

Biological imaging systems

The present invention relates to methods and systems for determining physical properties within a biological structure such as a portion of a human or animal body (e.g. head, foot, leg, etc) or an organ, a cell, a tissue or a sub-cell structure, etc.

Technical Background

Reconstructing the spatial distribution of physical properties within a biological structure based on observations of a field surrounding the structure is the subject of extensive study, e.g. for non-invasively diagnosing diseases. For instance, computerised tomography (CT) scanning is used to produce detailed images of human or animal body parts by detecting X-rays which have passed through the body at a series of different angles.

Determining physical properties of a system based on measurement results is often referred to as solving an “inverse problem” (i.e. in contrast to the “forward problem” of predicting measurement results from a known system). Generally, the behaviour of a physical system can be modelled, for the l -th measurement, as:

$$L(u_l) + K_l(u_l) = g_l \quad (1)$$

where u_l is the field in the system (which can be scalar or vector depending on the type of physical fields and/or the type of measurement being made), $L(\cdot)$ is a linear operator that is independent of the properties of the medium in the system, $K(\cdot)$ is another linear operator that is dependent on the medium properties, and g_l is the source for the l -th measurement. Equation (1) can be a differential equation or an integral equation.

For instance, Figure 1 illustrates schematically a physical system 100 featuring a domain of interest $\mathcal{D}$. The domain of interest $\mathcal{D}$ includes multiple unknown scatterers (not shown) that scatter the incident field. Figure 2 illustrates a prior-art approach to determining the spatial distribution of one or more physical properties in the domain of interest $\mathcal{D}$ (e.g. a spatial distribution of the refractive index) using measurements of the electric field outside the domain of interest.

In a first step 202, the domain is illuminated with N_{inc} incidences from sources outside of the domain $\mathcal{D}$ having angular frequency ω , and several measurements of the electric field $E(\mathbf{r})$ produced by these illuminations are taken at a variety of locations outside the domain $\mathcal{D}$.

In this example, the electric field $E_l(\mathbf{r})$ for the l -th illumination can be modelled using the Helmholtz wave equation:

$$[\nabla \times \nabla \times - k^2(\mathbf{r})]E_l(\mathbf{r}) = g_l. \quad (2)$$

Here, $L(\cdot) = \nabla \times \nabla \times$ and $K_l(\cdot) = -k^2$, with $k(\mathbf{r}) = \omega\sqrt{\epsilon(\mathbf{r})\mu_0}$ being the wave number (assuming the domain is essentially non-magnetic).

In a second step 204, the model is discretised to make it suitable for numerical computation.

One method for discretisation is the finite element method. For instance, the domain of interest $\mathcal{D}$ may be split into a large number of small cells in which the field and physical properties are assumed to be constant. This discretisation produces what is often referred to as a full order model (FOM), with one or more coefficients of the model associated with each cell.

Estimating directly the coefficients of this full order model that generate responses matching the measurements is often computationally demanding, due to the large number of unknowns involved. For instance, modelling a three-dimensional domain at reasonably high accuracy may involve a discretized model with hundreds of thousands of cells.

Therefore, in step 206, by parameterizing the concerned medium properties, a reduced order model (ROM) of the system is determined by projecting the full-order model onto a reduced-order solution subspace. The basis of the reduced-order solution space is selected carefully to capture characteristic behaviour of the system whilst requiring significantly fewer dimensions than the full discretised model. The coefficients of the reduced order model are functions of medium parameters. There are many known approaches to producing a reduced-order model (ROM) of a physical system, such as proper orthogonal decomposition (POD). Model order reduction is discussed in "Basic ideas and tools for projection-based model reduction of parametric partial differential equations", Rozza, G., Hess, M., Stabile, G., Tezzele, M. & Ballarin, F. (2021). 1. In P. Benner, S. Grivet-Talocia, A. Quarteroni, G. Rozza, W. Schilders & L. Silveira (Ed.), Volume 2 Snapshot-Based Methods and Algorithms: Volume 2: Snapshot-Based Methods and Algorithms (pp. 1-47). Berlin, Boston: De Gruyter. <https://doi.org/10.1515/9783110671490-001>.

In step 208, the medium parameters (of which the coefficients of the ROM are functions) that cause the ROM to best match the measurements are found through an optimisation method, e.g. using a Newton-type or genetic optimisation algorithm.

The optimised parameters are then used to produce an estimate of the field in the domain of interest (e.g. $E(r)$) in the solution subspace, which can then be projected back into the full-order space and used to find the spatial distribution of one of more physical properties.

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However, in some situations conventional reduced order modelling approaches may not be able to reconstruct physical properties within a biological structure to a desired accuracy due to the restriction of parameterized space. For instance, typical reduced order modelling may utilise pre-existing assumptions about the biological structure, which can lead to modelling errors when the biological structure varies beyond these assumptions (e.g. beyond expected ranges for properties such as location, shape, size, material properties). In biological imaging high accuracy is often needed and so an improved approach may be desired.

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Summary

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According to a first aspect of the present invention there is provided a biological imaging system for determining a spatial distribution of one or more physical properties within a biological structure, the system comprising:

a data input arranged to receive a plurality of measurements relating to one or more physical fields; and

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a processing device arranged to determine a spatial distribution of one or more physical properties within the biological structure using said plurality of measurements;

wherein the processing device is arranged to:

form a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;

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determine a reduced order model of the biological structure, the reduced order model comprising a second, lower number of reduced order model coefficients;

determine optimised values for the reduced order model coefficients based on the plurality of measurements such that the reduced order model coefficients describe a baseline spatial distribution of the one or more physical properties within the biological structure;

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form a hybrid model of the biological structure comprising the reduced order model coefficients and a set of full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;

determine optimised values for the reduced order model coefficients and the full order model coefficients of the hybrid model based on the plurality of measurements; and

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determine the spatial distribution of one or more physical properties within the biological structure using optimised values of the full order model coefficients and the reduced order model coefficients of the hybrid model.

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According to a second aspect of the present invention there is provided a computer implemented biological imaging method for determining a spatial distribution of one or more physical properties within a biological structure, the method comprising:

- 5 receiving a plurality of measurements relating to one or more physical fields;
- forming a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;
- determining a reduced order model of the biological structure, the reduced order model comprising a second, lower number of reduced order model coefficients;
- 10 determining optimised values for the reduced order model coefficients based on the plurality of measurements such that the reduced order model coefficients describe a baseline spatial distribution of the one or more physical properties within the biological structure;
- forming a hybrid model of the biological structure comprising the reduced order model coefficients and a set of full order model coefficients which describe a deviation from the
- 15 baseline spatial distribution within the biological structure;
- determining optimised values for the reduced order model coefficients and the full order model coefficients of the hybrid model based on the plurality of measurements; and
- determining the spatial distribution of one or more physical properties within the biological structure using the optimised values of the full order model coefficients and the
- 20 reduced order model coefficients of the hybrid model.

Thus, it will be recognised by those skilled in the art that embodiments of the present invention may allow physical properties of a biological structure (e.g. part of a human or animal and/or one or more sub-cell structures, cells, tissues or organs) to be more accurately and/or more

25 efficiently determined from measurements. Because the hybrid model embeds a full order model with the reduced order model, optimising the coefficients of the hybrid model can lead to more accurate estimates of the physical properties within the biological structure. However, because the full order coefficients of the hybrid model only describe a deviation from the baseline spatial distribution described by the reduced order model, the computational

30 complexity of optimising the hybrid model is far less than using a full order model to rebuild the baseline and deviation. The use of the hybrid model may also help to avoid non-physical results for the spatial distribution which could arise from modelling errors if only the full order model was used (e.g. because forming the reduced order model may use pre-existing assumptions and uncertainties about the biological structure).

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In other words, embodiments of the present invention may facilitate more accurate and/or more efficient solving of the inverse problem of determining physical properties within a biological structure from measurements relating to the biological structure.

5 It will be appreciated that the full order model is formed by discretizing the biological structure (or a larger domain of interest) into discrete sections (sometimes called cells). The full order model coefficients describe physical properties of the biological structure in each of these discrete sections (i.e. with one or more coefficients corresponding to each section). This means that, due to the full flexibility, the full order model coefficients can describe either the baseline
10 structure or deviations. The reduced order model coefficients also describe physical properties of the biological structure, but they may not have this direct spatial correspondence with different regions in the biological structure. The reduced order model coefficients may be functions of one or more medium parameters which describe directly the physical properties of the biological structure. The reduced order model coefficients may be functions of the spatial
15 distributions of one or more medium parameters.

In some embodiments, the full order model is built using a reference domain (e.g. rather than in a physical domain in which each cell matches exactly a volume in physical space). For instance, geometric variations of a structure in the domain of interest can be mapped to a carefully
20 designed reference domain, where the FOM is built. In such a reference domain, the geometric variations can be parameterized through the corresponding geometric transformation coefficients of the built FOM. This may facilitate the efficient building of the reduced order model. In some embodiments material variations can also be parameterized in the reference domain, allowing a ROM for both geometric and material parameterizations to be built.

25 In some embodiments, optimised values for the coefficients of the (e.g. parameterised) full order model are determined based on the plurality of measurements such that the (e.g. parameterised) full order model coefficients describe an initial baseline spatial distribution of the one or more physical properties within the biological structure. Determining optimised values for
30 the reduced order model coefficients in the hybrid model may start from initial values for reduced order model coefficients corresponding to this initial full order baseline model.

Reconstructing the baseline structure in a properly defined reference domain can effectively regulate the inversion and can therefore provide improved accuracy.

35 Selecting the reference domain may comprise using pre-existing knowledge and/or assumption(s) about the biological structure (e.g. expected ranges for one or more parameters such as shapes, sizes and/or medium properties).

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Forming the reduced order model may involve using pre-existing knowledge and/or assumption(s) about the biological structure (e.g. expected ranges for one or more parameters such as shapes, sizes and/or medium properties). This may comprise taking into account an uncertainty associated with one or more assumptions. In some embodiments, the reduced order model coefficients describe a biological background of the structure being examined (e.g. a spatial distribution of the one or more physical properties within one or more expected uncertainty ranges associated with a healthy biological structure). For instance, the reduced order model coefficients may be able to represent accurately (by taking appropriate values) the one or more physical properties within the biological structure within an uncertainty range that would normally be expected for an (e.g. average) healthy specimen. In such embodiments, the optimised values for the reduced order model coefficients that are determined based on the plurality of measurements (i.e. before the hybrid model is used) may correspond to a best-guess of the spatial distribution within the biological structure within the constraints of normally-expected ranges and patterns for a healthy specimen. In such cases it will be recognised that the full order model coefficients of the hybrid model describe one or more abnormalities in the biological structure that deviate from the expected uncertainty ranges (i.e. unexpected changes to the physical properties beyond the scope of the reduced order model).

However, embodiments of the invention are not limited to the reduced order model describing only a healthy biological structure. In some embodiments, the reduced order model coefficients describe an enhanced background that includes one or more variations to the biological background of the biological structure (e.g. one or more regions in which the spatial distribution of the one or more physical properties departs from the expected uncertainty ranges). In other words, the reduced order model may represent a healthy biological structure with one or more atypical regions. In such embodiments, the full order model coefficients of the hybrid model may capture abnormalities in the biological structure compared to this enhanced background, e.g. additional details in the suspected atypical regions.

The full order model coefficients of the hybrid model may account for the total field (i.e. the sum of scattered and incident fields). However, in some embodiments the full order model coefficients of the hybrid model may account for only scattered fields. The hybrid model may represent the total field due to the baseline spatial distribution and the deviations. In other embodiments the hybrid model may represent the scattered field due to deviations from the baseline spatial distribution only.

Forming the hybrid model may comprise assigning initial values to some or all of the full order model coefficients. Because the full order model coefficients in the hybrid model describe only a

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deviation from the baseline, in some embodiments the initial value for some or all of the full order model coefficients of the hybrid model is zero.

5 Some of the full order model coefficients of the hybrid model may not need to change very much from their initial values to result in an accurate hybrid model. In a set of embodiments, it may be expected that many or most of the optimised values for the full order model coefficients of the hybrid model are equal or very close to their initial values (e.g. most of the full order model coefficients of the hybrid model may have an optimised value that is zero or near zero).

10 Because optimising the hybrid model involves determining optimised values for the reduced order model coefficients, it will be appreciated that this step may also improve the reduced order model itself (which only uses the reduced order model coefficients) and the baseline spatial distribution it describes. In other words, determining optimised values for the reduced order model coefficients and the full order model coefficients of the hybrid model based on the
15 plurality of measurements may comprise determining reduced order model coefficients that describe more accurately a baseline spatial distribution of the one or more physical properties within the biological structure.

20 The biological structure may comprise a portion (or all of) a human or animal body, e.g. a head, a foot, a leg. Embodiments of the invention may comprise methods and systems of medical imaging. Some embodiments of the invention may comprise methods and systems for *in vivo* imaging. Of course, the biological structure under examination may not comprise the whole of a human or animal body part and may be a very specific portion of said part (e.g. a small region of tissue within a leg). In some embodiments, the biological structure comprises one or more cells,
25 tissues or organs. Some sets of embodiments of the present invention may be used to image biological structures that are not inside a human or animal body, e.g. some embodiments of the invention may comprise methods and systems for *in vitro* imaging.

30 In some embodiments the domain of interest consists of the biological structure (i.e. some or all of the models only model the biological structure being examined). However, this is not essential and the domain of interest is not limited to being just the biological structure. In some embodiments, the biological structure forms part of a larger domain of interest that is also taken into account when determining the spatial distribution of one or more physical properties within the biological structure. For instance, the biological structure of interest may be a specific region
35 within a larger human or animal body part that acts as the domain of interest of some or all of the models. In some embodiments, the whole domain of interest is modelled to determine the spatial distribution of one or more physical properties within the smaller biological structure. In

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other words, the full order model, the reduced order model and/or the hybrid model may be of a domain of interest containing (but not limited to) the biological structure. Such embodiments may involve determining the spatial distribution of the one or more physical properties within part or all of the whole domain of interest (i.e. within more than just the biological structure).

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Embodiments of the invention may be useful for determining the spatial distribution of many different physical properties. In a set of embodiments, the determined spatial distribution is of one or more of the group comprising: density, refractive index, dielectric constant, resistivity (or electric conductivity), permittivity and permeability.

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Embodiments of the invention may not necessarily produce a literal image (i.e. a visual depiction or reconstruction) of the biological structure being examined. However, in a set of embodiments the spatial distribution comprises a map or image of the biological structure. In other words, determining the spatial distribution may comprise producing a depiction of the biological structure (e.g. suitable for identifying different categories and/or types of tissue by a user). The map or image may include false colours to represent the spatial distribution of the physical properties in the biological structure.

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Embodiments of the present invention may determine spatial distributions in one or two dimensions (e.g. for body portions in which a physical property of interest are known to only vary meaningfully in one or two dimensions). However, preferably the spatial distribution comprises a three-dimensional spatial distribution.

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Moreover, embodiments of the invention may utilise measurements relating to many different physical fields. In a set of embodiments, the plurality of measurements comprises a measurement relating to (e.g. of) one or more of the group comprising: electric field strength and/or phase and/or direction, magnetic field strength and/or phase and/or direction, electromagnetic wave intensity and/or propagation direction and/or frequency and/or phase and/or polarisation, acoustic field intensity and/or frequency and/or phase. The measurements may be made in the frequency domain or in the time domain. In some embodiments the measurements may be direct measurements of the field (e.g. a measurement of electric field strength E), however alternatively the measurements may be indirect measurements of the physical field (e.g. a measurement of the energy of the field, such as $|E|^2$).

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The physical properties that are determined may depend on the physical fields that are measured. For instance, where one or more electromagnetic fields are measured, the

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determined spatial distribution may be of permittivity or permeability. When an acoustic field is measured, the determined spatial distribution may be of density.

5 The data input may receive one or more of the measurements from another separate system (e.g. that was previously operated to take the measurements). However, additionally or alternatively, in a set of embodiments the system comprises one or more sensing devices arranged to obtain one or more of the plurality of measurements and provide said measurements to the data input. For instance, the system may comprise one or more electric field sensors, magnetic field sensors, light sensors or sound sensors.

10 Using a sensing device to obtain measurement of a physical field typically involves the sensing device outputting a measurement signal (e.g. a voltage) which can be used to derive a value for the physical field (e.g. electric field strength). The relationship between the actual physical field and the output measurement signal is commonly referred to as the transfer function of the
15 sensing device. Different sensing device may have different transfer functions. It may be advantageous to take the transfer function(s) associated with the measurements into account when comparing a modelled physical system with measurements of said system, e.g. to ensure that predictions from the model also account for the transfer function. In a set of embodiments, determining optimised values for the reduced order model coefficients and/or the full order
20 model coefficients comprises taking one or more transfer functions associated with the plurality of measurements into account. The transfer function might also account for uncertainties in the baseline spatial distribution.

25 The measurements relating to the one or more physical fields may be done without exact knowledge of an incident source of the fields (e.g. without knowing a type and/or strength and/or position and/or orientation of the source). For instance, the reduced order model and/or the hybrid model may take into account one or more uncertainties related to one or more sources of the physical fields, e.g. the field may be modelled by assuming that the source is acting within a certain reasonably assumed parameterized space. In such embodiments the spatial distribution
30 may be determined without using exact information of the incident source of the measured physical fields.

However, in a set of embodiments information regarding one or more sources of the measured field(s) is used when determining the spatial distribution. For instance, a type and/or strength
35 and/or position and/or orientation of the source may be taken into account, e.g. when forming the reduced order model. The source(s) may comprise one or more from the group comprising: an electromagnetic source (e.g. one or more antennas), light source (e.g. one or more LEDs,

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incandescent lights, fluorescent lights or natural light sources), an acoustic source (e.g. an ultrasonic transducer, or a seismic source) or a radiographic source (e.g. an X-ray source, or another penetrative radiation source).

5 In a set of embodiments, the system comprises one or more sources of the one or more physical fields that are measured. The source(s) may be controlled to provide specific stimuli to the biological structure being examined. For instance, the system may be arranged to position and/or orient one or more light sources to provide a desired illumination profile for one or more of the measurements.

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In a set of embodiments, one or more sources of the one or more physical fields are provided by the same physical device(s) as one or more sensing devices. For instance, when electromagnetic fields are used, the same antenna can be used as a source (e.g. to generate an incident electric field) and as a sensing device (e.g. to measure a resulting electric field).

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The measurements relating to the one or more physical fields may be performed in a plurality of different locations and/or with a plurality of different sensing orientations. This may be useful, for instance, to obtain information on the propagation of one or more penetrating waves along different paths in the biological structure.

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The measurements relating to the one or more physical fields may be performed under a variety of different conditions. For instance, the measurements may be performed when the biological structure is subject to various different sources of physical fields (e.g. different positions and/or types of source). The measurements may all be performed simultaneously (e.g. at a plurality of different positions), or some or all of the measurements may be performed at different times.

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In some embodiments, the system comprises a data collection sub-system that controls one or more sources of a physical field and one or more sensing devices arranged to measure said physical field. For instance, the data collection sub-system may comprise one or more light sources and one or more light sensors, or one or more X-ray sources and one or more X-ray detectors. The data collection sub-system may be controlled by the processing device, or by another controller.

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The measurements relating to the physical field(s) can be used to determine accurately a spatial distribution of one or more physical properties in the biological structure because the field(s) interact with these physical properties. Whilst, in theory, many physical fields extend infinitely it will be appreciated that, in practice, the locations at which the physical field(s) are

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measured must be sufficiently close to the biological structure being examined for there to be a meaningful interaction between the biological structure and the physical field that is being measured (i.e. above a noise floor). In a set of embodiments one or more of the measurements are of fields perturbed by penetrating waves (e.g. EM or acoustic waves) that have propagated through the biological structure.

In some embodiments, all of the measurements are taken at locations outside the biological structure. For example, all of the sensing device(s) used to collect the measurements may be located outside of the biological structure being examined. In some embodiments the measurements are taken externally to a biological body (e.g. human or animal body) comprising the structure being examined. In other words, some embodiments may comprise non-intrusive testing. Alternatively, some or all of the measurements may be taken inside the biological structure.

The reduced order model describes the biological structure using fewer parameters (and thus fewer parameter coefficients) than the full discretised model. It will be recognised that determining the reduced order model may thus involve identifying characteristics or patterns in the biological structure that can be used to simplify the model whilst preserving the underlying physics. There are many ways of producing a reduced-order model (ROM) of a physical system. In a set of embodiments, determining the reduced order model comprises proper orthogonal decomposition (POD) and/or empirical interpolation method (EIM). In some embodiments, determining the reduced order model comprises performing an affine decomposition. The affine decomposition separates medium properties from the model operators, with the medium properties put into affine coefficients.

Determining optimised values for the reduced order model coefficients and/or the full order model coefficients may comprise forming an objective function (e.g. a cost function) that depends on said coefficients, and finding values for the coefficients that cause the value of the objective function to approach or reach a goal (e.g. a minimum or a maximum). In a set of embodiments, the objective function comprises a measurement mismatch term which quantifies how accurately the reduced order model and/or the hybrid model replicates the plurality of measurements. This may comprise a sum of errors between values obtained from the plurality of measurements (e.g. measured strengths of the physical field at a series of locations) and corresponding values obtained from the reduced order model coefficients and/or the full order model coefficients (e.g. modelled strengths of the physical field at the same locations). In such embodiments, an accuracy of the reduced order model and/or the hybrid model may be

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estimated using the measurement mismatch term. For instance, it may be the measurement mismatch term that is compared to accuracy thresholds.

For instance, a first estimate for values for the reduced order model coefficients and/or the full order model coefficients may be determined and used to determine a corresponding first estimate of the spatial distribution of one or more physical properties within the biological structure. This first estimate for the spatial distribution may then be used to determine an expected physical field at each of the sensed locations (i.e. solving the forward problem of predicting the physical field from an estimated medium), which can be compared to the measured values to produce the measurement mismatch sum of errors. The first estimate for the reduced order model coefficients and/or the full order model coefficients may then be refined and the process repeated until the measurement mismatch term is sufficiently minimised. In other words, determining optimised values for the reduced and/or full order model coefficients may comprise finding coefficient values which minimise a difference between a modelled field and the measurements.

In some embodiments, the hybrid model and/or the reduced order model are treated as hard constraints of an optimization problem for finding the reduced order model coefficients and/or full order model coefficients. The measurement mismatch term may take into account one or more transfer functions associated with the plurality of measurements, i.e. to enable a modelled physical field to be compared to a measured physical field.

Additionally or alternatively, the objective function may include one or more model mismatch terms. The objective function may comprise a mismatch term for the reduced order model. The objective function may comprise a mismatch term for the hybrid model. In other words, the hybrid model and/or the reduced order model may be taken into account in the optimization with mismatch terms and are not necessarily met perfectly by the optimised values for the reduced order model coefficients and/or the full order model coefficients. This approach may involve using physical quantities such as physical fields as arguments of the optimisation problem. The model mismatch term(s) may include a modelled physical field as an argument. The model mismatch term(s) may be a measure of how accurately the model coefficients and physical fields obey the relevant physical equations (e.g. a difference between two sides of the wave equation).

The objective function may comprise a sum of a plurality of mismatch terms. Different terms in the objective function may be given different weightings. For instance, a measurement mismatch term may be given a measurement weighting, a reduced order model mismatch term

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may have a reduced order model weighting and the hybrid model mismatch term may have a hybrid model weighting. In some embodiments, one of the reduced order model and the hybrid model may be treated as a hard constraint, and the other taken into account with a mismatch term. Some embodiments may involve determining optimised weightings of different terms in the objective function at the same time as determining optimised values of the model coefficients (i.e. the weightings may also be optimisable arguments of the objective function).

Separate objective functions may be used to optimise only the reduced order model coefficients, and to optimise the reduced order model coefficients and the full order model coefficients of the hybrid model. However, in a set of embodiments, the same objective function is used for both optimisations by using appropriate weightings. For instance, in embodiments featuring a hybrid model mismatch term, a hybrid model weighting may be set to zero when only the reduced order model coefficients are being optimised, and set to a non-zero value when the reduced order model coefficients and the full order model coefficients of the hybrid model are being optimised. In embodiments where the hybrid model is treated as a hard constraint, this hard constraint may simply be ignored when only the reduced order model coefficients are being optimised.

In some embodiments the objective function may include additional terms (e.g. with additional weightings). For instance, the objective function may comprise one or more regularisation terms arranged to mitigate instabilities in the objective function and/or to avoid unphysical solutions. For instance, this term might add a penalty if values of the reduced order model coefficients and/or the full order model coefficients are physically unreasonable (e.g. a large value if the optimization is to minimize the objective function).

Determining optimised values for reduced order model coefficients and/or full order model coefficients based on the plurality of measurements (e.g. minimising the objective function) may comprise any suitable optimisation technique known in the art *per se* including Monte Carlo methods, gradient-based methods and/or evolutionary algorithms. In some embodiments the optimising comprises an iterative process.

As explained above, the reduced order model coefficients may be functions of one or more medium parameters. In some such embodiments, finding optimised values of the reduced order model coefficients may comprise using the medium parameters as optimisation inputs (e.g. varying the medium parameters to minimise or maximise an objective function). It will be recognised that in such embodiments the reduced order model coefficients are intermediate variables of the optimisation.

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However, in an alternative set of embodiments, finding optimised values of the reduced order model coefficients comprises using the reduced order model coefficients as optimisation inputs (e.g. to minimise or maximise an objective function that depends on the reduced order model coefficients). In such embodiments the reduced order model coefficients are not intermediate variables of the optimisation but are the direct variables to be optimised. This may improve efficiency.

The optimising may continue until the reduced order model coefficients and/or the full order model coefficients produce a reduced order model and/or a hybrid model that reproduces the plurality of measurements within an accuracy threshold (e.g. when a measurement mismatch term of the objective function is below the accuracy threshold). The accuracy threshold when only the reduced order model coefficients are optimised may be higher than a final accuracy threshold used when the reduced order model coefficients and the full order model coefficients of the hybrid model are optimised, because the reduced order model may be expected to yield less accurate results. Additionally or alternatively, the optimising may continue until further optimisation leads to changes to the reduced order model coefficients, the full order model coefficients, or a combination of the two that are below a coefficient change threshold (i.e. until further optimisation leads to sufficiently small changes in the coefficients).

As explained above, embedding a full-order model with the reduced order model with the hybrid model may allow the spatial distribution of one or more physical properties within the biological structure to be determined with better accuracy and/or more efficiently than conventional techniques that use only a reduced order model. However, in some implementations the initial reduced order model optimisation may nevertheless provide sufficiently accurate results (i.e. in some cases the baseline spatial distribution described by the reduced order model coefficients may be sufficiently accurate). In a set of embodiments therefore, after only optimised values for the reduced order model coefficients have been determined, an initial accuracy of the reduced order model is checked (i.e. an accuracy with which the reduced order model reproduces some or all of the plurality of measurements). Checking the initial accuracy may comprise comparing it to a final accuracy threshold. If the initial accuracy is below the final accuracy threshold (i.e. if the reduced order model is sufficiently accurate that the use of the hybrid model is not needed), the spatial distribution of the one or more physical properties within the biological structure may be determined using only the optimised reduced order model coefficients. In other words, the processing device may be arranged to only proceed to form the hybrid model if the reduced order model is not sufficiently accurate.

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The spatial distribution of one or more physical properties may be determined from the optimised values of the reduced order model coefficients, the full order model coefficients of the hybrid model or a combination of the two using any suitable techniques known in the art *per se*. For instance, the baseline spatial distribution may be restored via a parameterizing method used to build the reduced order model, and then the deviation from this baseline may be restored from the full order model parameters.

In some embodiments, the spatial distribution is simply used for further calculations by the processing device that determines it. However, a set of embodiments comprises outputting the spatial distribution. The system may comprise an output device arranged to output the spatial distribution. In a set of embodiments the system comprises a user output device arranged to output the spatial distribution to a user (e.g. an electronic display such as a computer monitor). For instance, the spatial distribution may comprise an image or map of the biological structure, which a user can interpret e.g. for aiding medical diagnosis and/or treatment. Additionally or alternatively, the output device may comprise an output data interface, e.g. for outputting the spatial distribution to another system.

The biological imaging system may be provided by a single physical computing device, or by a collection of networked computing devices (e.g. connected over a local network or located remotely and connected via the internet). The processing device may be a single physical processor of a computing device, or it may be a distributed processing device comprising several physical processors, e.g. in different computing devices. The processing device may comprise one or more computational accelerators such as a Graphical Processing Unit (GPU) or a Field Programmable Gate Array (FPGA).

The invention extends to computer software that, when executed by a computer causes said computer to perform a method disclosed herein. The computer may comprise a memory storing said software. The computer may comprise a processor arranged to execute said software. The invention also extends to a non-transitory computer readable medium storing said software.

It has been recognised that use of a reduced order model may not be essential in all embodiments and that an alternative approach may be used in which a parametric full order model is used to describe the baseline. According to another aspect of the present invention there is provided a biological imaging system for determining a spatial distribution of one or more physical properties within a biological structure, the system comprising:

a data input arranged to receive a plurality of measurements relating to one or more physical fields; and

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a processing device arranged to determine a spatial distribution of one or more physical properties within the biological structure using said plurality of measurements; wherein the processing device is arranged to:

- 5 form a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;
- use the full order model to describe a baseline spatial distribution of the biological structure, said baseline spatial distribution being described by a set of coefficients;
- determine optimised values for the coefficients describing the baseline spatial distribution based on the plurality of measurements;
- 10 form a hybrid model of the biological structure comprising the baseline spatial distribution coefficients and a set of deviation full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;
- determine optimised values for the baseline spatial distribution coefficients and the deviation full order model coefficients of the hybrid model based on the plurality of
- 15 measurements; and
- determine the spatial distribution of one or more physical properties within the biological structure using optimised values of the deviation full order model coefficients and the baseline spatial distribution coefficients of the hybrid model.

20 According to another aspect of the present invention there is provided a computer implemented biological imaging method for determining a spatial distribution of one or more physical properties within a biological structure, the method comprising:

- receiving a plurality of measurements relating to one or more physical fields;
- forming a discretized full order model of the biological structure, the full order model
- 25 comprising a first number of full order model coefficients;
- use the full order model to describe a baseline spatial distribution of the biological structure, said baseline spatial distribution being described by a set of coefficients;
- determining optimised values for the coefficients describing the baseline spatial distribution;
- 30 forming a hybrid model of the biological structure comprising the baseline spatial distribution coefficients and a set of deviation full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;
- determining optimised values for the baseline spatial distribution coefficients and the deviation full order model coefficients of the hybrid model based on the plurality of
- 35 measurements; and

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determining the spatial distribution of one or more physical properties within the biological structure using the optimised values of the deviation full order model coefficients and the baseline spatial distribution coefficients of the hybrid model.

5 In a set of embodiments, using the full order model to describe a baseline spatial distribution of the biological structure comprises determining a reduced order model as described above. However in some embodiments the baseline spatial distribution of the biological structure may be described by full order model coefficients (e.g. in a suitably selected reference domain). The baseline spatial distribution may be described by geometric transformation coefficients and
10 physical property coefficients.

Determining a full order model to describe the baseline spatial distribution may comprise first determining a reduced order model and optimising this to describe the baseline spatial distribution as described above with reference to the first aspect, and then using the ROM to
15 determine a (e.g. parameterised) full order model which describes the baseline spatial distribution and using this in the hybrid model.

In such embodiments, the hybrid model of the biological structure may comprise the baseline biological structure full order model coefficients (geometric transformation coefficients and the
20 physical property coefficients) and a set of full order model physical property coefficients which describe a deviation from the baseline structure.

If geometric transformation coefficients and the physical property coefficients of the full order model are used for the baseline biological structure (e.g. instead of the corresponding reduced
25 order model coefficients), the optimised values for them may provide such a best-guess of the baseline structure.

The baseline biological structure may describe an enhanced background that includes one or more variations to the biological background of the biological structure. The baseline biological structure may represent a healthy biological structure with one or more atypical regions.
30

It will be recognised that options described above with reference to the reduced order model may also be applied, where relevant, to the baseline spatial distribution of the biological structure described by full order model coefficients. For instance, options described above relating to refining reduced order model coefficients may also be applied to refining full order
35 model coefficients describing a baseline spatial distribution of the biological structure (e.g. in a suitably selected reference domain), such as geometric transformation coefficients and/or physical property coefficients.

5 Finding optimised values of the geometric transformation coefficients and/or physical property coefficients may comprise directly using the geometric transformation coefficients and physical property coefficients as optimisation inputs (e.g. to minimise or maximise an objective function that depends on these coefficients).

10 The baseline spatial distribution coefficients (e.g. the geometric transformation coefficients and physical property coefficients) can be parameterised. Determining an optimized baseline biological structure then may comprise using the resultant parameters that control the variations of the geometric transformation coefficients and physical property coefficients as optimisation inputs.

15 Determining the spatial distribution of one or more physical properties within the biological structure using optimised values of the deviation full order model coefficients and the baseline spatial distribution coefficients may then comprise inverting the parameterisation of the baseline spatial distribution coefficients (i.e. to go back to the physical property coefficients).

20 Features of any aspect or embodiment described herein may, wherever appropriate, be applied to any other aspect or embodiment described herein. Where reference is made to different embodiments, it should be understood that these are not necessarily distinct but may overlap. It will be appreciated in particular that all of the preferred features of the system according to the first aspect described above may also, where appropriate, apply to the other aspects of the invention.

25 Detailed Description

One or more non-limiting examples will now be described, by way of example only, and with reference to the accompanying figures in which:

30 Figure 1 is a schematic diagram of a physical system for use with embodiments of the present invention;

Figure 2 is a flow diagram illustrating a prior art approach to determining a spatial distribution of one or more physical properties of a domain or interest;

Figure 3 is a schematic diagram of a system according to an example of the present invention; and

35 Figure 4 is a flow diagram illustrating an approach to determining a spatial distribution of one or more physical properties of a domain or interest according to an embodiment of the invention.

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Figure 3 shows a system 300 for determining a spatial distribution of one or more physical properties within the head 301 of a human patient 303. The system 300 comprises a field response measuring device 302, a processing and controlling device 304, and an output 306. In other examples, the system 300 may be used to determining a spatial distribution of one or more physical properties within another biological structure.

The system 300 obtains measurements relating to a physical field surrounding the head 301, and uses these to determine an internal spatial distribution of physical properties of the head 301 (e.g. dielectric permittivity).

The field response measuring device 302 comprises a plurality of sources 308 for applying various physical stimuli to the head 301, and a plurality of sensing devices 310 for making a plurality of measurements of the resulting field responses from outside the head 301. For instance, the sources 308 may produce several incident electric fields, and the sensing devices 310 may measure the resulting total electric fields. In some examples the sources 308 and the sensing devices 310 could be provided by the same physical devices.

The processing and controlling device 304 is arranged to control the field response measuring device 302 perform the method described below with reference to Figure 4 to determine a spatial distribution of one or more physical properties (e.g. dielectric permittivity) within the head 301 using the measurements made by the field response measuring device 302.

Once the spatial distribution has been determined, it is provided (e.g. to a user) via the output 306. For instance, the output 306 may comprise an electronic display for outputting the spatial distribution as a map or image 312 of the head 301.

The operation of the system 300 will now be described in detail with additional reference to the flow diagram of Figure 4.

In a first step 402, the sensing devices 310 obtain a series of measurements of a physical field u_l (e.g. electric field $E_l(r)$) for l different incident fields produced by the sources 308.

The head 301 (and potentially the rest of the body 303 if needed) can be modelled generally using equation (1) above:

$$L(u_l) + K_l(u_l) = g_l \quad (1)$$

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where $L(\cdot)$ and $K(\cdot)$ are linear operators. For the example of u_l being the vectorial electric field, equation (1) may be based on the vector form of the Helmholtz equation (2):

$$[\nabla \times \nabla \times - k^2(r)]E_l(r) = g_l \quad (2)$$

Some background information is known about the head 203 (e.g. a baseline biological structure of a healthy head and expected limits on how much the actual structure will vary from this baseline). Equation (1) can therefore be re-written as:

$$L(u_l^{(b)}) + K_l^{(b)}(u_l^{(b)}) = g_l \quad (3)$$

where the medium-dependent operator $K_l^{(b)}$ accounts for the background media and possible expected variations to this.

In step 404, this model is discretized using the finite element method to produce:

$$\bar{\bar{A}} \bar{u}_l^{(b)} = \bar{g}_l \quad (4)$$

where $\bar{\bar{A}}$ is a matrix accounting for both linear operators in equation (3), along with a suitable boundary condition. $\bar{\bar{A}}$ therefore includes the physical properties of the head 203.

In step 406, the discretised model is transformed into a reduced order model (ROM). First, equation (4) is rewritten as:

$$\sum_{q=1}^{N_A} \theta_q^{(A)} \bar{\bar{A}}_q \cdot \bar{u}_l^{(b)} = \sum_{p=1}^{N_g} \theta_{l,p}^{(g)} \bar{g}_{l,p} \quad (5)$$

in which $\bar{\bar{A}}$ and $\bar{g}_l$ are decomposed into respective sums with coefficients $\theta_q^{(A)}$, $\theta_{l,p}^{(g)}$ that depend on the head's physical properties. This example uses the affine decomposition, i.e. $\bar{\bar{A}}$ is written as the sum of a series of operators $\bar{\bar{A}}_q$ with $\theta_q^{(A)}$ as the affine parameters, i.e., $\bar{\bar{A}} = \sum_{q=1}^{N_A} \theta_q^{(A)} \bar{\bar{A}}_q$.

$\bar{\bar{A}}_q$ and $\bar{g}_{l,p}$ are independent to medium properties. The affine coefficients are functions of medium parameters $\bar{\mu}$ (a vector with a few elements μ_i) which act independently to control the medium's physical properties within a designed scope to parameterize the medium properties in the concerned domain of interest. The affine decomposition separates the medium properties from the operators and puts them into the affine coefficients. This decomposition may be done using the empirical interpolation method (EIM). Equation (5) is a good approximation of equation (4). In other examples of kinds of decomposition may be used.

This decomposition is then projected onto a lower-order solution subspace with a basis being the columns of $\bar{\xi}$.

5 The resulting reduced-order model is:

$$\sum_{q=1}^{N_A} \theta_q^{(A)} \bar{A}_q^{(r)} \cdot \bar{u}_l^{(br)} = \sum_{p=1}^{N_g} \theta_{l,p}^{(g)} \bar{g}_{l,p}^{(r)} \quad (6)$$

where $\bar{A}_q^{(r)} = \bar{\xi}^* \cdot \bar{A}_q \cdot \bar{\xi}$ and $\bar{g}_{l,p}^{(r)} = \bar{\xi}^* \cdot \bar{g}_{l,p}$. Eq. (6) is referred to as the reduced order model (ROM) hereafter, and $\theta_q^{(A)}$, $q = 1, 2, \dots, N_A$, are referred to as parameterized medium coefficients (i.e. coefficients of the reduced-order model).

10

To provide improved accuracy, in step 408 the processing device 304 produces a hybrid model that embeds a full order model with the reduced order model. The full order model is used to capture changes to the domain medium that go beyond the expected limits built into equation (5) above, i.e. to describe a deviation from the baseline structure of the head, e.g.

15

due to unexpected abnormalities).

Two approaches to embedding a full order model into the reduced order model will now be explained.

20

The first approach considers the scattered field due to changes in the medium beyond that taken into account in the ROM. This scattered field is:

$$u_l^{(s)} = u_l - u_l^{(b)} \quad (7)$$

Substituting this into equation (1), and subtracting equation (2) leads to:

$$L(u_l^{(s)}) + K_l^{(b)}(u_l^{(s)}) = -K_l^{(\Delta)}(u_l^{(s)} + u_l^{(b)}) \quad (8)$$

25

where $K_l = K_l^{(b)} + K_l^{(\Delta)}$ and $L(\cdot)$ is medium-independent.

Replacing $-K_l^{(\Delta)}$ with a matrix $\bar{\chi}$ and using the reduced order basis $\bar{\xi}$ along with the decomposition in equation (5) leads to:

$$\sum_{q=1}^{N_A} \theta_q^{(A)} \bar{A}_q \cdot \bar{u}_l^{(s)} = \bar{\chi} \cdot (\bar{u}_l^{(s)} + \bar{\xi} \cdot \bar{u}_l^{(br)}) \quad (9)$$

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This is a hybrid model for the field $\bar{u}_l^{(s)}$ (i.e. with reduced order model coefficients $\theta_q^{(A)}$ and full order model coefficients $\bar{\chi}$) that can account for due to medium changes beyond that taken into account by the reduced order model alone (i.e. a deviation from the baseline structure of the head described by the reduced order model).

5

The second approach to embedding the full order model in the ROM considers the total field u_l . Using equation (1) directly in the decomposition in equation (5) leads to an alternative hybrid model:

$$\sum_{q=1}^{N_A} \theta_q^{(A)} \bar{A}_q \cdot \bar{u}_l = \bar{\chi} \cdot u_l + \sum_{p=1}^{N_g} \theta_{l,p}^{(g)} \bar{g}_{l,p} \quad (10)$$

10 Determining the spatial distribution of physical properties within the head 203 involves finding the values of the reduced and full order model coefficients that lead to the best replication of the measured fields. This inverse problem can be cast as an optimization problem, and there are many ways to do so. In the following, an option is given to show how such an optimization problem can be formed using the first approach of the hybrid model described above (equation
15 (9)). To find these optimised values an objective function is formulated:

$$f(\bar{\theta}^{(A)}, \bar{\theta}^{(g)}, \bar{u}^{(br)}, \bar{\chi}, \bar{u}^{(s)}) = \sum_{l=1}^{N_i} \alpha_l \Delta_l^{(br)} + \beta_l \Delta_l^{(f)} + \gamma_l \Delta_l^{(d)} + \eta_l \Delta_l^{(rg)} \quad (11)$$

Where $\Delta_l^{(br)}$ is a mismatch term for the reduced order model (equation (6)), $\Delta_l^{(f)}$ is a mismatch term for the hybrid model (e.g. equation (9)).

20 These mismatch terms could take the form of appropriate norms. For instance, if L2 norm is used and equation (9) is used for the FOM embedding:

$$\Delta_l^{(br)} = \left\| \sum_{q=1}^{N_A} \theta_q^{(A)} \bar{A}_q \cdot \bar{u}_l^{(br)} - \sum_{p=1}^{N_g} \theta_{l,p}^{(g)} \bar{g}_{l,p} \right\|^2 \quad (12)$$

$$\Delta_l^{(f)} = \left\| \sum_{q=1}^{N_A} \theta_q^{(A)} \bar{A}_q \cdot \bar{u}_l^{(s)} - \bar{\chi} \cdot (\bar{u}_l^{(s)} + \bar{\xi} \cdot \bar{u}_l^{(br)}) \right\|^2. \quad (13)$$

$\Delta_l^{(d)}$ is a measurement mismatch term, between the measurements $\bar{y}_l$ of the physical field made by the sensors 308 and the predicted corresponding measurements given the fields produced
25 from the full and reduced order models, $\bar{u}_l^{(s)}, \bar{u}_l^{(br)}$:

$$\Delta_l^{(d)} = \left\| \bar{y}_l - \bar{h} \left(\bar{u}_l^{(s)}, \bar{u}_l^{(br)} \right) \right\|^2. \quad (14)$$

The $\bar{h} \left(\bar{u}_l^{(s)}, \bar{u}_l^{(br)} \right)$ function converts the predicted physical fields into the measured signals (i.e. accounting for the transfer function(s) of the deployed sensors . Different sensors 308 may have different transfer functions and thus different elements in $\bar{h}$.

5

$\Delta_l^{(rg)}$ is a regularization term to mitigate instabilities in the objective function, e.g. to avoid non-physical medium properties. This could include the constraints on the relationships between the reduced order model coefficients and the original medium parameters, or those hyperparameters reflecting the original medium parameters. $\alpha_l, \beta_l, \gamma_l$ and η_l are weights applied to the different mismatch terms. These weights may be chosen according to some criteria or may be optimisable. Typically, the weight of the measurement mismatch term γ_l is set to one.

15

Using the models to determine the spatial distribution of one or more physical properties within the head involves finding the values of the coefficients of the reduced and hybrid models which best replicate the measured fields. In some cases (e.g. when the head is healthy and doesn't contain unexpected abnormalities), the baseline structure described by the reduced order model may be sufficient for determining the spatial distribution within a required accuracy.

20

Therefore, in step 410, the processing device 304 optimises the objective function (equation (11)) for the ROM coefficients only. β_l is set to zero, and values of the reduced order model coefficients ($\bar{\theta}^{(A)}, \bar{\theta}^{(g)}$ and $\bar{u}^{(br)}$) are found for which the objective function is minimised, using a suitable iterative optimisation technique. It will be appreciated that in embodiments of the invention the reduced order model coefficients (e.g. $\theta_q^{(A)}$) are optimized instead of the parameter $\bar{\mu}$, which is conventionally used for ROM optimization.

25

In step 412 it is checked whether the accuracy of the optimised reduced order model is below a predefined accuracy threshold. This is done by comparing a sum of the measurement mismatch term for all measurements $\Delta^{(d)}$ with an accuracy threshold $\delta^{(d)}$.

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If the accuracy is sufficient, the processing device 304 proceeds to step 414, where the optimised ROM coefficient values are output. Finally, in step 416, the processing device 304 uses these coefficients to determine the spatial distribution of the physical property of interest.

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However, if the accuracy is not sufficient, the processing device 304 proceeds to step 418, where the objective function (equation (11)) is optimised including the hybrid model term. As explained above, the hybrid model describes a deviation from the baseline structure of the head described by the reduced order model. Therefore, the full order model coefficients $\bar{\chi}$ of the hybrid model are initialised with a value of zero.

β_l is set to a non-zero value and the values of the reduced and full order coefficients (i.e. $\bar{\theta}^{(A)}, \bar{\theta}^{(g)}, \bar{u}^{(br)}, \bar{\chi}, \bar{u}^{(s)}$), and the weights ($\alpha_l, \beta_l, \gamma_l, \eta_l$) for which the objective function is minimised are found. Because the hybrid model only describes a deviation from the baseline structure of the head described by the reduced order model, most of the full order model coefficients $\bar{\chi}$ remain close to their initial value of zero during this minimisation.

In step 420, the optimised values for the reduced order coefficients and the full order model coefficients are output, and the processing device 304 proceeds to step 416 and uses these coefficients to determine the spatial distribution of the physical property of interest.

While the invention has been described in detail in connection with only a limited number of embodiments, it should be readily understood that the invention is not limited to such disclosed embodiments. For instance, the ROM used in both equation (9) and (10) for the background media can be replaced by the original parameterized FOM (with a few parameters to control the variations of the background media) to describe the background media to form the hybrid model. Subsequent optimisation problems can be formed accordingly.

More generally, the invention can be modified to incorporate any number of variations, alterations, substitutions or equivalent arrangements not heretofore described, but which are commensurate with the scope of the invention. Additionally, while various embodiments of the invention have been described, it is to be understood that aspects of the invention may include only some of the described embodiments. Accordingly, the invention is not to be seen as limited by the foregoing description, but is only limited by the scope of the appended claims.

Claims

1. A biological imaging system for determining a spatial distribution of one or more physical properties within a biological structure, the system comprising:
- 5 a data input arranged to receive a plurality of measurements relating to one or more physical fields; and
- a processing device arranged to determine a spatial distribution of one or more physical properties within the biological structure using said plurality of measurements;
- wherein the processing device is arranged to:
- 10 form a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;
- determine a reduced order model of the biological structure, the reduced order model comprising a second, lower number of reduced order model coefficients;
- determine optimised values for the reduced order model coefficients based on the
- 15 plurality of measurements such that the reduced order model coefficients describe a baseline spatial distribution of the one or more physical properties within the biological structure;
- form a hybrid model of the biological structure comprising the reduced order model coefficients and a set of full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;
- 20 determine optimised values for the reduced order model coefficients and the full order model coefficients of the hybrid model based on the plurality of measurements; and
- determine the spatial distribution of one or more physical properties within the biological structure using optimised values of the full order model coefficients and the reduced order model coefficients of the hybrid model.
- 25
2. The biological imaging system of claim 1, wherein the reduced order model coefficients describe a spatial distribution of the one or more physical properties within one or more expected uncertainty ranges associated with a healthy biological structure, and the full order model coefficients of the hybrid model describe one or more abnormalities in the biological
- 30 structure that deviate from the expected uncertainty ranges.
3. The biological imaging system of claim 2, wherein the reduced order model coefficients describe an enhanced background of the biological structure that includes one or more regions in which the spatial distribution of the one or more physical properties departs from the
- 35 expected uncertainty ranges.

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4. The biological imaging system of any preceding claim, wherein forming the hybrid model comprises assigning an initial value of zero to some or all of the full order model coefficients.
5. The biological imaging system of any preceding claim, wherein initial values for some or all of the full order model coefficients of the hybrid model are determined using optimised values for the reduced order model coefficients determined previously.
6. The biological imaging system of any preceding claim, wherein the determined spatial distribution is of one or more of the group comprising: density, refractive index, dielectric constant, resistivity, permittivity and permeability.
7. The biological imaging system of any preceding claim, wherein the plurality of measurements comprises a measurement relating to one or more of the group comprising: electric field strength and/or phase and/or direction, magnetic field strength and/or phase and/or direction, electromagnetic wave intensity and/or propagation direction and/or frequency and/or phase and/or polarisation, acoustic field intensity and/or frequency and/or phase.
8. The biological imaging system of any preceding claim, comprising one or more sensing devices arranged to obtain one or more of the plurality of measurements and provide said measurements to the data input.
9. The biological imaging system of any preceding claim, wherein information regarding one or more sources of the field(s) is used when determining the spatial distribution.
10. The biological imaging system of claim 9, wherein the reduced order model and/or the hybrid model takes into account one or more uncertainties related to one or more sources of the physical fields.
11. The biological imaging system of any preceding claim, comprising one or more sources of the one or more physical fields that are measured and arranged to control the source(s) to provide specific stimuli to the biological structure.
12. The biological imaging system of claim 11, wherein the one or more sources of the one or more physical fields are provided by the same physical device(s) as one or more sensing devices arranged to obtain one or more of the plurality of measurements and provide said measurements to the data input.

13. The biological imaging system of any preceding claim, wherein the measurements relating to the one or more physical fields are performed in a plurality of different locations outside the biological structure.
- 5
14. The biological imaging system of any preceding claim, wherein determining optimised values for the reduced order model coefficients and/or the full order model coefficients comprises forming an objective function that depends on said coefficients, and finding values for the coefficients that cause the value of the objective function to approach or reach a goal.
- 10
15. The biological imaging system of claim 14, wherein the objective function comprises a measurement mismatch term which quantifies how accurately the reduced order model and/or the hybrid model replicates the plurality of measurements.
- 15
16. The biological imaging system of claim 15, wherein the measurement mismatch term takes into account one or more transfer functions associated with the plurality of measurements.
17. The biological imaging system of any of claims 14-16, wherein the reduced order model and/or the hybrid model act as hard constraints of an optimization problem.
- 20
18. The biological imaging system of any of claims 14-17, wherein the objective function comprises a mismatch term for the reduced order model and/or a mismatch term for the hybrid model which includes a modelled physical field as an argument.
- 25
19. The biological imaging system of any of claims 14-18, wherein the objective function comprises one or more regularisation terms arranged to mitigate instabilities in the objective function and/or to avoid unphysical solutions.
- 30
20. The biological imaging system of any of claims 14-19, wherein the objective function comprises a sum of a plurality of mismatch terms and different terms in the objective function are given different weightings.
- 35
21. The biological imaging system of any preceding claim, wherein the reduced order model coefficients are functions of one or more medium parameters which describe directly physical properties of the biological structure, and finding optimised values of the reduced order model coefficients comprises using the reduced order model coefficients as optimisation inputs.

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22. The biological imaging system of any preceding claim, wherein the processing device is arranged, after only optimised values for the reduced order model coefficients have been determined, to compare an initial accuracy of the reduced order model to a final accuracy threshold, and if the initial accuracy is below the final accuracy threshold to determine the spatial distribution of the one or more physical properties within the biological structure using only the optimised reduced order model coefficients.
23. The biological imaging system of any preceding claim, wherein the full order model is built using a reference domain.
24. The biological imaging system of any preceding claim, wherein the processing device is arranged to determine optimised values for the first number of full order model coefficients based on the plurality of measurements such that the full order model describes an initial baseline spatial distribution of the one or more physical properties within the biological structure.
25. A computer implemented biological imaging method for determining a spatial distribution of one or more physical properties within a biological structure, the method comprising:
- receiving a plurality of measurements relating to one or more physical fields;
 - forming a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;
 - determining a reduced order model of the biological structure, the reduced order model comprising a second, lower number of reduced order model coefficients;
 - determining optimised values for the reduced order model coefficients based on the plurality of measurements such that the reduced order model coefficients describe a baseline spatial distribution of the one or more physical properties within the biological structure;
 - forming a hybrid model of the biological structure comprising the reduced order model coefficients and a set of full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;
 - determining optimised values for the reduced order model coefficients and the full order model coefficients of the hybrid model based on the plurality of measurements; and
 - determining the spatial distribution of one or more physical properties within the biological structure using the optimised values of the full order model coefficients and the reduced order model coefficients of the hybrid model.
26. Computer software that, when executed by a computer causes said computer to perform the method of claim 25.

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27. A non-transitory computer readable medium storing the software of claim 26.
28. A biological imaging system for determining a spatial distribution of one or more physical properties within a biological structure, the system comprising:
- 5 a data input arranged to receive a plurality of measurements relating to one or more physical fields; and
- a processing device arranged to determine a spatial distribution of one or more physical properties within the biological structure using said plurality of measurements;
- wherein the processing device is arranged to:
- 10 form a discretized full order model of the biological structure, the full order model comprising a first number of full order model coefficients;
- use the full order model to describe a baseline spatial distribution of the biological structure, said baseline spatial distribution being described by a set of coefficients;
- 15 determine optimised values for the coefficients describing the baseline spatial distribution based on the plurality of measurements;
- form a hybrid model of the biological structure comprising the baseline spatial distribution coefficients and a set of deviation full order model coefficients which describe a deviation from the baseline spatial distribution within the biological structure;
- 20 determine optimised values for the baseline spatial distribution coefficients and the deviation full order model coefficients of the hybrid model based on the plurality of measurements; and
- determine the spatial distribution of one or more physical properties within the biological structure using optimised values of the deviation full order model coefficients and the baseline spatial distribution coefficients of the hybrid model.
- 25
29. The biological imaging system of claim 28, wherein the full order model is built using a reference domain.
30. The biological imaging system of claim 28 or 29, wherein the baseline spatial distribution of the biological structure is described by full order model coefficients.
31. The biological imaging system of any claim 30, wherein the processing device is arranged to:
- 35 determine a reduced order model of the biological structure, the reduced order model comprising a second, lower number of reduced order model coefficients;

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determine optimised values for the reduced order model coefficients based on the plurality of measurements such that the reduced order model coefficients describe a baseline spatial distribution of the one or more physical properties within the biological structure; and

5 use the reduced order model coefficients which describe the baseline spatial distribution to determine the full order model coefficients which describe the baseline spatial distribution.

32. The biological imaging system of any of claims 28-30, wherein the baseline spatial distribution coefficients are parameterised and determining optimised values for the coefficients
10 describing the baseline spatial distribution based on the plurality of measurements comprises using parameters of the baseline spatial distribution coefficients as optimisation inputs.

33. The biological imaging system of claim 32, wherein determining the spatial distribution of one or more physical properties within the biological structure using optimised values of the
15 deviation full order model coefficients and the baseline spatial distribution coefficients comprises inverting the parameterisation of the baseline spatial distribution coefficients.