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Design and prototyping of a synthetic eggshell for the ex ovo engineering of frontier models of microvascular physiopathology and advanced therapeutics

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INTRODUCTION: The microvascular network is a target in traditional, antibody-based and small molecule-based drug development for diabetes, retinal disease, virology and cancer research. The chorioallantoic membrane (CAM) model is a valuable tool in this field [1]. In this work, we designed and developed a synthetic eggshell for the engineering of study models ex ovo, to allow fast and versatile assays of the microvasculature in response to injected drugs. We used computational modelling to predict oxygen consumption of an avian embryo at different embryonic incubation days (EID). We then identified a synthetic eggshell substitute material and relevant thickness allowing a physiological oxygenation of the embryo while maintained ex ovo.
METHODS: We modeled the oxygen consumption of a living chicken embryo in its own eggshell, during its development from EID 4 to 14. The computational model was set-up using Comsol Multyphysics. We modeled the egg as a prolate ellipsoid having radius of 1.4 and 1.7cm, using a finite element mesh of 500k tetrahedral elements. We assumed the eggshell as a porous material having a thickness of 365µm, porosity ~0.0248% and tortuosity=1. We assumed the air sac volume ranging from 1.37 to 5.28cm³. For the CAM, i.e. the embryo respiratory organ, we assumed a consuming surface of ~41cm² with a peak oxygen consumption, Vmax=2.05 x 10^{-6}mol/m²s, and a consumption rate governed by the Michaelis-Menten kinetics. We assumed three values of PDMS thickness for the eggshell substitute material: 100,365,and800µm. Finally, we fabricated a prototype of the synthetic eggshell, in which we maintained chick embryos in culture ex ovo.
RESULTS: The simulations predicted an oxygen concentration drop, alongside the eggshell thickness, in the range of 1.5-14% with respect to saturation value (EID4-14). The air sac average oxygen concentration was equal to 8.152mol/m³. In the eggshell substitute made with the PDMS membrane, we predicted a decrease in air sac concentration ranging from 20% to 80%. We fabricated the first prototype of the synthetic eggshell by means of stereolithography and replica molding. The PDMS membrane of 365µm allowed to reach a good viability on the embryos up to EID8 (n=3), allowing for optical accessibility and ease of access of the CAM microvascular network.
DISCUSSION & CONCLUSIONS: Our computational predictions of oxygen drop in the egg were in good agreement with measured values found in literature[2] with a mean error lower than 5%. The eggshell prototype allowed unprecedent versatility and ease of access of the embryo microvascular system.
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REFERENCES: 1.Conci,Adv.Opt.Mat.2022; 2.Ackerman&Rahn,1980

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