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COMPUTATIONAL METHODS TO SIMULATE SPROUTING ANGIOGENESIS – NUMERICAL ANALYSIS WITH EXPERIMENTAL VALIDATION

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Summary: Sprouting angiogenesis is the formation of new blood vessels from pre-existent vasculature. This process is regulated by several biological factors, being the vascular endothelial growth factor (VEGF) the main pro-angiogenic one. Angiogenesis is a complex process and computational models permit to study this process in different scales and using less time-consuming, reproducible and cheaper methodologies. Accordingly, this study aimed to simulate the chemoattractant effect of VEGF in angiogenesis. In our model, angiogenesis was simulated in a 5x5 mm^2 square domain, using a regular nodal mesh with 2601 nodes. Therefore, the endothelial cells migrate according to a reaction-diffusion equation for VEGF and the Radial Point Interpolation Method was used to solve its governing equations. A chick chorioallantoic membrane (CAM) assay was used to model the branching process. To validate the computational model and to analyse its predictive capacity, the capillary network profile and the angiogenic response for different VEGF concentrations, released from a biomaterial, were analysed and compared with experimental results. The developed computational model could simulate the angiogenic process modulated by VEGF diffusion. In all the performed simulations, endothelial cells migrated accordingly to the chemotaxis effect. Regarding the capillary network morphology obtained *in silico* and *in vivo*, some parameters were compared - total branching number, total vessel length and branching angle - and similar results were obtained (p-value higher than 0.05). Moreover, the capillary network pattern was compared between the *in vivo* and the *in silico* methodologies using the difference between the total capillary volume fractions and a good agreement was obtained with values between 10% and 15%. To analyse the predictive capacity of our model, the angiogenic response for different VEGF concentrations was analysed. The obtained quantitative results were very similar between the two methodologies used. In both CAM assay and simulation, the treatments with VEGF increased the total vessel number [CAM assay: VEGF 50ng increased 37% (vs. control, $p < 0.01$) and VEGF 100ng increased 82% (vs. control, $p < 0.01$); Simulation: VEGF 50ng increased 25% (vs. control, $p < 0.01$) and VEGF 100ng increased 75% (vs. control, $p < 0.01$)]. The treatments with VEGF also increased the total vessel length in both methodologies used [CAM assay: VEGF 50ng increased 20% (vs. control, $p < 0.01$) and VEGF 100ng increased 36% (vs. control, $p < 0.01$); Simulation: VEGF 50ng increased 18% (vs. control, $p < 0.01$) and VEGF 100ng increased 44% (vs. control, $p < 0.01$)]. Moreover, the capillary network profile obtained in these simulations showed similarities to the one obtained *in vivo*. In conclusion, the capillary network from an *in vivo* assay was simulated with realist structure and morphology. Moreover, for the angiogenesis quantitatively analyses, the numerical results agree with the experimental ones, allowing us to conclude that our model could mimic the angiogenesis response modulated by different VEGF concentrations.

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