Upscaling of fluid flow in spatially heterogeneous bone tumors

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1. Introduction

Osteosarcoma is a malignant bone tumor that preferentially arises in adolescents and young adults. Like many sarcomas with complex genomics, this type of tumors exhibits strong spatial heterogeneities in terms of micro-architecture or differentiated response to treatments due to localized effect of chemotherapy. Clinical images at a tissue scale such as histological and immunohistological sections, exhibit three phases: fluid, solid, cells populations. Therefore the tumor can be considered as a porous medium. The objective of this work was to develop a mechanical approach based on upscaling methods to study the interstitial flow within the tumor at the tissue scale. The statistical study of the micro-architecture of the media shows that the identification of characteristic lengths is complex and that a separation of spatial scales is not necessarily identified. We therefore chose a special sequential upscaling technique, named Grid-Block approach [2] to solve this problem.

2. Methods

This work is based on a database of images of osteosarcomas from patients of Centre de Ressources Biologie-CHU Toulouse. The images of osteosarcoma (figure 1a), stained with hemalun and eosine, are segmented and binarized (figure 1b ; A. Mancini, PhD thesis). Mesh (figure 1b) is obtained using Gmsh and direct numerical simulations are performed with the open source computing platform FEniCS.

We decided to use a Grid-Block multi-scale approach to model the flow within this spatially heterogeneous tumor. We use a two-step upscaling technique [5] which introduces a mesoscopic scale between the microscopic (pore size $\sim 100\ \mu$m) and the macroscopic scales of the entire section ($\sim$ cm). The double upscaling method allows a faster calculation of the permeability tensor and a reduction in the amount of memory required [5] through a splitting of the numerical matrices involved and a simplification of the PDEs to be solved at the second upscaling level.

The first step is to split our domain into $N_x \times N_y$ subdomains and to compute an equivalent (in the sense that it is not calculated on a REV) permeability tensor on each sub-domain. The incompressible Stokes equation (1) considered at the microscopic scale is :

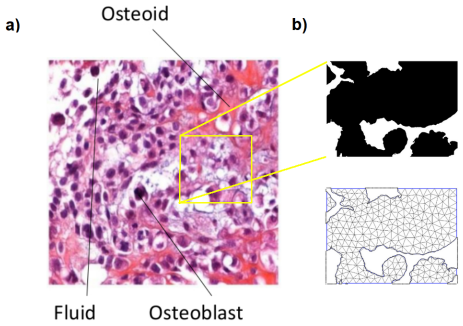

Figure 1: a) Histological section of osteosarcoma stained with H&E ; b) Binary image and a corresponding coarse unstructured mesh for the finite element methods implementation.

$$\begin{cases} \mu\nabla^2\mathbf{u} - \nabla p = -\rho\mathbf{g}, & \text{at the pore scale} \\ \nabla.\mathbf{u} = 0 \\ \text{BCs} \end{cases} \tag{1}$$

We obtain a Darcy's law [7] at the second scale (mesoscopic) which introduces a total permeability tensor with discontinuous coefficients in space $\mathbf{K}^\star(x)$, defined on the entire initial domain.

$$\begin{cases} \mathbf{U} = -\dfrac{\mathbf{K}^\star(x)}{\mu}.(\nabla P - \rho\mathbf{g}), & \text{at the mesoscopic scale} \\ \nabla.\mathbf{U} = 0, \\ \text{BCs} \end{cases} \tag{2}$$

The second step is to apply the upscaling method once again, but this time on the Darcy's equations (2) with the permeability $\mathbf{K}^\star(x)$ previously calculated [2]. By doing so, we get the Darcy's equation (3) [6] with a total permeability tensor $\mathbf{K_{eq}}$:

$$\begin{cases} \mathbf{V} = -\dfrac{\mathbf{K_{eq}}}{\mu}.(\nabla Q - \rho\mathbf{g}), & \text{at the macroscopic scale} \\ \nabla.\mathbf{V} = 0, \\ \text{BCs} \end{cases} \tag{3}$$

Several types of boundary conditions for (1) and (2) are imposed to evaluate their role on the resulting permeability tensor: wall, symmetry, linear pressure and

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periodicity. The ”extend-local” (unlike the so-called local case described above) Grid-Block method [4] is applied to reduce the bias introduced by the boundary conditions. The borders of the calculation region are moved away from the sub-domain considered. The influence of neighboring subdomains is taken into account and this relaxes the bias of the boundary conditions selection.

3. Results and discussion

Initially, we evaluate the role of boundary conditions on the uspcaling methodology from microscopic to mesoscopic scale. A simplified structure with isotropic periodic geometries was computed [3] (figure 2a). Converging results were obtained (figure 2b).

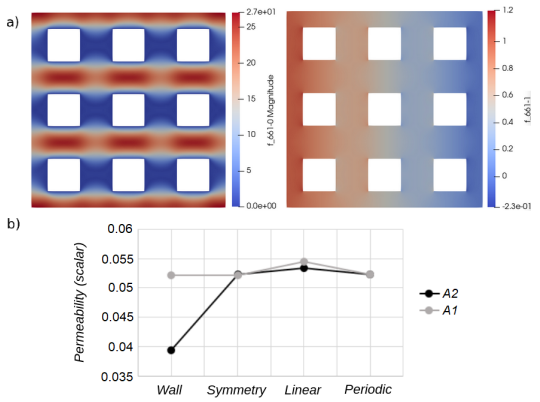

Figure 2: a) Velocity and pressure profile in the case of a periodic geometry A2 with linear pressure BCs ; b) Sensitivity of the permeability (scalar) to the boundary conditions in the case of two periodic geometries A1 and A2.

The methodology was applied on an histological section of osteosarcoma after segmentation (figure 3) in the ”local” and ”extend local” cases. Equivalent permeabilities are shown for the local case and wall boundary conditions on figure 3.

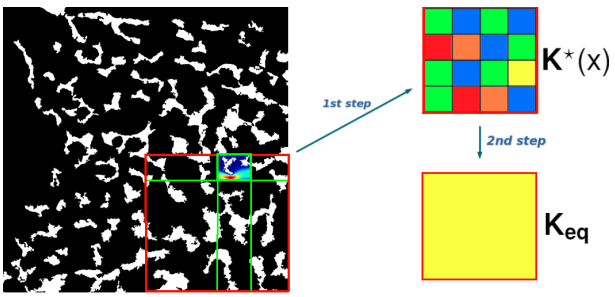

Figure 3: Double local Grid-Block with wall BCs: obtaining the discontinuous tensor in space $\mathbf{K}^{\star}(x)$ and the constant tensor $\mathbf{K_{eq}}$ on the red frame.

4. Conclusion

We have applied Grid-Block methods with double upscaling to osteosarcoma imaging data.
The choice of the boundary conditions is a significant question although attenuated by the extend local to improve the reliability of equivalent permeability tensors. This can also be improved by using an adaptive local-global upscaling methodology [1].
Permeability maps at the meso-scale can be correlated with cellular population distribution pattern to propose mechanobiological strategies to explore and possibly improve patient-specific chemotherapy.

5. References

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