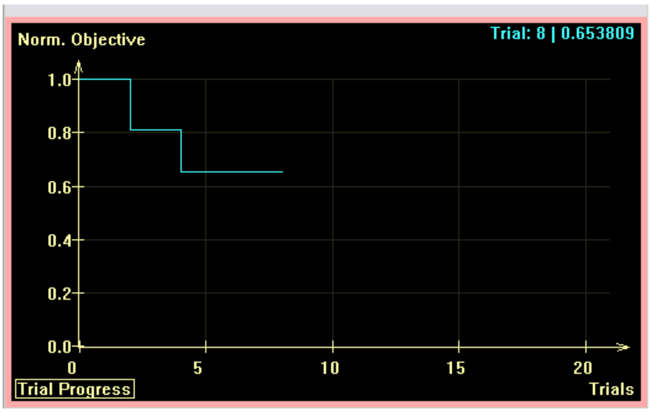
The user by pressing the button ***Calculate*** enforces the execution of the HIPO inverse planning engine. First, HIPO is finding out all catheters (so-called *feasible catheters*) that can be inserted according to the ***Placement Settings*** defined by the user. During this process the message “Inserting catheters xx%” appears in the status bar in the GUI. xx stands for the percentage of the feasible catheters already found.

Thereafter HIPO begins to search for the best placement of the user-defined number of catheters, based on the total number of feasible catheters and the objectives and penalties defined by the user. The system switches then to the HIPO-specific GUI, that is shown in the following Figure.



Here the upper-right and lower-left windows in the GUI are adapted to display HIPO specific information.

Lower-Left window. In this window the system now displays the reference plane including only the VOI-contours, the template grid and the currently used catheters, displayed as circles at the corresponding template holes. The US or CT or MR image is switched off during the HIPO run. Here user can follow the placement efforts of HIPO and can intervene at any time as will be explained in the following.



Upper-Right window. In this window and during the execution of HIPO the trial progress is shown. The value of the total aggregate objective function according to HIPO inverse optimization algorithm (see Equation 14), normalized to its initial value (its value at the first trial) and for the current trial is shown, both, graphically as a curve, and numerically at the upper right part of this window.

These two windows offer all the adequate information user needs to intervene and interrupt the HIPO execution at any time. The user can interrupt by pressing the **Escape** button. This is meaningful, **(a)** if the user by evaluating the current catheter placement geometry decides that it is adequate, or wishes to evaluate this placement dosimetrically utilizing DVHs and isodose distributions, **(b)** if HIPO runs over at least 200 trials and a plateau is achieved in the normalized total objective function curve that extends over more than 30 trials.

The latest is an indication that further improvement of the dosimetric results (dose distribution) expressed as improvement in the aggregated total objective function for the given penalties and dose limits, by changing the catheter geometry/placement, is more or less not to be expected. Although HIPO makes use also of stochastic technology (hybrid-technology), that means that the more trials are executed the more is probable that the system approaches/approximates the “global” optimum, studies with runs with very high number of trials have shown that the improvements can or will be achieved thereafter do not justify the extra time spent (for most of the cases).

<u>If the user does not interrupt HIPO, HIPO will finish after executing the maximum number of trials, as defined in the Optimization Settings.</u>

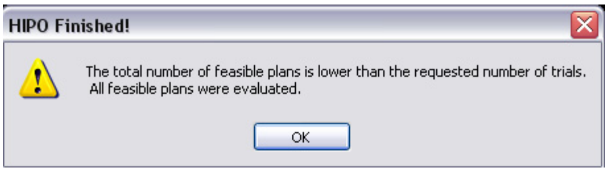
For getting a feeling for the performance of HIPO, let discuss an example, regarding an applicator with Nucetron Vienna CT/MR Ring 60°/26mm, having 7 holes. Let’s assume that, for the given catheter placement settings, there are seven feasible positions and 4 catheters are required. Then HIPO has to find which 4 out of the 7 feasible are giving the best plan according to the user defined optimization parameters. There exist 210 different catheter combinations, i.e., the possible combinations of 7 catheters taken 4 at a time:

$$\frac{7!}{4!x(7-4)!} = 210$$

When using a very fast PC (Core 2 Duo technology) the HIPO inverse optimization run takes approximately a second. This means that for analyzing all these possible catheter combinations we should wait less than 3 minutes for getting the result.

It must be mentioned that in a typical Oncentra GYN plan all possible feasible plans are some hundreds and <u>the execution time for HIPO in order to explore and evaluate **all** feasible plans is some minutes (typically 1-2 minutes)</u>.

If the total number of possible catheter combinations is less or equal the maximum number of trials defined by the user, HIPO will obviously analyze all these possible combinations and in this case user can be sure that the “global” optimum, the best implant, has been achieved. In this case the following message appears after the execution of HIPO.


HIPO Finished!

The total number of feasible plans is lower than the requested number of trials.
All feasible plans were evaluated.

HIPO internally calculates the number of feasible plans, and if they are less than the maximum number of iterations, it automatically rescales the horizontal axis of the upper right window.

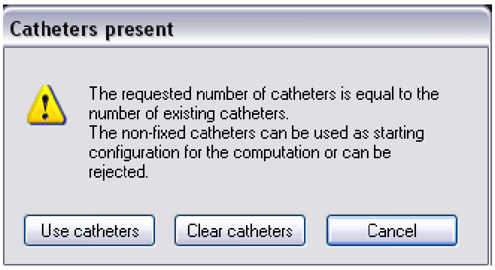
We have to mention, that the time needed to get a good implant according to the criteria explained above, depends on **(a)** the target volume, **(b)** the number of holes on the ring e.g. for the case of the Vienna applicator, **(c)** the total number of sampling points used for the evaluation of the objective functions and thus the number of objective functions selected, **(d)** the number of catheters the user has decided to place and **(e)** the source step selected that influences the resulting total number of active source dwell positions.

User-Scenarios supported by HIPO

The following different scenarios regarding the automatic placement of catheters, inverse planning, are supported by HIPO.

HIPO improves user-proposed catheter placement

Here the user can propose a catheter placement, e.g. using the manual catheter placement tool, or by loading a plan. Then user can execute HIPO. Let take the example that user has placed manually 2 catheters according to his experience, which is exactly the number of catheters decided to be used for the current clinical case. Setting in the Optimization Settings for HIPO the number of catheters to 2 (plus any number of catheters in the applicator) and pressing Calculate, HIPO will react with the following message:


Catheters present

The requested number of catheters is equal to the number of existing catheters.
The non-fixed catheters can be used as starting configuration for the computation or can be rejected.

Pressing the button ***Use Catheters*** the user enforces HIPO to keep the 2 user proposed catheters and try to improve their placement. The criteria for termination/interruption of HIPO run are here exactly the same as discussed previously for the standard HIPO run. If the user presses the button ***Clear Catheters*** HIPO will delete the available 2 catheters and begin the inverse planning procedure looking for the best placement of 2 catheters as described in the standard HIPO run.

HIPO searches for appropriate additional catheters

There are two scenarios that are supported here by HIPO. To explain this more clearly let keep the case that user is looking for the best placement of 4 catheters.

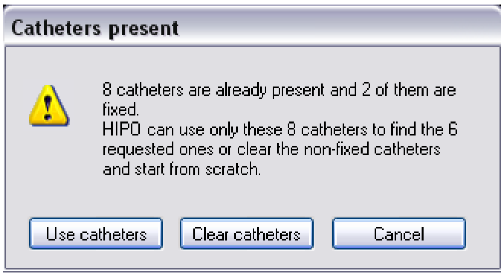
First case
This is the case when the user has manually placed part of the wished number of catheters, e.g. 2 catheters, since according to his experience these applicator holes/catheter positions are mostly appropriate and wishes that HIPO will then complete the implant, by keeping these 2 user-defined catheters unchanged.
This means that HIPO has to look for the best placement of the remaining 2 catheters. This could be also the case, when these 2 catheters have been already implanted into the prostate by the physician (these 2 are then live catheters). For HIPO this makes no difference. In both cases user has to define **firstly** the positions (template holes) of the 2 catheters and then to enter the total number of wished catheters to 4 (plus any catheters in the applicator) in the ***Optimization Settings*** for HIPO. Then the user locks the inserted catheters (lock ***Activation***). Thereafter user runs HIPO.

HIPO will keep the 2 user-defined catheters (and the catheters in the applicator) unchanged and run the inverse planning engine for the remaining 2 catheters. The criteria for termination/interruption of HIPO run are here exactly the same as discussed previously for the standard HIPO run.

Second case
This is the case when user has already an adequate catheter configuration with the wished number of catheters, in our example 4, and wants to check if 1 or 2 additional catheters will significantly improve the dosimetry. It does not matter how the placement of the available 4 catheters was realized. It could be the result of manual placement, of loading of a previous saved plan or the result of an initial HIPO run with 4 catheters (plus applicator catheters). In this case the user has to insert this current implant (4 catheter configuration) in the **Multi-Plan basket** and to run then HIPO with 4+1=5 or 4+2=6 catheters (plus the applicator catheters) depending on user's aims. The HIPO execution scenario thereafter is exactly that described above. After termination of HIPO run, the user has to insert the new plan (catheter placement) in the **Multi-Plan basket** and then to open the **Multi-Plan module** for comparing the two plans, the first with 4 catheters and the second including these 4 catheters and one or two catheters in addition, and to select the one plane to be used.

HIPO considers only user-defined feasible catheters

In this scenario the user can define the feasible catheters out of which HIPO has to look for the best to be really used. In this case the user places manually or using some of the automatic tools in ***Catheter Placement*** module of Oncentra GYN system a higher number of catheters than this he really wishes to place, e.g. user places firstly 8 catheters and likes to get the best 6 (4 catheters placed in ring holes plus 2 in the applicator) out of these 8 to be used clinically. In this case user has to enter the total number of catheters to 6 (4+2 in the applicator) in the ***Optimization Settings*** for HIPO. Thereafter the user runs HIPO. In our example the following message will be then displayed:



8 catheters are already present and 2 of them are fixed.
HIPO can use only these 8 catheters to find the 6 requested ones or clear the non-fixed catheters and start from scratch.

By pressing ***Use catheters*** HIPO will keep the 8 user-defined catheters as the total of feasible catheters and run the inverse planning engine for the best 6 out of these 8 catheters (ring holes). The criteria for termination/interruption of HIPO run are here exactly the same as discussed previously for the standard HIPO run. If user presses the button ***Clear Catheters*** HIPO will delete the available 6 non-fixed catheters and begin the inverse planning inferring for the best placement of 4 catheters as described in the standard HIPO run.

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