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Abstract. High Intensity Focused Ultrasound (HIFU) uses the energy of an ultrasonic beam to cause localized heating to alter or destroy the targeted tissues. Due to its limited collateral effects, this minimally invasive therapy is, in its field of application, an alternative to surgical treatments and is rapidly expanding in terms of both clinical research and industrial development. In this context, the use of simulation is a crucial element to reduce both the development time and prototype costs, as well as the number of preclinical and clinical experiments. To this aim, CEA-LIST has been developing the simulation platform, CIVA HealthCare in partnership with INSERM for several years, which uses optimized and validated modules for the simulation of a whole HIFU therapy protocol. However, multi-parametric studies for treatment optimisation (probe design, protocol definition, etc.), sensitivity analysis, and tissue characterisation are very time-consuming, since they involve many simulations. We propose an alternative solution of replacing the computationally expensive direct solver with a surrogate model built from a database of simulation results. The procedure breaks down into two stages First, the database is adaptively constructed to maximise the fidelity of the associated interpolator computed from the pairs (Input/Output) of the database. Then in the second step, the interpolator, also called surrogate model or metamodel, enables the generation of results in near real time for configurations covered by the range of the database. This procedure and its related tools have been implemented in CIVA-HealthCare. To highlight the potential offered by such intensive HIFU simulation based on surrogate models strategy, two applications are presented: The first concerns real-time pressure field computation, and the second is based on thermal simulations and deals with sensitivity analyses according to uncertainties in tissues parameters. Work supported by French Nation Research Agency (ANR SATURN -15-CE19-0016)

1. Introduction

The ability of ultrasound technology to modify or destroy biological tissues has been known for decades. Specifically, High Intensity Focused Ultrasound (HIFU) can induce a temperature increase at the focal point, generating localized coagulation necrosis at this point. Due to the limited collateral effects on the neighbouring organs and/or on the healthy parts of the treated organ, this minimally invasive therapy is of great interest for the treatment of numerous pathologies and is currently developing rapidly in terms of clinical research and industrial development [1]. Already used to treat certain cancers (prostate cancer, liver metastases, brain tumors, etc.) [1] and to treat other types of pathologies such as uterine fibroids or glaucoma, HIFU treatment has also proven to be a valuable option for local recurrence after external-beam radiation therapy [3] or combined with the growing field of immunotherapy [4].

The implementation of such HIFU therapies for a given treatment always requires the design of complex ultrasound probes (phased-array transducer) and the design of precise operating protocols to control the development of spatiotemporal damages during the heating - both in the targeted tissues and in the risk areas. Therefore, new therapeutic methods often needs several years of research, and any protocol established must then be adapted to preclinical experimentation and finally confronted with the individual specificities of each patient (clinical tests). In this context, modelling of the physical phenomena involved while taking into account the control of the ultrasound beam and the thermal response of biological tissues, is a crucial element to reduce both the development time, the prototyping costs, and the number of preclinical and clinical experiments. Unfortunately, the tools available to laboratories are limited and developments made are very specific, require significant development time and are rarely sustainable.

In this context, CEA-LIST has been developing the simulation platform CIVA HealthCare in partnership with INSERM for several years. This platform enables the simulation of a whole HIFU therapy protocol, including the design of probes and protocols, the propagation of the pressure field inside the tissues, the induced temperature rise and finally the estimation of the created thermal lesions. However, since they involve a large number of parameters, design processes require a large amount of simulation results. Therefore, they rapidly become very time-consuming using standard approaches, especially for complex configurations and/or when physiological parameters are poorly defined.

One solution to speed up these design stages is to use the concept of surrogate models also known as metamodels or emulators. This method consists in replacing the computationally expensive direct solver with a surrogate model built from a database of simulation results. This surrogate model enables fast and accurate generation of simulation results in near real time for any configuration covered by the range of the database. Generation of a metamodel has been recently successfully applied in the field of Non-Destructive Testing (NDT) [5] using tools available in the CIVA platform (dedicated to NDT simulations). This procedure can be divided into two stages. In a first step (offline part), the database is adaptively constructed in order to maximise the accuracy of the associated interpolator calculated from the (Input / Output) pairs of the database, which can be time-consuming. In a second step (online part), the interpolator (also called database metamodel) is used to generate results in near real time. Importantly, results can only be obtained in the range of input data used for the generation of the database. Several interpolation approaches have been developed in the literature to generate metamodels [6]. Recent contributions, linked to NDT applications, involve particular interpolators based on Kriging estimation [7], [8], [9] and on Radial Basic Functions (RBF) [10]. Very recent alternative algorithms based on Support Vector Regression (SVR) have been applied for inversion purposes [11]. Finally, the Least Square Support Vector Regression (LSSVR) [12] algorithm has been used to carry out sensitivity analysis studies and calculation of probability of detection curves in ultrasonic NDT applications [13].

After introducing the CIVA HealthCare Platform, we will describe the specific tools (parametric variation, database creation, metamodel generation and statistical analysing) that have been integrated into the platform to define a surrogate model dedicated to HIFU simulations. We will focus on two applications: real-time pressure field computation, and sensitivity analysis according to the uncertainties of the tissues parameters for a treatment protocol.

2. Materials and methods

Description *of the CIVA* ***HealthCare simulation platform.***

This platform allows for easy simulation of 3D pressure field induced by HIFU in the linear regime, as well as the corresponding thermal damages in tissues and phantoms. The computation steps are represented in *Figure 1*. Specific Graphic User Interfaces (GUI) have been designed to intuitively define all of the parameters influencing the acoustic field and the tissue eating, i.e.

- Geometric and structural description of probes (single crystal or phased array including positioning, cutting and electrical interconnections of the elements)
- Geometric description of the organs and the acoustic, biological and thermal parameters of each tissue.
- Probe positioning relatively to the organs
- Modes of activation to be implemented (input signal, power, frequency, shoot duration, phase laws, etc.)

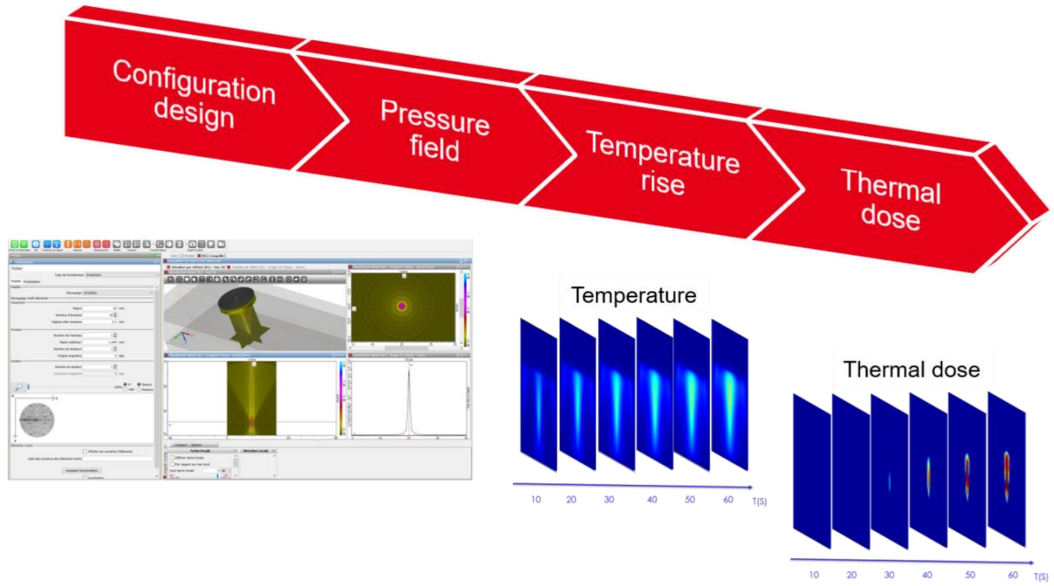

Figure 1: Computation steps of a HIFU protocol in the CIVA HealthCare Platform

Pressure field computation module

Two algorithms for calculating acoustic fields in a linear regime have been developed and validated. The objective is to cover all of the tissue configurations encountered in ultrasound therapy, and to ensure numerical efficiency necessary for intensive use of the model by using analytical formulations whenever possible, that is to say whenever it involves no loss of generality. These two algorithms are based on the resolution of the Rayleigh integral.

- The *PressureField* calculation code: This code assumes longitudinal mode propagation (compression wave) by considering that the tissues behave, from the elastic point of view, like liquids. The crossing of organs and soft tissues of different characteristics therefore only results in variations in attenuation of the longitudinal wave (the speed is assumed to be uniform throughout the medium crossed as in [14]). The *PressureField* code, resulting from a CEA-LIST / LabTAU collaboration, is an optimised and parallelised (CPU / GPU) code.
- The *CIVA* calculation code: This code comes from the evolution of the CEA-LIST library initially dedicated to NDT and experimentally validated in many complex NDT configurations [15]. Unlike the previous code, it allows computation in harmonic and impulse mode, and the consideration of complex configurations including possible solid obstacles (bones, prostheses, brachytherapy grains, etc.) or media with spatially continuously varying parameters (for example inhomogeneous velocity due to local heating) that can modify the transmitted beam and disturb the tissue insonification. When considering solidvolumes to which elastic characteristics are attributed, the ultrasonic propagation model, using the pencil (or ray-beam) method, takes into account the refractions / reflections of the waves at the surface of these volumes as well as the local inhomogeneities of the wave speed, such as those produced by local heating of the tissues [16]-[19].

By addressing different issues, these two algorithms are therefore complementary, with the computation performances of the former being optimal within its domain of validity. These two models collect all the input data of the simulation configuration using the dedicated GUI. The simulation results provide the 3D pressure field induced in the tissues which, can be visualised and analysed using several specific tools available in the software.

Temperature rise and thermal dose computation module
The temperature rise induced by HIFUs in biological tissues is calculated by solving the Bio-Heat Transfer Equation (BHTE) [20] where the heat deposition in tissues is proportional to the ultrasound beam intensity. The resolution of the BHTE is carried out using the method proposed by Chato [21]. The chosen method consists of an explicit resolution by finite differences. From the temperature map obtained at each instant t, the thermal dose "deposited" in the tissues is calculated using the empirical formula proposed by Sapareto and Dewey [22]. This method makes it possible to estimate the shape, position, and degree of thermal damage within the tissue [23].

Intensive HIFU simulation based on surrogate models
Previous modules give the CIVA platform the ability to perform, even in complex configurations, 3D pressure field simulations and induced damage estimation. To perform near real-time simulations allowing multi-parametric studies for probe and treatment optimisation or for tissue characterisation using parametric inversion, numerical tools for an intensive HIFU simulation based on surrogate models have been implemented into the CIVA HealthCare platform. In addition to the creation of the database and the generation of metamodels, some numerical tools and their specific GUI allow for complex studies, such as sensitivity analysis, to be performed easily.

3. Applications of intensive HIFU simulation based on surrogate models
To highlight the potential offered by the intensive HIFU simulation based on surrogate models strategy, two application examples are proposed: The first concerns a real-time pressure field calculation, and the second concerns a sensitivity analysis to study the effects of parameter uncertainty on the estimation of the treated volume.

Real-time pressure field simulation
The chosen application, developed in collaboration with EDAP-TMS, relates to the treatment of prostate cancer using an endorectal probe. In order to integrate a simulation module into a medical device, the objective here is to generate a real-time pressure field simulation module, whose input parameters can be personalized according to the anatomical specificities of the patient. The simulation configuration used to generate the metamodel is represented in *Figure 2*. The probe is inserted into a cylinder, made of three layers, corresponding respectively to the rectum wall, a fat layer and the prostate tissue.

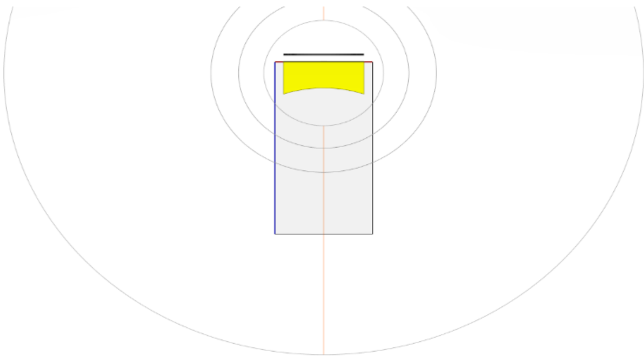

Figure 2: Pressure computation configuration for database generation.

The acoustical parameters of the tissues are reported in the table below:

Tissue	Speed (M/S)	Density (Kg/M^3)	Attenuation $\alpha = a_0 f^b$	
			a_0 (Np/M/MHz)	b
Water	1483	1000	0	1
Rectum	1483	1088	5.74	1
Fat	1483	911	4.36	1.09
Prostate	1483	1045	9.32	1

Table 1: Acoustical parameters of the tissues ([24])

For each focal depth (8 in this application), the database is constructed by varying the following four parameters in their respective range:

- The height of the water pocket (distance from the probe to the rectal wall): $21 \leq d \leq 26$
- The inner radius of the rectum: $21 \leq R \leq 26$
- The thickness of the rectum: $3 \leq eRec \leq 11$
- The fat layer thickness: $0.1 \leq eGr \leq 12$

The GUI corresponding to the generation of the associated metamodel is shown in *Figure 3*. Taking into account the regularity of the field maps obtained on the ranges of variations, we used a sampling of the database of the type "experiment plan". In this case, the database is sampled regularly in the volume of parameters. Here, we therefore carry out $3^4 = 81$ field maps computations with the direct model from CIVA HealthCare, corresponding to all the configurations defined by the ranges of variation of the four parameters. For each calculation, the complete map of the field is extracted and stored in the database. For this example, the RBF-based interpolation method was used to create the metamodel.

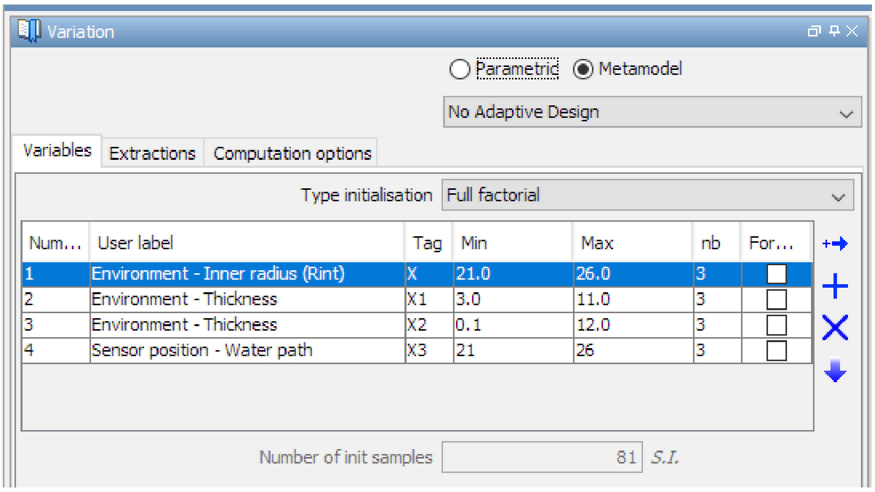

Figure 3: Variation range of the four metamodel parameters

A cross-validation phase was carried out by deleting 27 elements, among the 81 from the complete database, and constructing the metamodel with the 54 remaining elements. For each of the 27 elements used for the test, it is possible to compare the reference pressure field obtained using the CIVA HealthCare simulation tool with that approximated pressure field obtained with the metamodel. The goal here is to validate the metamodel by comparison to the reference, regardless of its validity, which must be the subject of a specific study.

In a first validation phase, we have compared the L2 norms of the reference (CIVA HealthCare) and predicted (metamodel) pressure field maps. On the graph represented in *Figure 4*, obtained for all 27 elements of the test base generated for a given focal depth, we note a very good correlation between calculated and predicted maps, with all the comparisons being located on the bisector.

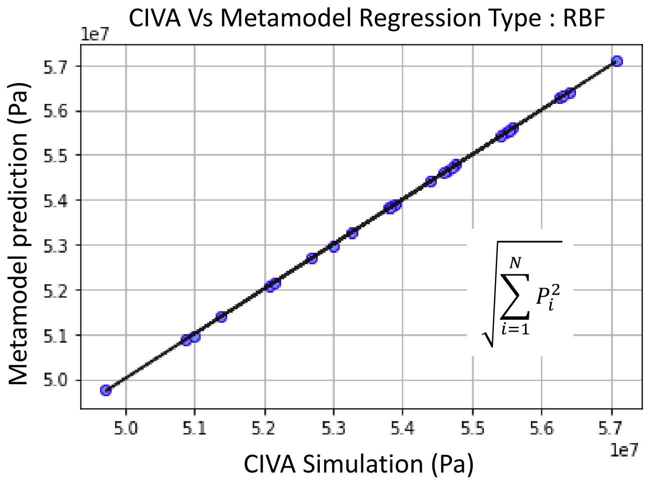

Figure 4: Comparison of the L2 norms of pressure fields predicted by the metamodel *vs* computed by CIVA HealthCare

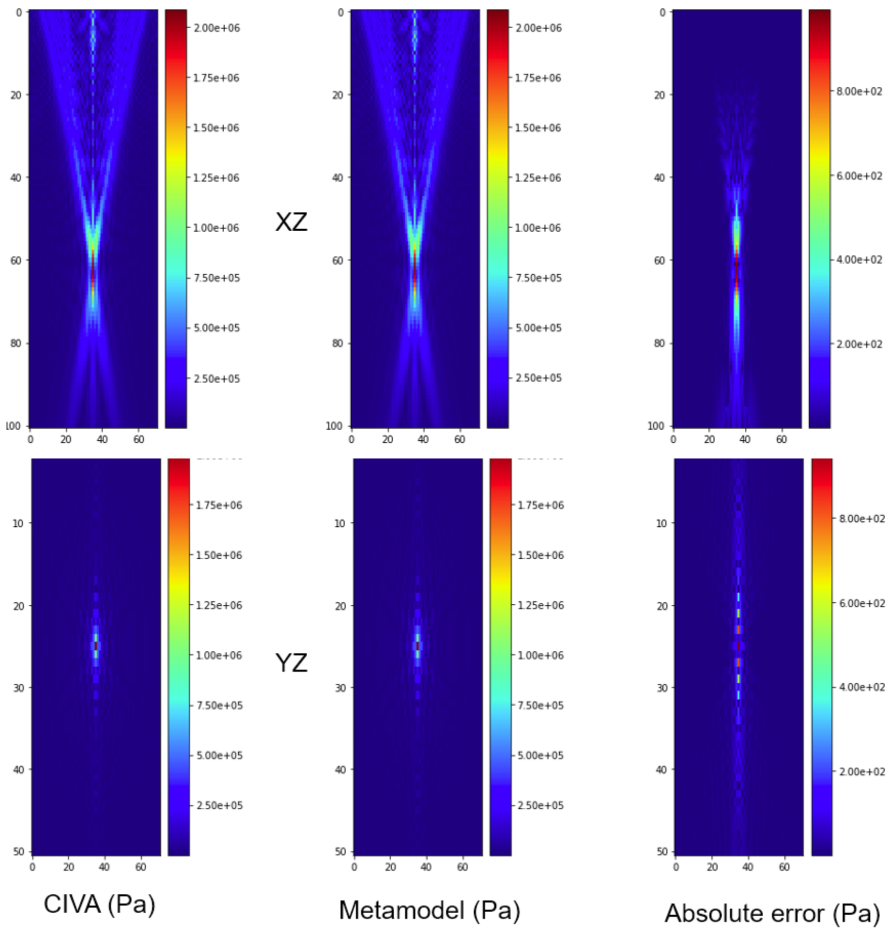

Figure 5: Example of comparison of field maps in the XZ and YZ plane of the probe

In a second validation phase, a comparison of the reference and predicted pressure fields has been obtained by calculating the map of their difference. In *Figure 5*, we present the comparison of the 2D field maps obtained in the XZ and YZ planes of the probe for an element in the test group. We observe that there is more than three orders of magnitude between the observed error and the actual mapping of the field.

In a general way, for the eight focal depths and all the elements among the 27 retained for the test, we obtained a maximum error of less than one percent (corresponding to low pressure points located far from the focal zone). It should be also noted that in our application, the accuracy of the final metamodel is certainly greater than that, since the 27 test elements have been reintegrated into the whole database composed of 81 results. Finally, in terms of performance, one field calculation with the standard approach from CIVA HealthCare requires about 10 minutes on a standard laptop with four cores, while a result is obtained instantly with the metamodel. Therefore, surrogate models enable real-time simulation of the pressure field with a controlled error for any configuration within the range of variation of the parameters.

Sensitivity analysis

The simulation configuration is very close to the one previously shown. In this case, we simulate the lesion generated for an established treatment protocol (*Figure 6*) and we aim at studying the evolution of its volume according to the variations of a set of three parameters considered uncertain or variable: the emitted power, the rectum thickness, and the attenuation coefficient of the target. We have generated the metamodel, dedicated to the lesion volume estimation, based on the parameter ranges illustrated *Figure 7*.

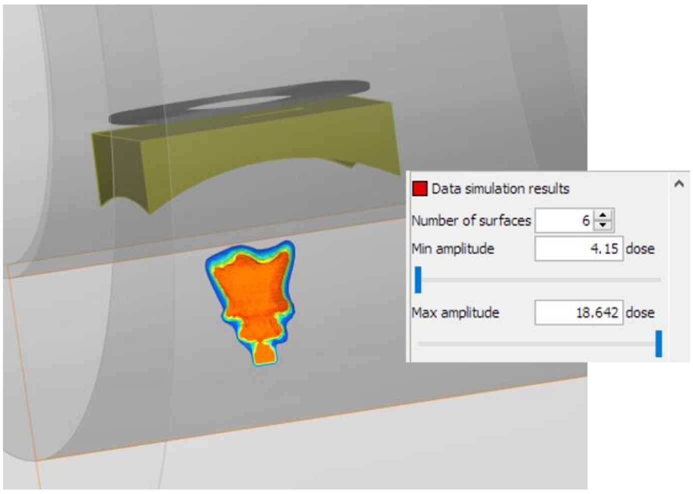

Figure 6: Example of treatment simulation result

This metamodel can then in particular be used in the context of statistical studies requiring a very large number of simulations generated randomly using a Monte Carlo procedure according to a specific statistical law (uniform, Gaussian ...) applied to each parameter in its domain of variation. *Figure 8* represent the result of a sensitivity analysis performed using this metamodel. A thousand simulations have been performed in less than one second using a specific Gaussian distribution applied on each parameter (red curve on the left side). The pink graph represents, for the whole set of the 1000 simulation configurations, the value of the three input parameters and the lesion volume estimated by the metamodel. We can verify that this random procedure respects the statistical law applied on each parameter. For this set of statistical laws applied to each parameter, which does not correspond to a real application case, the first-order Sobol index shown at the bottom of the figure clearly indicates that the most influential parameter is the attenuation coefficient in the targeted tissue (almost 85%), while that of the thickness of the rectum seems negligible (less than 2%). This sensitivity analysis has been very useful to determine the physiological parameters that has to be accurately measured to obtain reliable simulations.

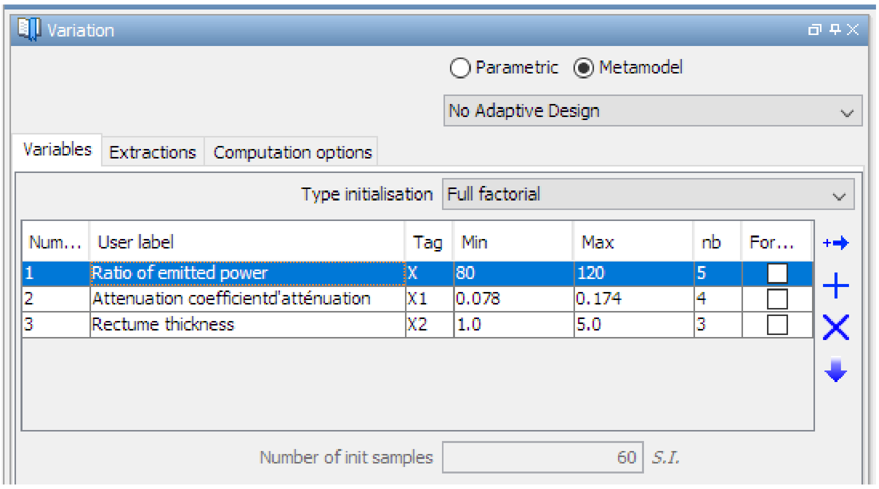

Figure 7: Variation range of the three metamodel parameters

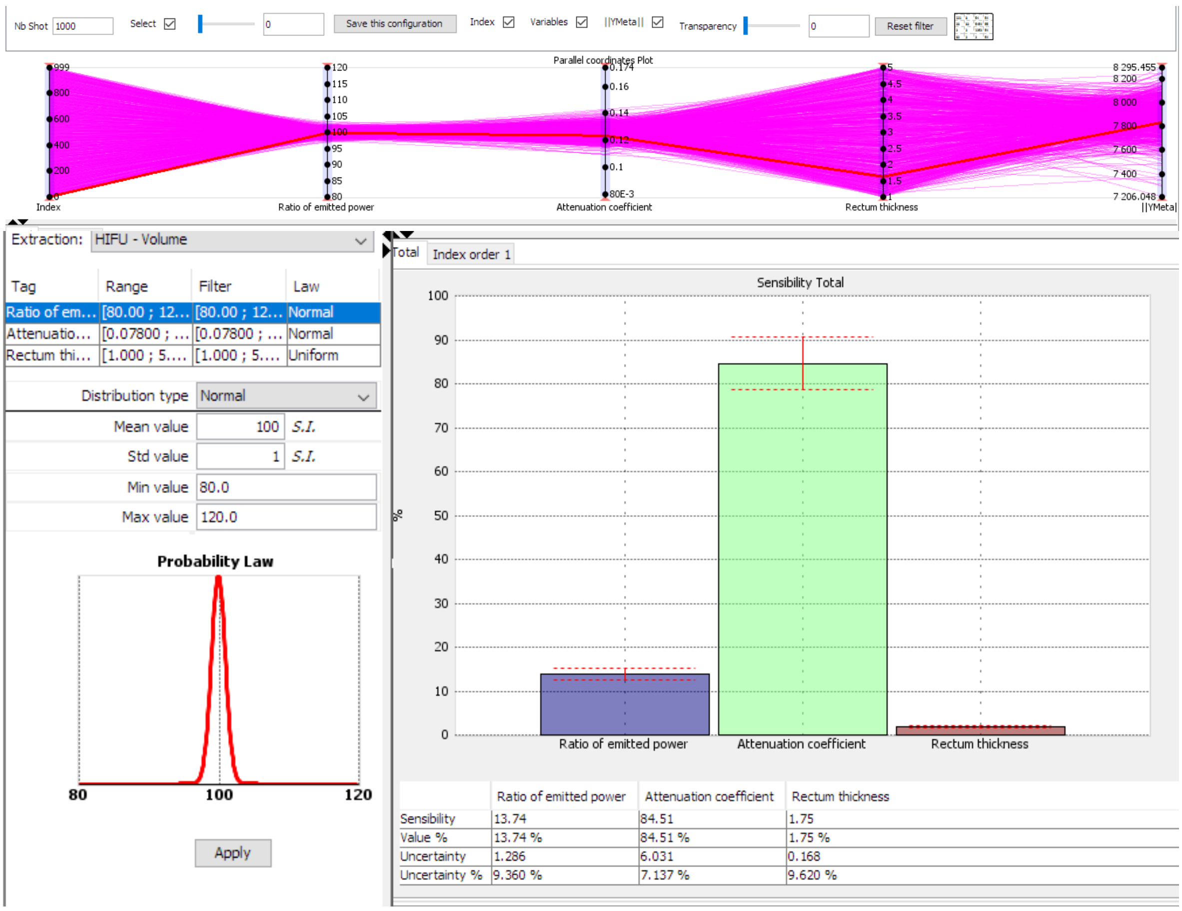

Figure 8: Example of sensitivity analysis applied on a simulated protocol

4. Conclusions

Currently, HIFU simulation tools are commonly used to design or optimize HIFU treatment protocols. Unfortunately, currently available models are time consuming and do not yet seem sufficiently robust to provide sufficient accuracy in real world applications, leading to simulation results are not always consistent with clinical results. There are multiple causes, but the most critical one is undoubtedly the lack of knowledge concerning the physiological parameters, and more particularly, their variability as a function of temperature and/or tissue denaturation. Actually, research is underway to measure and, if possible, to determine dynamic models of these variations. An example could be to account of velocity or attenuation variations according to temperature during the heating process simulation. HIFU simulation tools taking into account dynamic aspects are already under development within the CIVA HealthCare Platform. However, while awaiting these new features, simulation users spent significant time to realise intensive simulations such as multi-parametric studies. In this paper, an alternative solution, based on a surrogate model strategy, has been proposed to provide near real-time simulations and related tools for statistical analysis.

The next steps will concern the continuation of experimental validations and benchmarking of field computations, especially in complex configurations. Specific procedures dedicated to protocol parameters optimisation (probe design, shoots sequence…) and tissue characterisation based on metamodels will be developed.

Finally, it is important to note that the metamodel approach developed in CIVA HealthCare is completely generic and can be applied to any type of simulation tool. Thus, the new models that should be integrated in the long term for simulating complex phenomena such as motion [25], cavitation [26], [27] and field calculation in a non-linear regime [28] will be able to benefit from this strategy whatever their complexity and their numerical performances.

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