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# A microfluidic architecture with multidirectional diffusion for modelling the stromal compartment of pancreatic ductal adenocarcinoma

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# A MICROFLUIDIC ARCHITECTURE WITH MULTIDIRECTIONAL DIFFUSION FOR MODELLING THE STROMAL COMPARTMENT OF PANCREATIC DUCTAL ADENOCARCINOMA

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The fibrotic layer (stroma) that arises from unregulated production of matrix proteins is an essential component of the tumor microenvironment (TME), particularly with respect to the heterogeneous and hostile nature of pancreatic ductal adenocarcinoma (PDAC) [1]. Biomicrofluidic systems that attempt to recapitulate these processes within 3D geometries have largely been limited to using either laterally adjacent channels in a single plane or vertically stacked single-channel arrangements. As a result, lateral (transverse) or vertical (normal) diffusion have been isolated with their respective designs only, thus limiting access to nutrients and 3D communication that typifies *in vivo* microenvironments [2]. Here we report a novel microfluidic architecture which enables multiplanar arrangements of aligned channels with 3D diffusive access to a central hydrogel compartment.

Device geometries were created by thermally-assisted solvent bonding of stacked CNC-micromilled thermoplastic layers to create 3D planar microfluidic chips (Fig. 1A). Internal ridge-like features called phaseguides were orthogonally positioned and facilitated interfacial “pinning” of a hydrogel and other fluids delivered into the microchannels (Fig. 1B). We tested diffusion experimentally and compared the data to a computational model developed in COMSOL (Fig. 1C), where dextran was allowed to diffuse across an endothelial barrier into a channel containing the bulk collagen mixture. By fitting data to the COMSOL model, values for diffusivity and porosity were obtained and used to simulate diffusion in single-plane (SP) and dual-plane (DP) channel arrangements, with a connected upper channel present. We then assessed the viability of pancreatic stellate cells (PSCs) embedded in the type I collagen gel and used atomic force microscopy (AFM) to measure the on-chip stiffness of this gel after 7 days of culture with pancreatic tumor cells (PCs) (Fig. 1D).

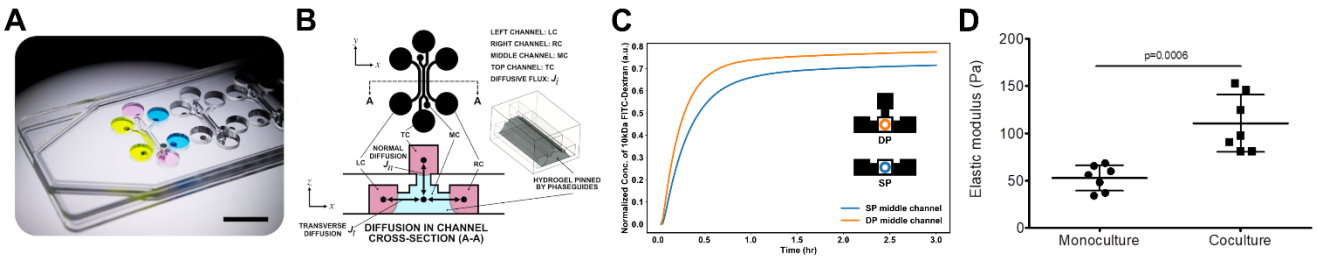


*Figure 1 – (A) Fabricated microfluidic architecture with colored water diffusing across channels. Scalebar = 8mm. (B) Illustration of diffusion processes and phaseguide pinning in channel cross-section. (C) Simulated increase of dextran concentration in DP and SP. (D) On-chip mechanical stiffness measurement in mono- and cocultures after 7 days.*

Our COMSOL model uniquely accounted for (i) porous media transport through the hydrogel and (ii) barrier transport through endothelial monolayers. By fitting our experimental data a posteriori, we found dextran diffusivity and porosity to be 170μm²/s and 60% respectively, with low porosity attributed to possible dehydration and microbubble formation over the 3hr diffusion period. Subsequent simulation of SP and DP designs showed that the DP design had faster diffusion rates (Fig. 1C), suggesting that more nutrients would be delivered to gel-embedded cells in the DP design. We found that PSC viability after 72hr also showed significantly higher live fractions in the DP designs. Finally, we observed a significant increase in mechanical stiffness measured by AFM in the coculture models as compared to monocultures after the 7-day period.

We have presented a novel multilayer microfluidic architecture to model the stromal compartment of PDAC. Our COMSOL-based computational transport model showed that DP designs in all cases had enhanced diffusion. We found that collagen gel-embedded PSCs had higher cell viability in DP designs and on-chip mechanical stiffness of the gels were significantly higher when gel-embedded PSCs were cocultured with PCs. The enhanced diffusion and 3D access to hydrogel components in this platform allows for increased *in vivo* accuracy in future TME organ-on-chip models.

[1] H. J. Hwang, M. S. Oh, D. W. Lee and H. J. Kuh, *J. Exp. Clin. Cancer Res.*, 2019, **38**, 1–14.
[2] M. D. Mohan and E. W. K. Young, *Lab Chip*, 2021, **21**, 4081–4094.