Supermodeling of tumor dynamics with parallel isogeometric analysis solver

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Abstract
We show that it is possible to obtain reliable prognoses about cancer dynamics by creating the supermodel of cancer, which consists of several coupled instances (the sub-models) of a generic cancer model, developed with isogeometric analysis. Its integration with real data can be achieved by employing a prediction/correction learning scheme focused on fitting several values of coupling coefficients between sub-models, instead of matching scores (even hundreds) of tumor model parameters as it is in the classical data adaptation techniques. We show that the isogeometric analysis is a proper tool to develop a generic computer model of cancer, which can be a computational framework for developing high-quality supermodels. We believe that the latent fine-grained tumor features, e.g., microscopic processes and other unpredictable events accompanying its proliferation not included in the model (that is, not included in direct way in the mathematical model), are present in incoming real data and will still influence in indirect way tumor dynamics.

Keywords: isogeometric analysis, tumor growth simulation, supermodeling, machine learning, GPGPU, GLUON environment

1. Introduction
Data assimilation is the key component of computer tumor simulations [1]. The modern computer simulators of tumor dynamics such as but not lim-
have several dozens of parameters that have to be adjusted to match with medical measurements, e.g. resulting from the MRI scans of the tumor obtained within some time intervals from patients.

For this inverse problem, we define the fitness function as some measure between the numerical simulations and measurement data. We are looking for such a set of parameters of the mathematical model, which minimizes this discrepancy. We seek for proper values of the model parameters. This is obvious that such the problem is ill-conditioned, and the solutions’ space ”explodes” with an increasing number of model parameters. Classical data assimilation algorithms result in prohibitively long computations \[^\text{12, 23, 24, 25, 26}\]. Moreover, the inverse problem itself may encounter a huge number of local minima, where our inverse algorithm gets stuck. In such a case, we obtain an imperfect approximation of the ground truth. Thus, the single tumor model itself may not be able to match the reality with adequate precision. Even if we find a good solution to our inverse problem, it may be still far from the real data that we want to match. The main contribution of this paper is to propose the supermodeling as a second abstraction layer to classical data assimilation procedures, which can improve their quality and computational performance.

This approach was first proposed to deal with climate simulations \[^\text{13, 27, 28, 29, 30}\]. The idea of the application of the supermodeling for tumor simulations was described in \[^\text{20, 21}\]. Herein, for the first time, we apply the supermodeling which couples and synchronizes three-dimensional tumor models realized numerically by using the isogeometric finite element method solver \[^\text{12}\] implemented in GALOIS \[^\text{18, 19}\].

Our mathematical model of tumor dynamics is described by the set of parabolic PDEs (mainly reaction-diffusion type) representing concentration fields (densities) of tumor cells, tumor angiogenic factor (TAF), oxygen concentration, extracellular matrix, and the degraded extracellular matrix. The progression of the model is controlled by over twenty model parameters. Our goal is to simulate the tumor progression, similar as much as possible to the realistic patterns.

Before the process of data assimilation, we propose to perform first the sensitivity analysis of our tumor model \[^\text{31, 32}\]. Finding the most sensitive parameters and dynamic variables allows us to focus better on the data adaptation process and thus to save computational time. Moreover, knowing the most important dynamic variables allows us to construct the most par-
simonious (in terms of the number of sub-models connections) supermodel. We identify the four more sensitive parameters. These are tumor cell proliferation time, tumor cell survival time, threshold oxygen concentration for tumor cells to multiply, or die. On this basis, we set up three different models resulting in different tumor growth evolution.

Next, we construct the supermodel by coupling the dynamic variables as well as by coupling the sub-models with the ground truth data. As shown in Figure 1, three sub-models with parameters sets S1, S2, and S3 are connected together, creating the supermodel through dynamical variables A and B. The strength of couplings is represented by the coupling matrix C. The matrix is trained to obtain the best synchronization between the sub-models. The supermodel of synchronized sub-models is then nudged towards the "ground truth" data. The value of nudging factor K is treated as a learning rate and can be selected as a constant during training. In fact, the models can be connected only by the most sensitive variable what eliminates the number of coupling factors.

We employed the learning scheme to fit both the sub-models coupling parameters and training constants to the "ground truth" data. We employ as the "ground-truth" the tumor dynamics snapshots (the number of tumor cells) simulated by our tumor model with the "reference" parameter set. Thus, by using the supermodeling approach, we can simulate this "reality" by synchronized in a nonlinear way a few different models. In other words, in this paper, we show how to speed up data assimilation for a complex multi-parameter dynamical process by adding the supermodeling abstraction layer.

Alternative approaches to solving the data assimilation problems include the selection and calibration of the tumor models based on the Occam Plausibility Algorithm approach using Bayesian statistical calibration of model classes [1].

2. Critical issues in supermodeling

The supermodel, illustrated in Figure 1 is composed of several, e.g. three sub-models $S_1(P_1)$, $S_2(P_2)$, $S_3(P_3)$. In general, these sub-models can represent various and heterogeneous models of tumor described by different sets of PDEs [8, 9, 10, 11] (provided that there exist similar dynamical variables which can be coupled), however, in case of data adaptation, they may also be defined as the same set of PDEs with different parameters [12]. Of
Figure 1: Coupling of three sub-models and the ground-truth.
Figure 2: Creation of a supermodel.

Thus, we may have a few homogeneous sub-models with respective parameters sets $P^1, P^2, P^3$, with admissible values. These sub-models define the following dynamics variables: tumor cell density scalar field $b$, tumor angiogenic factor (TAF) concentration $a$, vasculature network, oxygen concentration, the density of extracellular, and degraded extracellular matrix. These dynamic variables are coupled by using the coupling constants $C_{ai,j}^a, C_{bi,j}^b$, where $a$ and $b$ denotes the coupled dynamic variables, and $i, j$ denotes the pair of coupled sub-models. Finally, we couple all sub-models with the ground-truth data, using the training constant (nudging coefficient) $K$ that can be matched arbitrarily.

The general scheme demonstrating the construction of the supermodel is summarized in Figure 2. We start from the creation of some sub-models that try to match the ground-truth, in our case, the numerical models of
the tumor progression. These models, they may use identical or different sets of PDEs, e.g. kind of advection-diffusion-reaction models, as described in [8, 12], or Cahn-Hilliard based models, as described in [10, 11, 9]. The models are instantiated by a specific sets of parameters. There are at least a few methods to set up the ”proper” sub-models.

1. We can select the parameters on the base of general knowledge about the simulated process.
2. We can start with ”the most probable” set of parameters reported in the previous research, and generate sub-models perturbing the most sensitive ones.
3. We can use first a standard data assimilation procedure, and pre-train the model within a short time. We can select as the sub-models the parameter sets attaining the best local minima of a loss function.

In case of applying these strategies, it is good to know the results of sensitivity analysis to optimize the search.

We call this phase the pretraining. Having the three sub-models \(S_1, S_2, S_3\) with three sets of their parameters \(P^1, P^2, P^3\) where \(P^M = (p^M_1, ..., p^M_n)\), we can execute the learning phase, where we intend to find the values of the coupling factors \(C_{a1-2}, C_{a2-1}, C_{a1-3}, C_{a3-1}, C_{a2-3}, C_{a3-2}\) and \(C_{b1-2}, C_{b2-1}, C_{b1-3}, C_{b3-1}, C_{b2-3}, C_{b3-2}\). In other words, we parameterize the models with sets of parameters, and we couple the output of the models, expressed by selected dynamic variables. We run the three sub-models, and we find the values of the coupling parameters. Once we have the coupling factors learned, we can create the supermodel and run the simulation with the supermodel itself.

There are the following questions to be addressed when we construct a supermodel.

- Which sub-models should we choose, heterogenous or homogenous?
- How many sub-models do we need, and how many teaching samples are necessary to find the coupling constants [21].
- How to select the sub-models, so their synchronized supermodel will fit the ”ground truth’ (the real data).
- How many dynamic variables should be coupled? How do we perform the coupling, in a strong or in a weak way?
- What is the proper training procedure?
Different choices may lead to different supermodels, and there is no general answer to all these questions \[33\]. The general idea is to make predictions more accurate. For example, the solution of the inverse problem may lead to several local minima. Each of these local minima may be far from the ground truth, but the supermodel can use these local minima as sub-models and may synchronize well with the reality. Herein, we utilize the isogeometric analysis solver with 3D tumor model \[12\] parameterized with 21 model parameters. We use the supermodeling for prediction of the system trajectory. As ground truth, we use the results produced by another high fidelity simulation. Namely, we run parallel multi-GPU tumor simulator based on finite difference method \[14\] we have developed earlier.

The sets of parameters for the sub-models can be selected in two ways. The first way is to select a set of parameters for each sub-model randomly. The second way is to use pre-trained models as sub-models, using classical data assimilation procedures, e.g., resulting from inverse modeling and sensitivity analysis). We used the second method from those enumerated earlier to set up the parameters of sub-models. The rule of thumb is that we want the sub-models to be close to the ground truth, close to different ”good” local minima surrounding the ground truth, see Figure\[3\].

In the supermodel we couple the sub-models through only one but very sensitive variable, namely, the tumor density, to prevent the model from
being over wired and computationally demanding.

Summing up, to produce the supermodel we:

1. Select homogenous sub-models with sets of parameters \( P = (p_1, ..., p_n) \).
2. Perform sensitivity analysis to find the most sensitive parameters and dynamical variables.
3. Use the classical Approximated Bayesian Computation (ABC) method for data assimilation \([26]\) to pre-train the sub-models. After short training we select the \( M \) best results (which gave the smallest error in terms of loss function minimization) and find \( M \) sets of parameters \( P_1 = (p_1^1, ..., p_n^1), ..., P_M = (p_1^M, ..., p_n^M) \).
4. Create the supermodel by coupling the sub-models via the most sensitive dynamical variable.
5. Train the supermodel: estimate \( M! \) (6 in case of 3 sub-models) coupling coefficients by using the method from \([13]\) with a one-layered net.
6. Validate the supermodel on test data.

3. Supermodel of tumor

We used the one-phase mathematical model of tumor dynamics, which is based on the previously published seminal papers \([12, 12, 32]\).

Domain of the simulation is the cube \( \Omega = [0,5000] \times [0,5000] \times [0,5000] \) [\( \mu m \)] = 5mm \( \times \) 5mm \( \times \) 5mm.

In the model we consider the following main quantities.

- tumor cell density \( b \)
- tumor angiogenic factor (TAF) \( c \)
- endothelial cells network
- oxygen \( o \)
- density of the extracellular matrix (ECM) \( M \)
- density of the degraded extracellular matrix (ECM) \( A \)

There are also some auxiliary quantities, derived from the main quantities introduced above.

- tumor cell sinks \( b^- \)
• tumor cell sources \( b^+ \)
• tumor cell pressure \( P \)
• tumor cell flux \( J \)

The oxygen-starved tumor cells produce the TAF \( c \). It is performed because the tumor cell sends the signal to the vasculature that ,,more oxygen is needed here”. The TAF concentration influences the growth of the vascular network by the discrete vascular model. It is governed by

\[
\frac{\partial c}{\partial t} = \chi_c \Delta c - \gamma_c c + c^+
\]  

(1)

where \( \chi_c \) denotes TAF diffusion rate, \( \gamma_c \) stands for TAF decay rate, \( c^+ \) is the TAF “source” \( c^+ = b(1 - c) \) for \( o < o^{death} \), and \( o^{death} \) is the TAF hypoxia rate.

The healthy cells, as well as tumor cells live in the extracellular matrix \( M \). The density of the extracellular matrix decreases when the tumor cells grow.

\[
\frac{\partial M}{\partial t} = -\beta_M Mb
\]  

(2)

where \( \beta_M \) denotes the ECM decay rate. On the other hand, the density of the degraded extracellular matrix increases with the density of the tumor cells and it is expressed in the following equation

\[
\frac{\partial A}{\partial t} = \gamma_A Mb + \chi_A \Delta A - \gamma_{oA} A
\]  

(3)

where \( \gamma_A \) denotes the production rate of attractants, \( \chi_A \) stands for diffusion rate of degraded extra-cellular matrix, and \( \gamma_{oA} \) is the decay rate of degraded extra-cellular matrix.

When the tumor cells grow over the normal tumor cell density, they impose the tumor cell pressure \( P \). The tumor cell pressure varies linearly between 0 for the normal tumor cell density \( b^N = 1 \), up to 1, for the maximum tumor cell density \( b^M = 2 \).

\[
P = \begin{cases} 
0 & \text{for } b < b^N \\
\frac{b-b^N}{b^M-b^N} & \text{for } b^N \leq b \leq b^M
\end{cases}
\]  

(4)
The tumor cell pressure imposes the tumor cell flux \( J \)

\[
J = -D_b \frac{d}{d} (\nabla P + r_b \nabla A)
\]  

(5)

where \( D_b \) stands for the cell diffusion coefficient, which varies with the skin layer, and \( r_b \) denotes the tumor cell chemoattractand sensitivity.

Finally, the tumor cell density varies from \( b^m = 0 \) representing the state with no cancer cells, to \( b^M = 2 \) denoting the state with maximum tumor cell density. When the tumor cell density is larger than \( b^N = 1 \), it imposes the tumor cell pressure

\[
\frac{\partial b}{\partial t} = -\nabla \cdot J + b^- + b^+
\]  

(6)

where \( b^+ \), \( b^- \) denote tumor cell proliferation and apoptosis factors, where \( J \) is the tumor cell flux, and \( b^+ \), \( b^- \) describe tumor cell „sources” and „sinks”, corresponding to cell proliferation (creation of new cells) and apoptosis (death of cells). Tumor cell flux is induced by tumor pressure \( P = \theta(b) \)

\[
\theta(b) = \begin{cases} 
0 & \text{for } b < b^N \\
b\frac{b-b^N}{b^M-b^N} & \text{for } b^N \leq b \leq b^M 
\end{cases}
\]  

(7)

and interaction with degenerated extracellular matrix (ECM), sources and sinks are governed by the oxygen supply. Tumor cell source and sink terms depend mostly on oxygen supply.

\[
b^+ = P_{\text{prol}} \left( 1 + \frac{\tau_b A}{\tau_b A + 1} P_b \right) \left( 1 - \frac{b}{b^M} \right) \text{ for } o > o^{\text{prol}} 
\]

\[
b^- = -\frac{b}{T_{\text{death}}} \text{ for } o < o^{\text{death}}
\]

(8)

Cell proliferation is present when oxygen level \( o \) exceeds \( o^{\text{prol}} \), while cell death occurs when \( o < o^{\text{death}} \). Oxygen concentration \( o \) is computed as

\[
\frac{\partial o}{\partial t} = \alpha_o \Delta o - \gamma_o b o + \delta_o (o^{\text{max}} - o) o^{\text{src}}
\]  

(9)

where \( \alpha_o \) is the oxygen diffusion coefficient, \( \gamma_o \) is oxygen consumption rate, \( \delta_o \) describes how fast the oxygen is absorbed from the vasculature and \( o^{\text{max}} \) is the maximal oxygen concentration. Value of \( o^{\text{src}} \) is 1 if there is a vessel in the specified point and 0 otherwise.
We introduce the vasculature as a discrete graph, with edges representing vessel segments and vertices corresponding to the vessels connections. The graph is represented as a 3D bitmap of size $K \times K \times K$, and each cell is either set to either 1 or 0, which represents the presence or absence of the vessel, respectively.

The main task of the vasculature is to provide oxygen to cells. The vasculature grows in response to the density of tumor cells and presence of TAF. Vasculature evolution, similarly to the generation of the initial graph, has a stochastic nature and encompasses several processes:

- sprout creation
- vessel degradation
- vessel collapse
- vessel dilatation

Each process is simulated in every time step apart from sprout creation. The vasculature grows in response to presence of TAF. At each existing node a sprout may be created with probability $\Delta t/t_{\text{sprout}}$, provided the local TAF density exceeds $c_{\text{min}}$. The direction of growth is given by $\nabla c$, which is a direction of fastest growth of TAF and so points roughly to the nearby oxygen-starving cells. Length of the segment is given by $l_{\text{seg}}$ and initial radius by $r_{\text{sprout}}$.

Vessels inside the region with high density of tumor cells undergo a degradation. Each vessel segment has a stability coefficient $w$, initially $w_{\text{init}}$, that is decreased by $w_{\text{deg}} \Delta t$ during each update if the local cancer cell density $b$ exceeds $b_{\text{norm}}$.

When stability reaches 0, the vessel may collapse with probability $\Delta t/t_{\text{coll}}$ – once that happens, it is removed from the vasculature graph.

If the vessel has been in a region with high tumor concentration ($b > b_{\text{norm}}$) for at least $t_{\text{switch}}$ hours, process of vessel dilatation is initiated. If value of TAF is sufficiently high ($c > c_{\text{switch}}$), radius of the vessel is increased by $\Delta r \Delta t$ each step, until it reaches maximum radius $r_{\text{max}}$.

For the detailed description of the model, we refer to [12].

Summing up, the model is described by the following set of mainly parabolic,
diffusion-reaction type of PDEs equations.

\[
\begin{align*}
\frac{\partial b}{\partial t} &= -\nabla \cdot J - \frac{b}{T^{\text{death}}} [o < o^{\text{death}}] + \\
&\quad \frac{b}{T^{\text{prol}}} \left(1 + \frac{\tau_b A}{T_b + 1} P_b\right) \left(1 - \frac{b}{bM}\right) [o > o^{\text{prol}}] \\
\frac{\partial c}{\partial t} &= \chi_c \Delta c - \gamma_c oc + c^+ \\
\frac{\partial o}{\partial t} &= \alpha_0 \Delta o - \gamma_o bo + \delta_o \left(o^{\max} - o\right) \\
\frac{\partial M}{\partial t} &= -\beta_M Mb \\
\frac{\partial A}{\partial t} &= \gamma_A Mb + \chi_{OA} \Delta A - \gamma_{OA} A
\end{align*}
\]

We have denoted the most sensitive variable that we will use in coupling and synchronization of the models, namely the tumor cells density, by red color. We have also denoted the most sensitive model parameters, as found by the sensitivity analysis, by blue color.

The model is controlled by twenty-one parameters, presented in Table 3.
| Symbol | Value | Description                      |
|--------|-------|----------------------------------|
| $b_m$  | 0     | min tumor cell density           |
| $b_M$  | 2     | max tumor cell density           |
| $b_{norm}$ | 1 | normal tumor cell density       |
| $D_b$  | varies| tumor cell diffusion rate        |
| $r_b$  | 0.3   | tumor cells chemoattractant sensitivity |
| $o^{prol}$ | 10 | tumor proliferation threshold     |
| $o^{death}$ | 2  | tumor cell hypoxia threshold     |
| $T^{prol}$ | 10 | tumor cell proliferation time    |
| $T^{death}$ | 100 | tumor cell survival time         |
| $P_b$  | 0.001 | maximum stimulated mitosis rate  |
| $\tau_b$ | 0.5 | instantaneous reaction rate      |
| $\beta_M$ | 0.0625 | ECM decay rate                  |
| $\gamma_A$ | 0.032 | production rate of attractants   |
| $\chi_{aA}$ | 0.000641 | decay rate of digested ECM    |
| $\gamma_{oA}$ | 0.000641 | diffusion rate of digested ECM  |
| $\chi_c$ | 0.0000555 | TAF diffusion rate        |
| $\gamma_c$ | 0.01 | TAF decay rate                  |
| $\alpha_o$ | 0.0000555 | oxygen diffusion rate         |
| $\gamma_o$ | 0.01 | oxygen consumption rate         |
| $\delta_o$ | 0.4 | oxygen delivery rate            |
| $o^{max}$ | 60 | maximal oxygen concentration    |

Table 1: Tumor model parameters.

The tumor supermodel construction, as denoted in Figure 4 involves:

- Homogenous tumor PDEs model, using the isogeometric alternating directions solver [12] and the embedded dynamic discrete vasculature graph [35].
- The sub-models are created based on the pretraining with a genetic algorithm.
- An inverse algorithm, e.g., a genetic algorithm, finding local minima in the sensitive parameters space. The values of the parameters from these minima are selected to construct the three sub-models. More details are presented in the numerical results section.
Figure 4: Dynamic variable used for coupling: tumor cell density \( b \)

Most sensitive model parameters:
- tumor cell proliferation threshold \( o^{\text{prol}} \) and hypoxia threshold \( o^{\text{death}} \),
- tumor cell proliferation time \( T^{\text{prol}} \) and survival time \( T^{\text{death}} \).

- The coupling of sub-models is performed based on a single dynamic variable, namely the tumor cell density.

- As ”ground truth”, we use the results produced by high fidelity simulation, parallel multi-GPU tumor simulator based on finite difference method [14].

4. Parallel three-dimensional tumor simulator development for a cluster of GPUs

The solver performance is crucial from the point of view of practical applications of the supermodeling. The IGA solver discussed here was originally implemented in C++ and run on CPUs. Decomposition of calculations into threads and running computations on powerful supercomputers allowed to increase efficiency, however, in practical applications, it was still not enough, and the natural way to further (significantly) increase the performance of this solver was to implement and run calculations on GPUs.
The translation of the computational kernel of the solver into the GPU requires decomposition of the code into several basic tasks, including building portions of the right-hand side and partial factorizations.

The algorithm of the isogeometric solver is shown in the Listing 1 below.

```cpp
void simulation_base::run() {
    before();
    for (int i = 0; i < steps.step_count; ++i) {
        before_step();
        step();
        after_step();
    }
    after();
}

void step() override {
    compute_rhs();
    solve(u);
}
```

Listing 1: The algorithm of the isogeometric differential equations solver

At the start of the simulation, the solver performs pre-initialization in the `before()` function, and during multiple iterations of the loop `for` determines the following states for subsequent time steps.

Running the next `step()` means calculating the right-hand side of the differential equation and determining the result solution by `solve(u)` function.

Before and after each call of the `step()` function, `before_step()` and `after_step()` are executed, where, among the others, matrix replacement and saving to the file of the currently calculated time step take place.

From the point of view of computational complexity, the computation time is 'consumed' mainly by `compute_rhs()` (and `solve(u)`) functions appearing in the `step()` function, where the execution of the `compute_rhs()` function 'consumes' over 99% of time in simulations with reasonable mesh sizes.

```cpp
void compute_rhs(auto& rhs) {
    executor.for_each(elements(), [&] (index_type e) {
        auto U = element_rhs();
        float J = jacobian(e);
    });
```
for (auto q : quad_points()){
    double w = weight(q);
    value_type u = eval_fun(u_prev, e, q);
    for (auto a : dofs_on_element(e)){
        auto aa = dof_global_to_local(e, a);
        value_type v = eval_basis(e, q, a);
        float gradient_prod = grad_dot(u, v);
        float val = u.val * v.val - dt * gradient_prod;
        U(aa[0], aa[1]) += val * w * J;
    }
}
executor.synchronized([&](){
    update_global_rhs(rhs, U, e);
});
}

Listing 2: Original CPU C++ IGA solver implementation

void compute_rhs(auto& rhs){
    executor.for_each(dofs(), [&](index_type a){
        float J = jacobian(e);
        for (auto q : quad_points()){
            double w = weight(q);
            value_type u = eval_fun(u_prev, e, q);
            value_type v = eval_basis(e, q, a);
            float gradient_prod = grad_dot(u, v);
            float val = u.val * v.val - dt * gradient_prod;
            rhs(aa[0], aa[1]) += val * w * J;
        }
    });
    value_type eval_fun(vector_type& v, index_type e, index_type q){
        value_type u{};
        for (auto b : dofs_on_element(e)) {
            float c = v(b[0], b[1]);
            value_type B = eval_basis(e, q, b); u += c * B;
        }
    }
}
Listing 3: Improved CPU C++ IGA solver implementation

```cpp
void compute_rhs_prev(auto& rhs)
{
    executor.for_each(elements(), [&](index_type e)
    {
        for (auto q : quad_points())
        {
            value_type u = eval_fun(u_prev, e, q);
            TMP_U_eval_fun[e][q] = u;
        }
    });
}
```

```cpp
void compute_rhs_post(auto& rhs)
{
    executor.for_each(dofs(), [&](index_type a)
    {
        for (auto e : elements_supporting_dof(a))
        {
            float J = jacobian(e);
            for (auto q : quad_points())
            {
                double w = weight(q);
                value_type u = TMP_U_eval_fun[e][q];
                value_type v = eval_basis(e, q, a);
                float gradient_prod = grad_dot(u, v);
                float val = u.val * v.val - dt * gradient_prod;
                rhs(aa[0], aa[1]) += val * w * J;
            }
        }
    });
}
```

Listing 4: GPU IGA solver implementation

In its original C++ implementation, `compute_rhs()` function was implemented as it is presented in Listing 2.

The idea of this function consists of running the `for` loop on all E elements, and next in iterating through all Q quadrature points. At this place, there was the `for` iteration going through all local degrees of freedom A
(corresponding to local matrix rows and columns) and calculating the appropriate values and entering them to the element array U. Next the values from the arrays U from various calls of the loop

```cpp
evaluator.foreach(elements(), [\&](index typee) { ... });
```

were added to the global result matrix.

The parallelization of this algorithm in its original implementation consists of parallel execution of calculations for individual elements E. At the end of every step, the synchronized execution of the summation ensured the correctness of data but, unfortunately, at the expense of extended computation time.

This type of code construction is not optimal for GPU execution. Frequent threads synchronization on the GPU card often results in even longer code execution than for the reference CPU code.

Therefore, with the view to implementation on GPU, following the GPU code execution patterns and in-depth analysis of the IGA solver, the IGA algorithm has been slightly modified and is presented in Listing 3.

The proposed modification focuses on one of the most important disadvantages of the previous code, namely the aggregation of element matrices into the global matrix. In the previous version, in order to ensure the correct state of saved tables, synchronization was required when adding element matrices to the global matrix.

In the new version, no synchronization occurs at the time of saving the data. In this case, parallelization of calculations took place in the loop iterating over the global basis functions A (corresponding to global matrix rows), where each thread operates now on the loops iterating over all the elements in which the given global basis function A is defined. Finally, iteration over Q quadrature points occurs. This way, there is no need for any synchronization.

This solution is not without its drawbacks. Namely, this arrangement of for loop calls requires loading and recalculating certain data from memory many times. Nevertheless, the presented calculation scheme is very desirable from the point of view of GPU cards.

The version dedicated to GPU cards was created as a combination of both the aforementioned approaches. A two-stage GPU algorithm was created, presented in Listing 4, to take the advantages of smaller data loading in the solution presented in Listing 2 and the lack of synchronization in the version presented in Listing 3. The first step of GPU implementation uses the positive aspects of the solution presented in Listing 2. It allows us to calculate some values and then save them temporarily in GPU memory. The
second step, reading these calculated values, allows you to perform the next
time step calculation without synchronization.

```c
void compute_rhs_post_V1()
{
    int x = blockIdx.x * blockDim.x + threadIdx.x;
    int y = blockIdx.y * blockDim.y + threadIdx.y;
    int z = blockIdx.z * blockDim.z + threadIdx.z;
    int3 quad_order = make_int3(getDimX_quad_order(),
                                getDimY_quad_order(),
                                getDimZ_quad_order());
    int3 dofs = make_int3(getDimX_dofs(),
                          getDimY_dofs(),
                          getDimZ_dofs());
    int3 elements = make_int3(getDimX_elements(),
                              getDimY_elements(),
                              getDimZ_elements());

    float4 u = eval_fun(...);
    ...
}
```

Listing 5: Shared memory utilization–Less shared memory, more registers

```c
void compute_rhs_post_V2()
{
    __shared__ int3 quad_order, dofs, elements;
    __shared__ float4 u[256];
    int x = blockIdx.x * blockDim.x + threadIdx.x;
    int y = blockIdx.y * blockDim.y + threadIdx.y;
    int z = blockIdx.z * blockDim.z + threadIdx.z;
    if ((threadIdx.x == 0) && (threadIdx.y == 0) && (threadIdx.z == 0))
    {
        quad_order = make_int3(getDimX_quad_order(),
                                getDimY_quad_order(),
                                getDimZ_quad_order());
        dofs = make_int3(getDimX_dofs(),
                         getDimY_dofs(),
                         getDimZ_dofs());
        elements = make_int3(getDimX_elements(),
                              getDimY_elements(),
```
Another critical element examined in the (original) solver is the issue of loading the same data repeatedly. In Listing 5, the first CUDA implementation of the algorithm discussed before is presented. In this implementation, there was assumed such a parallelization of calculations that each thread would calculate the value for a particular row of the matrix. As it is shown, each thread, before performing the proper calculations, sets the value of some spatial variables that indicate the carrier point and loads several three-dimensional variables configuring the calculation.

From the point of view of graphics cards, the problematic is loading values for quad_core, dofs, and elements. This action causes that these values are placed in registers allocated to individual threads at compilation time. As the GPU card has a specific architecture, it also has a set of many restrictions affecting the efficiency, such as limiting the maximum number of threads per block, the maximum number of threads per multiprocessor, the maximum number of 32-bit registers per multiprocessor, block and thread. And the last-mentioned limitation plays a key role in the implementation presented in Listing 5. The compiler during the compilation process is able to determine the required number of registers for each thread, and in case of too high demand, it limits the number of physically performed calculations at the same time on multiprocessors. This results in slowing down the calculations.

The proposition of the more shared memory, fewer registers algorithm presented in Listing 6 is a solution to this problem. The shared memory referred to in this algorithm is also a memory built on registers, but it is an additional memory block. One additional advantage of shared memory in relation to registers is the ability to access it through all threads in a given calculation block. Therefore, the proposition of the algorithm presented in Listing 6 is based on loading repeated constants into shared memory, so that the vast majority of registers are distributed to perform proper calculations so that the number of realistically parallel threads on a given multiprocessor...
is definitely greater than during the first implementation of the program.

The last detected IGA code retarder on graphics cards is the organization of the algorithm loops. The loop has a counter initialization step whose value is compared to every iteration with the stop condition. If the condition is not met, the code placed in the body of the loop is executed, and the loop counter is incremented. If the condition is met, the loop is finalized. Problematic from the GPU’s point of view is the condition checking stage. In the case of parallel code not based on conditional instructions and executed on many threads in a given block, full uninterrupted operation of all threads used takes place. At the time of execution of the if control statement, all threads perform the condition checking process and are then separated (and synchronized) into two groups. For example, threads that meet the condition are executed first, and only then threads that do not meet the condition are executed. There is a risk of synchronizing the execution of all threads working in a given block, in the case of the code where there is the possibility of occurring nested for loops or the control instructions if.

```c
void compute_rhs_post_V1(int X, int Y){
    int x = blockIdx.x * blockDim.x + threadIdx.x;
    for(int y=0 ; y<Y ; ++y){
        for(int x=0 ; x<X ; ++x){
            M[y, x] = get_val(x, y);
        }
    }
    ...
}
```

Listing 7: Implementation with no unrolled loops

```c
template<int X, int Y>
void compute_rhs_post_V2(){
    int x = blockIdx.x * blockDim.x + threadIdx.x;
    #pragma unroll
    for(int y=0 ; y<Y ; ++y){
        #pragma unroll
        for(int x=0 ; x<X ; ++x){
            M[y, x] = get_val(x, y);
        }
    }
}
```

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**Table 2:** Time and memory consumption by IGA CPU and GPU solver versions.

| Size | Time | Memory |
|------|------|--------|
|      | CPU  | GPU 1 | GPU 2 | CPU  | GPU 2 |
| 8³  | 0.06 s | 0.01 s (x6) | 0.01 s (x6) | 88 MB | 77 MB |
| 16³ | 0.52 s | 0.03 s (x17.3) | 0.015 s (x34.6) | 89 MB | 90 MB |
| 32³ | 4.18 s | 0.09 s (46.4x) | 0.04 s (x104.5) | 92 MB | 141 MB |
| 64³ | 33.44 s | 0.45 s (x74.3) | 0.22 s (x152) | 123 MB | 354 MB |
| 128³ | 270 s | 3.17 s (x85.2) | 1.6 s (x169) | 356 MB | 1238 MB |
| 256³ | 2122 s | 24.42 s (x86.9) | 12.39 s (x171.2) | 2185 MB | 5050 MB |

In the case of the IGA algorithm presented in Listing 7, it can be seen that the standard implementation of this algorithm (in particular for three-dimensional space) can generate a fairly deeply nested for instructions. Fortunately, in its specification, the CUDA programming language has a directive requiring the compiler to unroll a loop. Unrolling the loop means, in fact, pasting subsequent iterations of the for loop body as many times as the condition of the loop indicates so that the final code does not have the repetitive conditional if instructions. To be able to achieve this type of unrolling, at the compilation time, the final value with which the current state of the loop counter is compared is required. Unfortunately, in the presented solution providing such a specific value is impossible because it is obtained from the dynamically loaded configuration. The algorithm schema presented in Listing 8 is the solution to that problem. In practice, during compilation, functions are expanded for all possible configurations of the parameter passed using template parameters. Thanks to this, it is possible to reduce the number of nested loops and significantly speed up the program.

In Table 2, speed-up and memory consumption for CPU original imple-
mentation presented in Listing 2 and for GPU optimized version from Listing 8 are presented for one and two GPUs. The GLUON library [15] glues several instances of GPU tumor simulators, executed on different GPUs, so they can simulate larger problems. Experiments have been performed on Prometheus supercomputer [16, 17], where CPU means Intel Xeon E5-2680v3 processor and GPU means Nvidia Tesla K40 XL. As one may see for 256³ dimension, the speed-up of more than 171 times can be observed.

5. Sensitivity analysis

We perform first the tumor model sensitivity analysis. We turned the IGA-ADS tumor solver to be a stand-alone code, executed with the input parameters provided from the command line, e.g.:

```
./tumor3d 4 12 2 120 300 1 0 2 1 0.3 10 2 10 100 0.001 0.5 0.0625 0.032 0.000641 0.000641 0.0000555 0.01 0.0000555 0.01 0.4 60
```

Where 4 corresponds to the number of nodes, 12 corresponds to the number of threads per node, 2 corresponds to the B-spline order, 120 corresponds to the mesh size, 300 corresponds to the number of time steps, 1 corresponds to the time step size (in dimensionless form), and then we follow with all the model parameters like in Table 3. The tumor cell diffusion rate \( D_b \) is a property of the tissue, where the simulation runs, so it is fixed.

We perform the sensitivity analysis of the model using the following method. We start with the above reference values of the parameters. We pick one parameter, and we run 20 simulations varying its values +/- 40 percent with respect to the reference values while keeping other parameters fixed.

For example, possible modifications of parameter tumor proliferation threshold \( \sigma_{\text{prod}} \) are

```
./tumor3d 4 12 2 120 300 1 0 2 1 0.3 6 2 10 100 0.001 0.5 0.0625 0.032 0.000641 0.000641 0.0000555 0.01 0.0000555 0.01 0.4 60
```

```
... ./tumor3d 4 12 2 120 300 1 0 2 1 0.3 10 2 10 100 0.001 0.5 0.0625 0.032 0.000641 0.000641 0.0000555 0.01 0.0000555 0.01 0.4 60
```

```
... ./tumor3d 4 12 2 120 300 1 0 2 1 0.3 14 2 10 100 0.001 0.5 0.0625 0.032 0.000641 0.000641 0.0000555 0.01 0.0000555 0.01 0.4 60
```

We find out that the model is most sensitive to the four parameters, denoted in Table 3 by blue color, namely tumor proliferation threshold, tumor cell hypoxia threshold, tumor cell proliferation time, tumor cell survival time.
Figure 5: Sensitivity of the tumor model with respect to tumor proliferation threshold.

The sensitivity analysis results for these four parameters are summarized in Figures 5-8.
Figure 6: Sensitivity of the tumor model with respect to tumor cell proliferation time.

Figure 7: Sensitivity of the tumor model with respect to tumor cell hypoxia threshold.
6. **Inverse problem solution with genetic algorithm**

With have executed the simple genetic algorithm to find the values of the four most sensitive parameters located at the local minima that approximates the ground truth. In other words, each of the individuals in the initial genetic population has some randomly selected values of tumor proliferation threshold, tumor cell hypoxia threshold, tumor cell proliferation time, and tumor cell survival time. As the ground truth, we took some numerical results generated with the high fidelity model using finite difference code with $512 \times 512 \times 512$ mesh executed on a cluster to two GPU cards [14]. As the fitness function, we measure the total tumor volume, namely, we sum up all the degrees of freedom for the tumor cells density, through entire mesh, through all the time steps, and we compute the difference between the total tumor volume between the ground truth results and a simulation executed for a set of parameters stored by the individual in the genetic simulation,

\[
\text{fitness}(GT, \text{sim}) = \left| \sum_{t=1,...,300} b_{i,j,k}^{t} - b_{GT} \right|
\]  \hspace{1cm} (10)
where $b^t_{i,j,k}$ denotes the degree of freedom (coefficient of B-splines $B^x_{i,2}(x)B^y_{j,2}(y)B^z_{k,2}(z)$ at time step $t$, and $b_{GT}$ corresponds to the total tumor volume as computed in the high fidelity model ground truth simulation. We execute the genetic algorithm with randomly selected initial population, we cross, mutate, and evaluate the individuals and observe the convergence of the algorithm to the solution.

The difference of the total tumor volume from the simulation and the ground truth in the initial population and in the following steps of the genetic algorithm is presented in Figure 9. Each dot represents a single individual, and we run 21 iterations of the genetic algorithm. The horizontal axis denotes the percentage differences of total tumor volumes with respect to the ground truth, while the vertical one shows the number of iterations.

The convergence of the total tumor volume, represented by the average, minimum, and maximum values of the fitness function (1) are presented in Figure 9. We can see that the populations do not want to converge to a single solution; they rather scatter in the local minima.

7. Supermodeling algorithm

The supermodel is developed in three consecutive phases.

1. Initialization
   - Perform sensitivity analysis to find the most sensitive parameters.
Optionally solve the inverse problem to find local minima of the fitness function, calculating the absolute squared error between the subsequent (in time) sizes of tumor obtained via simulation and from corresponding GT data.

Setup three sub-models $sim1$, $sim2$, $sim3$ with different parameters, resulting in different tumor progressions, illustrated in Figure 11.

2. Training

Assume identical initial states in each sub-model,
• Setup coupling weights \( C_{ij} \) for \( i, j = 1, 2, 3 \), and \( K \) coefficient.

• For STEP=1,...,300
  A Run one step in each simulator (sim1, sim2, sim3).
  B Modify obtained fields using the coupling constants

\[
b_i(x, y) + = \sum_{i=1,2,3} C_{ij}^b (b_j(x, y, z) - b_i(x, y, z)) + \sum_{i=1,2,3} K (b_i(x, y, z) - b_{meas}(x, y, z)).
\]

C Correct the coupling parameter

\[
C_{ij}^b = \int_\Omega (b_i(x, y, z) - b_{meas}(x, y, z)) (b_i(x, y, z) - b_j(x, y, z)) dV.
\] (11)

3. Supermodel simulation

• Setup identical initial states in each sub-model.

• Use coupling weights \( C_{ij}^b \) for \( i, j = 1, 2, 3 \), and \( K \) coefficient as obtained from training stage.

• For STEP=1,...,300
  A Run 1 step in each simulator (sim1, sim2, sim3).
  B Modify obtained fields using the coupling constants

\[
b_i(x, y) + = \sum_{i=1,2,3} C_{ij}^b (b_j(x, y, z) - b_i(x, y, z)) + \sum_{i=1,2,3} K (b_i(x, y, z) - b_{meas}(x, y, z)).
\]

8. Numerical results

We have performed several numerical experiments to verify the supermodeling approach. Below we demonstrate and discuss a summary of the selected three numerical experiments.
8.1. First experiment

In the first numerical experiment, we build three sub-models with randomly selected most sensitive parameters. We start the training phase with the coupling constants $C_{ij} = 0.5$, and the parameter coupling with the reality $K = 2.0$. We have set up the range of the $C_{ij}$ values between $[0.1, 0.9]$.

We present in Figure 12 the dynamics of the coupling coefficients $C_{ij}$ during training. We can see that they do not converge since they reach the minimum possible value of $0.1$. The horizontal axis denotes the number of time steps, and the vertical axis denotes the values of the coefficients.

We investigate the problem further by presenting in Figure 13 the convergence of the supermodel to the ground truth, measured in terms of the total tumor volume. This time the horizontal axis denotes the number of time steps and the vertical axis denotes the total tumor volumes. We present the volumes for particular sub-models, as well as for the average of the sub-models and the ground truth simulation ("reality"). We can read from this figure that the sub-models and the supermodel fell into oscillations, and we find out that the reason is that our coefficient $K$ coupling with the reality is too big, generating numerical oscillations.

8.2. Second experiment

In the second experiment, we also build three sub-models with randomly selected most sensitive parameters. But this time, we start the training phase with the coupling constants $C_{ij} = 0.5$, and the parameter $K = 0.9$. Since we
have decreased this parameter, we expect a much better stabilization of the results. We have set up the range of the \( C_{ij} \) values between \([0.1, 0.9]\).

In Figure 14 we demonstrate that the coupling coefficients \( C_{ij} \) converge indeed.

In Figure 16 we present the convergence of the supermodel and its sub-models to the ground truth, measured in terms of the total tumor volume. As before, we present the volumes for particular sub-models, as well as for the average of the sub-models and for the ground truth simulation.

We check now the quality of the supermodel, by comparing in Figure 16 the difference of the total tumor volume with respect to the ground truth, for the supermodel executed without the training phase (all \( C_{ij} = 0.5 \)), and after the training. The horizontal axis denotes the number of time steps, and the vertical axis denotes the difference between the simulated total tumor volume and the ground truth total tumor volume.

We can see the improvement of the convergence, but there is still quite a difference between the supermodel and the "reality". To improve the supermodel, we will employ the genetic algorithm to find local minima and the build sub-models based on the parameters located in the local minima.

8.3. Third experiment

In the third numerical experiment, we build three sub-models from the parameters from the best-fitted individuals, as found by the genetic algo-
Figure 14: Convergence of coupling coefficients $C_{ij}$ for the second simulation.

Figure 15: Convergence of tumor volumes for different sub-models $sim_1$, $sim_2$, $sim_3$, for the averaged model $(sim_1+sim_2+sim_3)/3$, for the supermodel, with respect to the "reality".
We start the training phase with the coupling constants $C_{ij} = 0.5$, and the parameter coupling with the reality $K = 0.9$. We set up the range of the $C_{ij}$ values between $[0.1, 0.9]$.

We present in Figure 17 the convergence of the coupling coefficients $C_{ij}$.

We present in Figure 18 the convergence of the supermodel to the ground truth, measured in terms of the total tumor volume.

Now, we distinguish the proliferation of tumor cells, which multiply due to the high local concentration of the oxygen, and the remaining quiescent tumor cells. The quiescent tumor cells are the cells which cannot proliferate due to unfavorable living conditions such as hypoxia or the high pressure (e.g., \cite{34}). We measure the total tumor volumes for the two types of cells. We present in Figure 19 the convergence of the supermodel measured in terms of the total proliferation tumor cells volume, as well as in Figure 20 the convergence of the supermodel measured in terms of the total quiescent tumor cells volume. We present the volumes for particular sub-models, as well as for the average of the sub-models and for the ground truth simulation ("reality").

We check now the quality of the supermodel, by comparing in Figure 21 the difference of the total tumor volume with respect to the ground truth, for the supermodel executed without the training phase (all $C_{ij} = 0.5$), and after the training.
Figure 17: Convergence of coupling coefficients $C_{ij}$.

Figure 18: Convergence of tumor volumes for different sub-models $sim1$, $sim2$, $sim3$, for the averaged model $(sim1+sim2+sim3)/3$, for the supermodel, with respect to the "reality".
Figure 19: Convergence of tumor volumes for proliferating cells, for different sub-models $sim_1$, $sim_2$, $sim_3$, for the averaged model $(sim_1+sim_2+sim_3)/3$, for the supermodel, with respect to the "reality".

Figure 20: Convergence of tumor volumes for quiescent cells, for different sub-models $sim_1$, $sim_2$, $sim_3$, for the averaged model $(sim_1+sim_2+sim_3)/3$, for the supermodel, with respect to the "reality".
9. Conclusions

We focused on the three-dimensional tumor growth model described by a system of PDEs with over 20 parameters. We simulated the tumor growth using a linear computational cost $O(N)$ alternating-direction isogeometric solver. We coupled the continuous model with a discrete vasculature graph. We performed the sensitivity analysis of the model, as well as the inverse simulation using a simple genetic algorithm. We found sets of model parameters that match the ground truth in the best way. As the ground truth, we use a high fidelity model executed on a GPU cluster, using parallel finite-difference code. We found out that the inverse problem solutions fit into local minima, and an additional data assimilation process is necessary. We proposed the supermodeling approach for intelligent coupling and synchronization of several sub-models. We trained the coupling coefficients $C_{ij}$, and build the supermodel with three sub-models using the sets of parameters resulting from the inverse analysis. The supermodel matches well the ground truth data. A good agreement of the supermodel with ”reality” is possible when proper training coefficient $K$ is selected and when we have a good selection of sub-models, surrounding the ground truth. The future work will involve the construction of a supermodel with sub-models using different PDEs and different simulators.

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