Comparing Different Strategies about Optimal Marker Placement in Image-Guided Neurosurgery

Abstract

Point-pair registration is widely used for registering the image space and the patient in image-guided neurosurgery. The number and the distribution of fiducial points are fundamental factors to guarantee a good level of accuracy at the target point. Several strategies set to find optimal marker configurations have been proposed recently. This study aims at comparing three of these methodologies. The first one uses standardized distribution templates, while the others are automatic methods, based on the recognition of taboo regions, followed by the elaboration of a solution through a genetic algorithm in the first case, or a simulated annealing logic in the second one. An actual patient’s head has been divided into specific regions, containing several simulated targets. Then, the methodologies have been statistically compared from the point of view of the target registration error (TRE), through the definition of a dimensionless index TREF, that only depends on the geometry and number of fiducial markers of the configuration. Experiments show that the stochastic methods report an about 20% TREF mean decrease with respect to the distribution templates. However, peaks of up to 40% have been detected. Moreover, no actual TREF difference arises between the genetic algorithm and the simulated annealing logics.

Keywords: Distribution of fiducial points; Distribution templates; Genetic algorithm; Image-guided neurosurgery; Point-pair registration; Genetic algorithm; Simulated annealing; Target registration error

Introduction

Image-Guided Neurosurgery (IGNS) has become a widely exploited technique in the neurosurgical operating room in recent years, due to its reliability and low invasiveness [1]. In particular, minimal invasive neurosurgery is essential in key-hole interventions, where brain shift can be neglected: for example, the aspiration of intracranial hematomas, the catheter insertion, and deep brain stimulation or tumour biopsies. In fact, all these operations require a precise individuation of the target point into the brain, and a system aimed at enhancing the accuracy of the surgical gesture of the insertion of a needle or a probe. The basic concept in IGNS is the use of routine pre-operative images to reconstruct a 3D virtual model of the patient’s head through image registration, providing a visual guidance to the surgeon during the operation. Such a registration phase is vital to guarantee the accuracy of the procedure: it can be performed by the surgeon through different techniques, each of them characterized by specific pros and cons [2]. Even if methods that rely on surface matching have been proposed, registration through point-pair matching is still the most used approach in neurosurgical practice, given its advantages of high accuracy and clinical effectiveness [3]. The fiducial points are usually skin adhesive markers, placed by the surgeon on the skin of the patient’s skull.

In point-pair registration, the patient’s head space and the image space are superimposed using the fiducial markers set. A minimum of three fiducial points is necessary to properly align the two spaces; however, the actual number of markers placed by the surgeon is higher, in order to increase the accuracy and reliability. On one hand, the set of fiducial points is identified in the image space; on the other hand, it is selected in the operating room through a tracked pointing device like a probe. Then, a superimposition of the set of points in the two spaces is obtained through a rigid registration, consisting of a translation and a rotation of the reference frames. However, because of the inevitable errors in locating the fiducial points, then the registration of the two spaces cannot be achieved perfectly Maurer CR [4] and leads to a certain level of inaccuracy in IGNS. Different categories of errors affecting point-pair matching in IGNS have been pointed out in [5-6]. In fact, the whole accuracy error is usually divided into the Fiducial Localization Error (FLE), the Fiducial Registration Error (FRE) and the Target Registration Error (TRE). The first one expresses the lack of positioning precision of the markers both in the image space and the operating room one. In fact, the images, that are typically computed tomography (CT) or magnetic resonance (MR) scans, are affected by distortion, noise, low resolution, and so on. On the other side, the inaccuracy of the tracked pointing device, as well as the human error associated with the positioning of the probe, constitute the source of FLE in the operating room. The second type of error, named as FRE, is instead defined as the root mean square distance between corresponding fiducial points.
Choosing a marker configuration optimized from the TRE point of view constitutes therefore a critical factor towards the TRE reduction. Some authors West JB & Hamming NM et al. [8,9] have dealt with the elaboration of qualitative guidelines aimed at optimal marker placement; however, no quantitative feedback is provided to the surgeon about the validity of the optimization. Various automatic strategies have been developed in order to find marker configurations that minimize the TRE index. These solutions are usually patient-specific, and they are obtained through non-deterministic stochastic logics, like genetic algorithm [10,11] or simulated annealing [12]. One of the main drawbacks of these automatic methods is the difficulty to define, recognize and properly exclude the so-called taboo regions that are the patient’s skin areas not suitable for marker positioning. A more flexible but less powerful strategy has been also proposed in [13]. The marker configuration can be built on the specific anatomy of the patient and the surgeon can easily exclude skin areas not suitable for marker positioning, but the optimal solution is not found automatically, requiring time and software expertise to the medical personnel. Moreover, Wang & Song [14] have also developed a method based on standardized, somehow flexible guidelines that have then evolved Wang M [15] into more structured distribution templates (DTs). Given the head region that contains the target point, then a configuration of fiducial points, specific to that sub-volume, is proposed. Such a strategy, however, cannot be patient-customized; moreover, no evaluation on the TRE increase when inevitably deviating from the template guidelines during marker placement is present.

The current paper is based on a recently delineated semi-automatic procedure [16], based on the manual recognition of the taboo region contour by the surgeon, performed on the patient-specific 3D head reconstruction, followed by a simulation running that automatically individuates an optimal marker configuration for the given target. The logic involved in this methodology consists in a genetic algorithm (GA) that elaborates a stochastic solution, finally visualized on the 3D patient’s head reconstruction. It acts as an interactive guideline for the surgeon, aimed at reproducing the marker configuration on the patient as close as possible to the optimized solution provided by the software. It has been demonstrated in Battazzato A [17] that such a strategy is highly effective concerning TRE minimization, even taking deviations into account, like the inaccuracy in marker placement, with respect to the ideal optimal configuration, and the presence of a non-punctual target. However, it could be interesting to compare and evaluate this strategy with respect to the previously described one, where some standardized DTs are directly provided to the surgeon, that chooses which one to apply by considering the position of the target point. The criterion to evaluate these strategies is primarily the TRE performance, seen as a statistical distribution, as the methodologies have to be proposed for several target points, in order to produce a global comparison. Moreover, a further point is analyzed in the current paper: in fact, as highlighted before, different stochastic methods have been applied in the past in order to solve the TRE minimization issue. Hence, the current GA methodology has also been compared with a strategy that relies on an alternative statistical logic. The simulated annealing (SA) one has been chosen for this purpose, and a novel algorithm based on its principles has been developed by the authors. Even if a lot of statistical methods are available to manage this problem, the SA approach has been selected, because of its previous application in the same field of optimal marker placement [12].

In conclusion, searching for optimal fiducial configurations that minimize the TRE index is a major problem, and a lot of solutions that handle this issue have been developed in recent years. Each of the proposed solutions manages to show that it could effectively support the current clinical procedure, providing guidelines as objective as possible and assisting activity of medical personnel [4,13,15]. However, no extensive analyses, that compare these optimized procedures, are present. The current paper aims at accomplishing this task: given equal input data, i.e. the same patient’s head and the same target point, to evaluate the alternative strategies, mainly from the TRE point of view. In order to perform a more complete study, a lot of simulated targets are posed: hence, a global, statistically significant TRE estimate can be provided. The methodologies selected for this study are:

- a) A set of static DTs, whose choice depends on the position of the target point;
- b) A semi-automatic strategy based on the individuation of taboo regions and a GA optimizer;
- c) A semi-automatic strategy, essentially analogous to the previous one but based on an optimizer that applies SA principles.

**Materials and Methods**

**An introduction to the three methodologies**

A 3D head reconstruction from thin layer MR scans has been used in order to evaluate different strategies for marker positioning. Several simulated targets, involving different areas of the head, have been set, in order to globally evaluate the efficiency of each methodology. In fact, according to the position of the target, the performances of the various methods could be different. The mathematical criterion that expresses such performances is
based on the TRE index. Given the head surface and the position of the target, a first method to be evaluated derives from the DTs described in [15]. The head is divided into seven parts: given the region that contains the target, then a specific template of fiducial markers is proposed to minimize the TRE value. These templates are intended to be quite fixed: given different targets belonging to the same head part, then a unique fiducial marker configuration is proposed, with the exception of 1 or 2 markers, whose position can be varied according to the target location. These templates, which are reproduced on a generic 3D head reconstructed, are intended to be a guidance for the medical personnel; moreover, descriptions about the marker placement in the templates are also provided. A second method relies on an automatic algorithm that, given the head surface, specific to the patient, and the target position, finds an optimal marker configuration from the TRE point of view. Differently from the previous methodology, now the medical personnel has to manually define the taboo regions on the 3D head reconstruction, specific to the patient. Consequently, given the set of points, belonging to the head surface and eligible for marker placement, a stochastic logic is applied in order to find an optimal configuration of fiducial points, that is a configuration that minimizes the TRE index. The output of this methodology is a 3D patient-specific head representation, where the optimal set of fiducial points is also shown: such a representation, analogously to the one provided by the previous method, constitutes the guideline for the surgeon for marker placement. A stochastic, non-deterministic algorithm has to be implemented in order to find an optimal solution, given the complexity and the high non-linearity of the task. These algorithms, in fact, are expected to be more performing, in terms of time consumption and final TRE value, than methods that simply investigate a high number of solutions through enumeration or Newton-like optimization algorithms that are more susceptible to be trapped into local minima. A first statistical logic applied to the optimized marker positioning procedure consists in the implementation of a GA, following the approach introduced in Gastaldi L [16]. By applying the principles of evolutionary biology, it manages to find fiducial configurations that minimize the TRE index value. Moreover, in order to test different algorithms and to compare their performances, another stochastic method is implemented: it is based on an SA procedure that mimics what happens during the annealing in metallurgy [18].

This part of the present work permits to investigate if, given the stochastic method is implemented: it is based on an SA procedure that mimics what happens during the annealing in metallurgy [18].

The second methodology to be examined and evaluated consists in the individuation of DTs of fiducial points, applied to the patient’s skin according to the position of the target point. In fact, the head has been divided into seven different regions, through some significant points and planes. The first one is a horizontal plane, passing through the inferior border of the frontal lobe, the second is a coronal plane, passing through the anterior border of the brainstem, while the third coincides with the sagittal plane. Hence, there are four sub-volumes that are above the horizontal plane: they are referred to as left-anterior (LA), left-posterior (LP), right- anterior (RA) and right-posterior (RP). On the other side, there are three other regions: the inferior posterior (IP), the central inferior anterior (CIA) and the lateral inferior anterior (LIA). A visual representation of these planes and regions is provided in [15]. Given the region that contains the target point, then a corresponding marker configuration is defined: such a methodology has been conceived in order to provide a solution that presents a good TRE performance, even if not optimal, at the same time requiring marker positions that could be easily recognizable thanks to anatomic landmarks and should not be critical from the point of view of skin movement. Each configuration of fiducial points belonging to the template series generally presents six markers (seven markers in the CIA case): their collocation is usually fixed, with the exception of one fiducial point, whose position is defined as the point nearest to the surgical target on the head surface. Some further corrections about marker collocation in the templates are possible, due to patient positioning, the presence of the stereotactic frame or nasal intubation.

**GA methodology**

The second methodology to be examined and evaluated consists in the strategy that has been presented in [15]: an automatic procedure, based on a GA is launched, aimed at finding an optimal configuration of fiducial points. As previously stated, statistical logics like GA are necessary in order to avoid trapping into local minima of the function to be optimized. In other words, given that the problem is non-linear, stochastic strategies are expected to be more effective with respect to deterministic optimization tools.

GA implements such a stochastic setting by considering a population of randomly generated individuals, each of them evaluated through a fitness function that establishes their
attitude to be selected as parents for the following generation of individuals. In the current case, each individual consists of a specific set of fiducial markers, described by a corresponding TREF value. The fitness function derives from this index, and individuals characterized by a lower TREF will have a higher probability to be selected by the algorithm. However, it is important to notice that even solutions with worse TREF performance have an other-than-zero probability to participate to the following generation: such a mechanism has been conceived in order to let the optimization process tend towards the global optimum. The process of creating new individuals from the current ones is represented in Figure 1. Two different mechanisms have been implemented: cross-over and mutations. When two parents mix their genetic material, i.e. the fiducial marker positions, then it is transmitted and randomly combined between the two new individuals. During this reproduction process, sometimes a new marker position, that does not belong to the parents, is generated and introduced into the genetic material of the children. Moreover, external migrations are scheduled: the overall genetic richness of the population is increased by inserting new individuals, randomly generated. All these actions have been set in order not to have a deterministic logic, that would be not so effective. Given the initial set of randomly generated individuals, then the population evolves thanks to these mechanisms, gradually leading to a progressive decrease of the mean TREF in the population. After a number of steps the simulation can be stopped, and the individual, belonging to the population, that presents the best TREF performance can be assumed as the solution for the surgeon: such a fiducial configuration can be represented on the 3D head reconstruction, specific to the patient, that acts as a guidance tool for the medical personnel. Moreover, if necessary, a number of other solutions, belonging to the population at the last iteration of the same simulation session, comparable to the best one from the TREF point of view but presenting alternative distributions of fiducial points, are available.

SA algorithm

An alternative to the previous method can be found by considering a different logic, however again applying non-deterministic principles to the task of TREF minimization. The first step of a procedure of optimal marker positioning based on an SA algorithm coincides with the previous methodology: the 3D head surface, specific to the patient, is reconstructed and permits the individuation of the taboo regions, where the placement of the fiducial points should be avoided. Thus, given the target position and the available marker collocations, an automatic algorithm is launched in order to find an optimal distribution of fiducial points, that aims at minimizing the TREF value. The SA method has been demonstrated to be effective in a wide range of optimization tasks. It mimics the annealing technique in metallurgy, where the heated material is progressively cooled in a controlled manner, in order to let the crystalline structure be more regular and defect-free, hence characterized by a state of minimum energy. In the initial phase, when the temperature is high, the atoms in the material can wander randomly, regardless of the level of internal energy.
of the system, that could even increase; then, the cooling process starts and the system tends towards situations where the internal energy is lower. The algorithm proposed here reproduces such a process: a random marker configuration is set as the initial step; the concept of energy is linked to the TRE performance of the distribution of fiducial points. Of course, states of lower energy correspond to marker solutions presenting lower TRE values. The following iteration involves the creation of a marker solution that is a neighbour of the previous one, for example slightly modifying the marker positions of the previous configuration. The acceptance probability of this new configuration depends on two parameters: the internal energy levels of the parent and the neighbour configurations, referred to as $E_i$ and $E'_i$, and the value of the parameter $T_i$ called temperature. If there is a decrease in energy, i.e. $E'_i < E_i$, hence this neighbour configuration is accepted as the solution for the next iteration. If, on the other side, the energy value increases, i.e. $E'_i > E_i$, then the probability that the neighbour solution is accepted as the new configuration for the following step can roughly be expressed as $\exp \frac{E_i - E'_i}{T_i}$, whose form derives from the Boltzmann equation. This mechanism, shown in Figure 2, permits to consider also solutions that temporarily worsen the TRE performance, saving the process from becoming stuck at local minima. During the simulation, the temperature parameter $T_i$ progressively decreases: the trend of the ratio $T_i / T_0$, where $T_0$ is the temperature value at the beginning of the simulation, is reported in Figure 2, too. This behaviour lets the optimization process be greedier, hence slowly converging towards solutions with a lower value of internal energy, that is a low TRE. The calculation can be stopped once a fixed number of iterations has been performed, or if the energy value goes lower than a set threshold. The marker configuration that, during the simulation, is associated with the lowest energy value can be represented on the patient’s head reconstruction as the optimal distribution of fiducial points, that constitutes the output of the algorithm and guidance for the medical personnel for marker placement.

**Figure 2:** Iterative algorithm relative to SA methodology. The trend of the temperature parameter $T_i$ is also reported, normalized with respect to the value of the same parameter at the initial step $T_0$. 

### Citation
Results

In order to evaluate the efficiency of each methodology, they have been extensively tested. Given an actual 3D head reconstruction, then it has been divided into the seven different regions, defined as the starting point of the DT strategy. Then, many simulated target points have been set for each region and the evidence methods have been applied. The taboo areas coincide for the two semi-automatic algorithms, and exclude the anatomic parts not suitable for marker positioning, like the ears and the eyes, or subject to skin movement, like the occipital zone. As stated before, the goal is to study the performance of the three methodologies, given the same initial conditions. The TRE\textsubscript{g} distribution, relative to each head region, is hence evaluated and statistically interpreted. Figure 3 reports an example of the visual output of each methodology: given the 3D head reconstruction of a patient and the position of the target, that belongs to a specific head sub-volume and is marked as a cross, then three optimized marker configurations are calculated. Each of them consists in an optimized solution, respectively reached through the DT technique, the GA strategy or the SA method. Cases relative to the same head region are aligned horizontally in figure 3, while each column shows the solutions provided by the same methodology.

TRE\textsubscript{g} performance of the methodologies

As a first step, given each target point, several random marker configurations have been generated: their TRE\textsubscript{g} values provide a measure of what can be achieved without using any particular strategy. Then, the TRE\textsubscript{g}, values derived from the DT solution are proposed. These two cases can be represented as classical statistical distributions: each head sub-volume is associated with many target points, each of them leading to a specific configuration of fiducial points and a consequent TRE\textsubscript{g} value. Finally, the solutions associated with the stochastic methods are exposed. Two considerations arise when applying these algorithms: the first one is that the TRE\textsubscript{g}, performance of an optimized configuration is practically independent of the subregion which contains the target itself; it depends instead on the number of markers that compose the configuration. Moreover, the TRE\textsubscript{g}, of the final configurations selected through GA or SA processes are substantially equivalent: in other words, the two methodologies are interchangeable from the point of view of the final result. An inductive reasoning can lead to the statement that optimal configurations that could be obtained with alternative stochastic strategies, provided that they are effective, are all equivalent from the TRE\textsubscript{g}, point of view. Hence, provided that the input parameters that control the calculation are properly set, there is no evidence of an actual difference among alternative statistical methodologies. Given a sufficient computation time, different stochastic algorithms are expected to converge at the same TRE\textsubscript{g}, value, even if the final marker configurations are different. In fact, a quantification of the difference between TRE\textsubscript{g} values obtained through GA and SA techniques leads to mean values and standard deviations of $10^{-8}$ magnitude that is low enough to be considered not significant. Consequently, the various tests that have been performed on these algorithms can be synthesised into a unique TRE\textsubscript{g} value that coincides with the mean value of a statistical distribution characterized by a roughly null standard deviation.

Figure 4 reports what happens when considering the seven head regions defined for DTs: given the targets belonging to each region, then the mean value and the standard deviation are provided for the randomly-generated configurations and the DT technique. On the other side, as stated before, the TRE\textsubscript{g} value of the stochastic algorithms SA/GA is represented. This analysis shows that the DT technique is far more effective than a randomly-selected marker configuration. However, worst-case solutions relative to DTs could be not so performing from a TRE\textsubscript{g} point of view. On the other side, if the parameters are properly set, the stochastic algorithms lead to a very robust solution; proximal to what could be interpreted as a theoretical asymptote relative to the TRE\textsubscript{g} value performance, given the desired number of markers of the configuration. Even if failure of the stochastic calculation due to poor setting of the input parameters never occurred during the simulations, it cannot be excluded a priori.

In order to avoid such a problem, some redundancy should be introduced, for example launching the algorithm on the same case several times and verifying that the resulting optimal TRE\textsubscript{g} value is roughly a constant.

While Figure 4 provides a representation of absolute mean TRE\textsubscript{g} values, Figure 5 shows the effective percentage TRE\textsubscript{g}, gain, that could be achieved considering DTs Figure 5a or the stochastic algorithms (Figure 5b), with respect to the random configuration. The two graphs describe the statistical distribution of such gains, as explained in the following: while the mean value is represented by the separation segment between the two hatchings, where the standard deviation bars lie, the mean-to-minimum distance is expressed by the pattern and the mean-to-maximum distance is described by the pattern. It descends from these graphs that the TRE\textsubscript{g}, gain, with respect to the random configurations associated with DT solutions is equal to $42.73\pm4.27\%$. On the other side, the analogous TRE\textsubscript{g}, gain, associated with stochastic algorithms like GA or SA, is equal to $54.51\pm5.21\%$. Finally, figure 6 reports the direct comparison between the two described methodologies, quantifying the decrease of TRE\textsubscript{g}, value derived from applying the statistical algorithms instead of DTs. As previously explained, given a specific head region, several target points have been generated, associated with different TRE\textsubscript{g} values: hence, such a TRE\textsubscript{g}, decrease again appears as a statistical distribution. Its mean value corresponds to the separation segment between the two hatched areas along each bar on the graph. Standard deviation bars lie on such a mean value segment. The mean-to-minimum distance is then represented by the pattern, while the mean-to-maximum distance is described by the pattern. Hence, the mean decrease of TRE\textsubscript{g} value, adopting the stochastic optimized techniques instead of DTs, is expected to be equal to $19.93\pm3.99\%$. However, a remarkable difference can be noted between the CIA case and the other ones. The former is associated with a TRE\textsubscript{g} mean improvement of about 12%, while the worst case is within a 20% difference. The other six head regions show similar trends and they are described by a $21.24\pm2.16\%$ TRE\textsubscript{g}, reduction, with worst-case solutions that present up to a 40% difference between the two methodologies. On the other side, the best performances that occur with the DT strategy tend to be quite similar to the automatic algorithms.

Figure 3: Representation of the optimized configurations according to different techniques: DT a) to g); GA h) to n); SA o) to u). The targets, marked as a cross, belong to: CIA in a), h) and o), LIA in b), i) and p), LA in c), j) and q), RA in d), k) and r), LP in e), l) and s), RP in f), m) and t), LP in g), n) and u).
The difference between the CIA case and the others is due to the different number of markers. In fact, the DT associated with the former has seven markers instead of six: a configuration template made of six markers probably would have been subject to unacceptably high TRE degradation, especially when dealing with the worst-case situations in the statistical population. In order to compare the two methodologies from the same basis, seven markers have been imposed for the automatic solution, too: thus, it results that increasing the number of markers in the templates reduces the gap with respect to the stochastic algorithms, that roughly stand as a sort of best reachable solution. Additional investigations can be developed in order to establish the TRE performance of a six-marker automatic solution, relative to the CIA case, with respect to the seven-marker DT. Such a case study is represented in Figure 6, labelled as CIA (2). It states that the six-marker solution provided by the automatic algorithm still presents a mean 5% TREF improvement with respect to the corresponding DT, however, now there are target positions where the DT strategy performs better than the GA/SA one.

**Discussion**

IGNS, coupled with point-pair registration, has recently become a popular technique in the neurosurgical operating room. As a consequence, its level of accuracy is highly dependent on the configurations of fiducial points adopted during the neurosurgical operations. During the recent years, some qualitative considerations, as well as more structured strategies, have been developed, acting as a guideline for optimal marker positioning. Among the others, a recent methodology based on DTs has been taken into account. When presented, it was demonstrated to be a valuable instrument to improve the TRE performance associated with the actual clinical practice. Moreover, a technique based on an automatic GA has been considered here; finally, a further new solution, similar to the previous one but based on an SA logic, has been implemented. These three methodologies have been statistically compared and evaluated from the point of view of TRE. This dimensionless index derives from TRE, but it is only dependent on the number of markers and their distribution on the patient’s head. Thus, it is invariant with respect to FLE, allowing a direct comparison among the different strategies.

**Evaluation of the methodologies**

Each of the strategies previously described presents some practical advantages, as well as specific criticalities. First of all, the DT methodology has the clear advantage of being simpler to apply and to be reproduced on the patient’s head, as the majority of the markers are collocated in proximity of specific anatomical surfaces and landmarks. In fact, these DTs provide direct and clear information to the medical personnel about marker placement, without the need of further software implementation. Given the division of the head into regions, then the knowledge of the collocation of the target point permits to choose which template to reproduce on the patient’s head. Hence, it is plain that the marker configuration is not the optimal one, even if the TRE performance could be not so far from the optimality and be largely satisfactory. Moreover, this strategy, establishing the position of fiducial points, implicitly assumes which are the taboo areas, where the marker placement has to be avoided: even if such a supposition is generally correct, there are also situations where the taboo regions are different with respect to the most general case, due to particular patient positioning or specific clinical requirements. Thus, it can happen that one or more of the planned markers cannot be positioned according to the templates: the deterioration of TREF performance cannot be quantified in the operating room and could be critical. The second strategy that has been introduced deals with the GA semi-automatic procedure: differently from the DT method, the solution is built considering the specific anatomy of the patient. Moreover, the identification of the contour of the taboo areas has to be performed by the...
medical personnel on the 3D head reconstruction with the aid of dedicated software: even if this involves a further activity preparatory to the surgical operation, it is more flexible than a standardized unique definition of the areas to be avoided, regardless of any particular condition. The same could apply for the number of markers: such a number now constitutes a variable element, while it is fixed with the DT method. Another advantage of the current procedure consists in the fact that the fiducial configuration suggested by the methodology is optimized for the target position, hence more performing with respect to DT from the point of view of the TRE index: the GA is expected to provide an optimal solution, visualized on the 3D head reconstruction, like the ones reported in Figure 3. This visual output, however, again requires the interaction between the medical personnel and the software, because of the fact that the digital 3D image is the only guidance for translating the virtual marker disposition into reality. Such a translation could not exactly correspond to the optimal solution, given the fact that the markers are not placed according to any specific anatomic landmark and their positioning could be less certain, depending on the ability and training of the medical personnel. However, such an issue would disappear if the task of marker placement was performed by a robotic arm: then, the configuration of fiducial points would be almost perfectly reproduced on the actual patient’s head, with an error comparable to the robot accuracy. Automatic algorithms, like GA or SA, of course would be ideal to be integrated with the control logic of such a robotic device.

The third methodology applies the same taboo area exclusion algorithm of the previous strategy, but a different calculation scheme is implemented. One of the main differences between the two consists in the fact that while the GA procedure ends with a list of distinct marker configurations available at the last step of simulation, comparable from the TRE point of view and constituting a whole population, the SA-based solution just considers an individual marker configuration, that evolves along a track set by the random generation of neighbour solutions. Therefore, if the final marker configuration is considered not satisfactory by the neurosurgeon, then the GA procedure could provide alternative solutions, while the SA one should be launched again, in order to obtain a new marker configuration. However, because of the lightness and high efficiency of the algorithm that converges at an optimal solution in just a few seconds, the procedure is highly performing. On the other side, figure 7b shows the TRE evolution of the solution of the SA technique, where the TRE decrease is just a bit slower that the previous case. However, the final optimal TRE values are practically coincident, as stated before. In addition, the fact that these automatic algorithms are so fast could be exploited to compensate for their stochastic nature: in fact, the final TRE that they can reach can be seen as a sort of asymptote, as affirmed before. However, even if it never occurred during the testing of the software, the probability that it could give a final TRE far from the best reachable value is not zero. The stochastic basis of the algorithms, even if it generally permits to avoid to be trapped into local minima, does not give the absolute certainty about this fact, especially in presence of an improper setting of the logic parameters or other factors. Thus, to
guarantee a reasonable confidence on the results of a simulation, given another initial set of parameters; it could be automatically re-launched in order to verify the repeatability of the final TRE value. As shown in Figure 7, such a procedure would be very light from the point of view of time consumption, and it could be set as an intermediate validation when running the software.

**Conclusion**

The current paper has presented a comparison among different strategies aimed at finding optimized marker placement in IGNS. Three different methodologies have been investigated, evaluating their main aspects: the DT solution, for example, can be more practical and simplier to adopt, since no dedicated software running is necessary and the markers are usually placed next to anatomic landmarks and other easily recognizable points. However, the automatic stochastic solutions not only permit to consider the presence of taboo regions, where marker placement has to be avoided, but also they are specific to the patient’s anatomy. In addition, if an optimized marker configuration calculated by the methodology is not satisfactory for whatever reason, the algorithm is able to provide alternative solutions immediately –it is the case of the GA solution- or within a couple of seconds for the SA one. However, the most important factor to be considered in such an evaluation process is the TRE index. First of all, all the three methodologies are very performing with respect to a set of randomly-generated marker configurations. When comparing the DT technique directly with an automatic solution like the GA one, the latter presents a roughly 20% mean TRE improvement. However, differences up to 40% have been detected, as well as situations where the two strategies lead to similar TRE results. On the other side, alternative automatic methods, like GA and SA, reach the same optimal TRE values, even if each simulation provides a different optimized marker configuration. This fact can be interpreted as a confirmation of the robustness of the procedure: different automatic strategies, provided that the internal parameters of the algorithms are properly set, succeed in coming to such an optimal TRE value, whose repeatability is consequently very high. Moreover, in practice this TRE value can be interpreted as a sort of asymptote, whose value cannot be significantly overcome by more empirical strategies like the DT one. Hence, at the best of its performance, the DT strategy is expected to equal the output of the automatic strategies like the DT one. Hence, at the best of its performance, the DT strategy is expected to equal the output of the automatic strategy.

Appendix

The criterion for evaluating the configurations of fiducial markers, applied with respect to a target point, is based on a formula that expresses the TRE expectation value, given by [7].

First of all, it states that this TRE is dependent on the FLE value, that is a random error: hence, the TRE has to be interpreted as a statistical measure, too. Moreover, the number N and the disposition of the fiducial markers also influence the TRE value.

In fact, it is:

$$TRE^2 = \frac{FLE^2}{N} \left( 1 + \frac{3}{2} \frac{d^2}{f^2} \right)$$

where $d_i$ is the distance of the target from principal axis $k$ and $f_i$ is the root mean square distance of the fiducials from principal axis $k$. The second member of equation (1) can be divided into two terms: $\frac{FLE^2}{N}$ expresses the translational error while the second part refers to the rotational one, being its three components inversely proportional to the spread of the markers about the corresponding axis. In order not to be influenced by the magnitude of the random error $FLE$, the following dimensionless squared $TRE_N$ index is defined and adopted throughout the present paper:

$$TRE^2 = \frac{TRE^2}{FLE^2} = \frac{1}{N} \left( 1 + \frac{3}{2} \frac{d^2}{f^2} \right)$$

Such a squared $TRE_N$ index coincides numerically with the $TRE^2$ one, given in equation (1), provided that the FLE error is equal to 1mm.

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**Conflicts of Interest**

Authors declare there is no conflict of interest.

**References**


