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Development of a 3D microfluidic model of pancreatic adenocarcinoma integrating the mechanical stimuli of the tumor microenvironment

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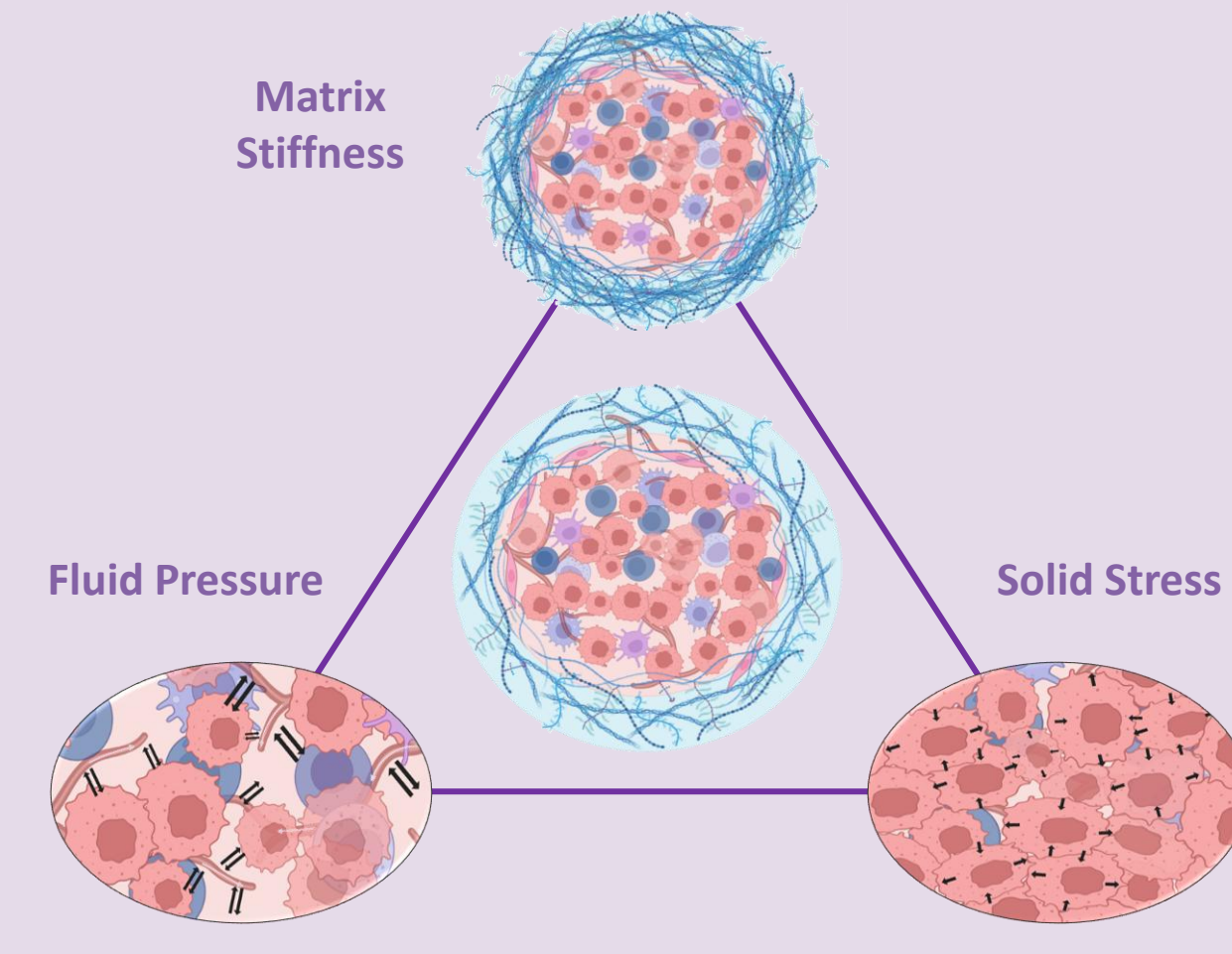
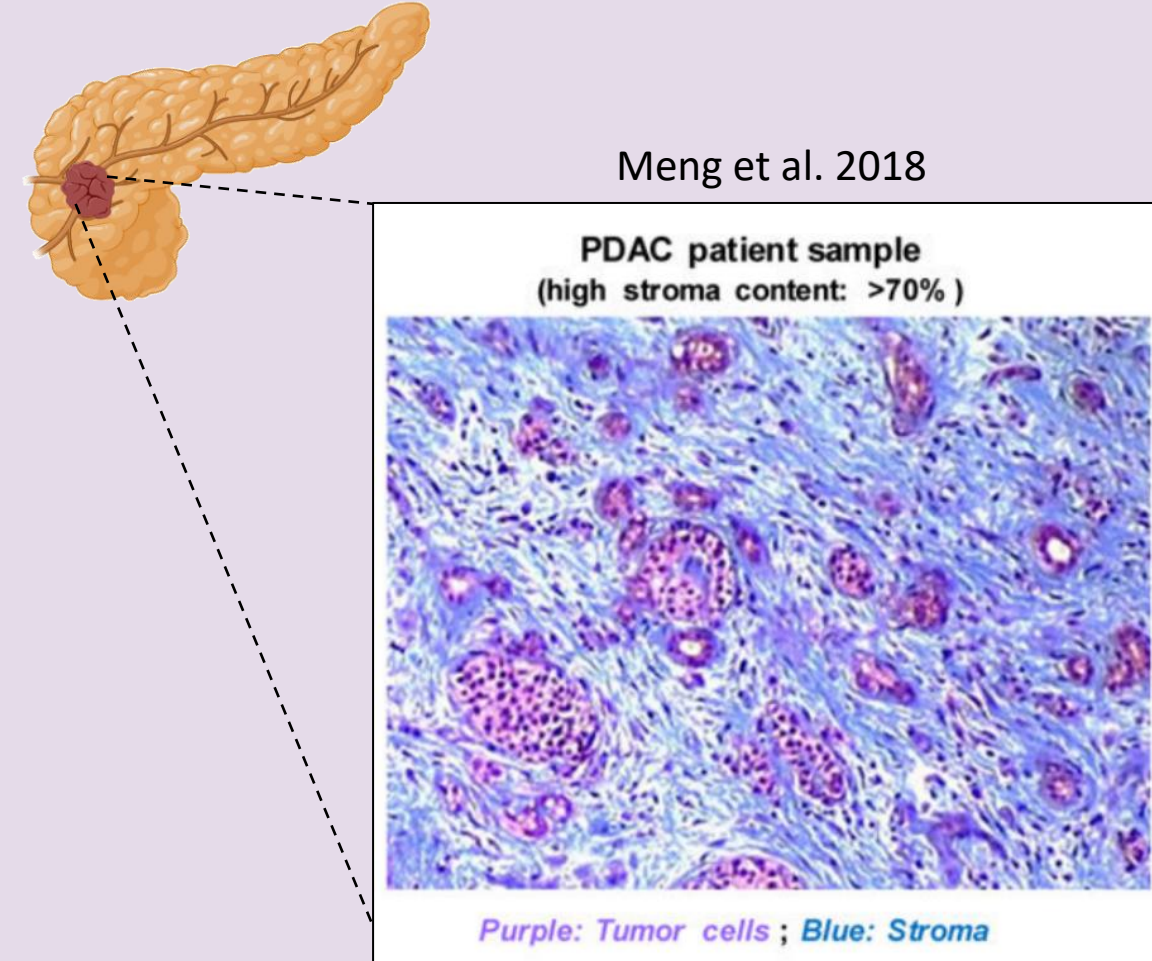
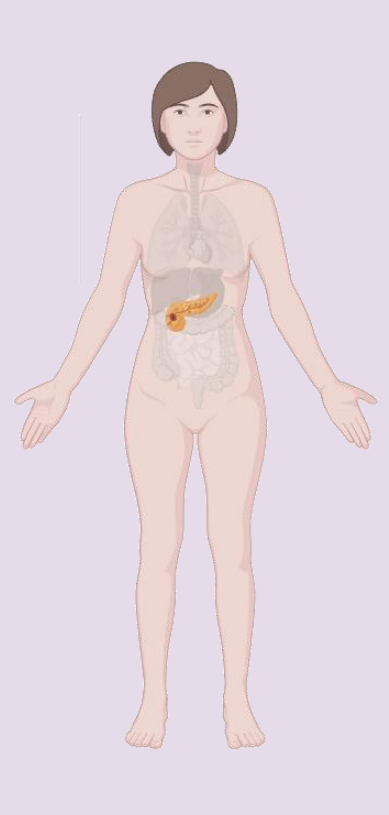


Pancreatic Ductal Adenocarcinoma: A Tumor Under Mechanical Constraint

Incidence
511k

Mortality
467k

GLOBOCAN, World 2022



- Pancreatic tumors are exposed to three main types of mechanical stresses:
- Matrix Stiffness:** ↑ rigidity of the extracellular matrix due to enhanced secretion of matrix components by activated stromal cells.
 - Fluid Pressure:** ↑ interstitial fluid pressure resulting from fluid accumulation in the tumor microenvironment.
 - Solid Stress:** ↑ tension and deformation of cells caused by matrix densification and proliferative pressure.

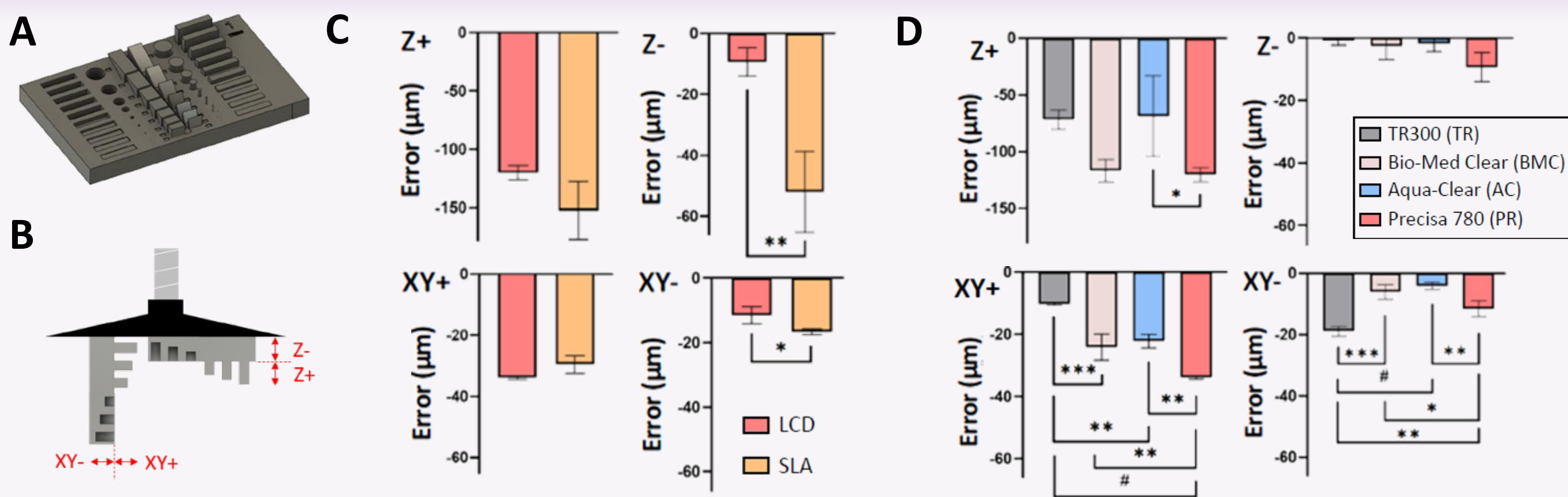
Objectives

- Develop a tumor-on-a-chip model that incorporates the key mechanical stresses of the pancreatic tumor microenvironment.
- Develop a multi-scale numerical simulation model to quantify the three main types of mechanical stresses on cells and matrix.

- Pancreatic Ductal Adenocarcinoma (PDAC):** The most common and aggressive form of pancreatic cancer, accounting for approximately 90% of cases.
- A Cancer with Poor Prognosis:**
 - Increasing incidence
 - 5-year survival rate: ~11%
 - Strong chemoresistance

- PDAC is characterized by a **dense stroma**, which can represent up to 70% of the tumor mass.
- The stroma includes both cellular components (fibroblasts, immune cells) and acellular components (collagens, fibronectin, growth factors, and cytokines).

1 Comparison of Printing Accuracy Across two 3D Printers (SLA and LCD) and Various Resins



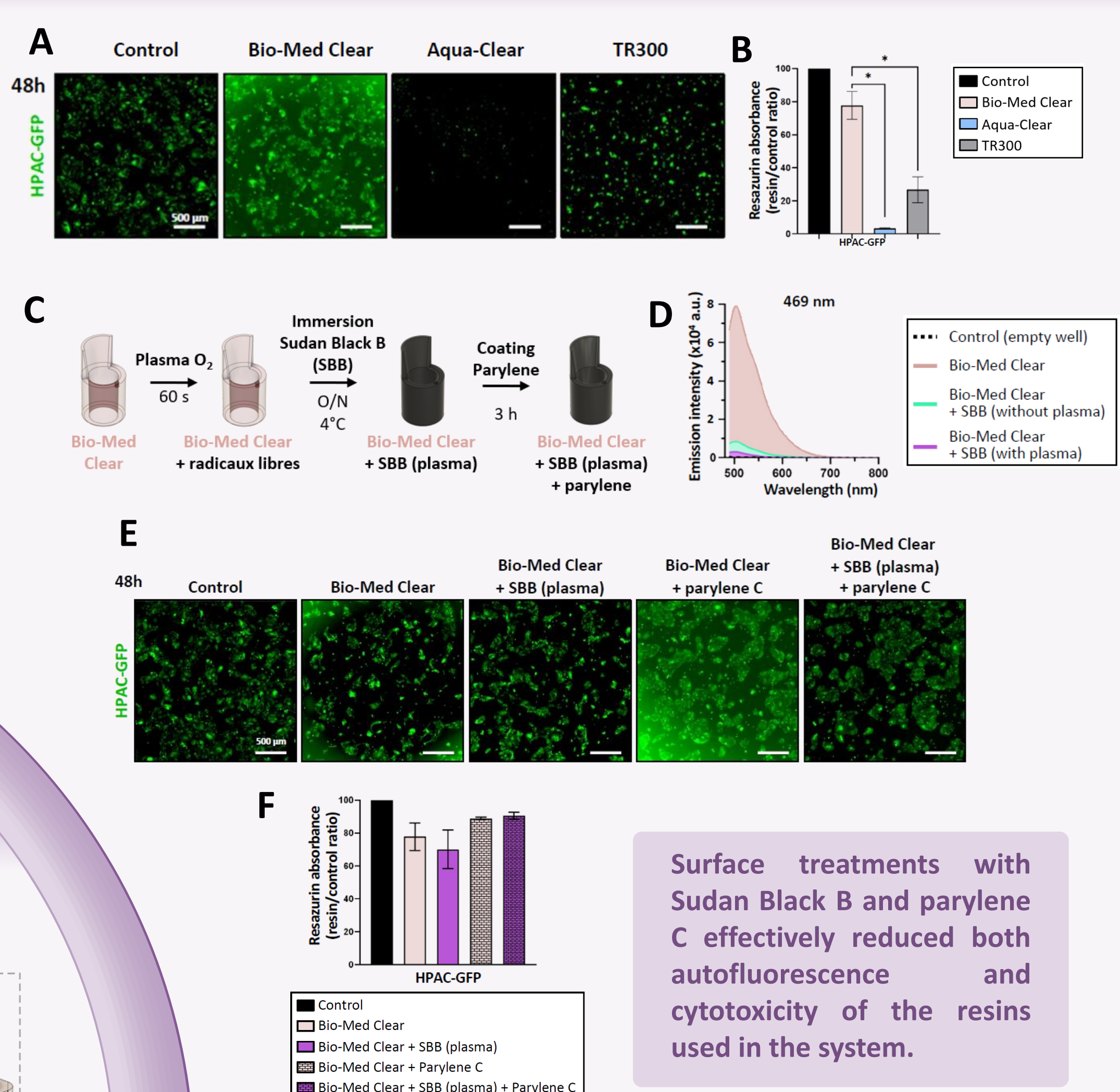
Assessment of the fabrication accuracy of 3D-printed components. (A) Geometry of the characterization platform. (B) Diagram of dimensional indicators ('Z+', 'Z-', 'XY+', 'XY-') used to evaluate printing accuracy across printers and resins. (C) Comparison of dimensional accuracy between two 3D printing technologies: SLA (XFAB) and LCD (Phrozen Sonic Mini 8K). A value of 0 on the graphs represents the expected (target) printing accuracy. (D) Similarly, comparison of dimensional accuracy for four resins printed using the LCD technology: TR300, Bio-Med Clear, Aqua-Clear, and Precisa 780.

Dimensional characterization allowed us to optimize the fabrication methodology of the microfluidic device, improving the dimensional accuracy of key components—particularly the compression lid. Based on these results, we selected LCD 3D printing to produce molds for casting parts in TR300 resin.

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2 Optimization of the Fabrication Protocol

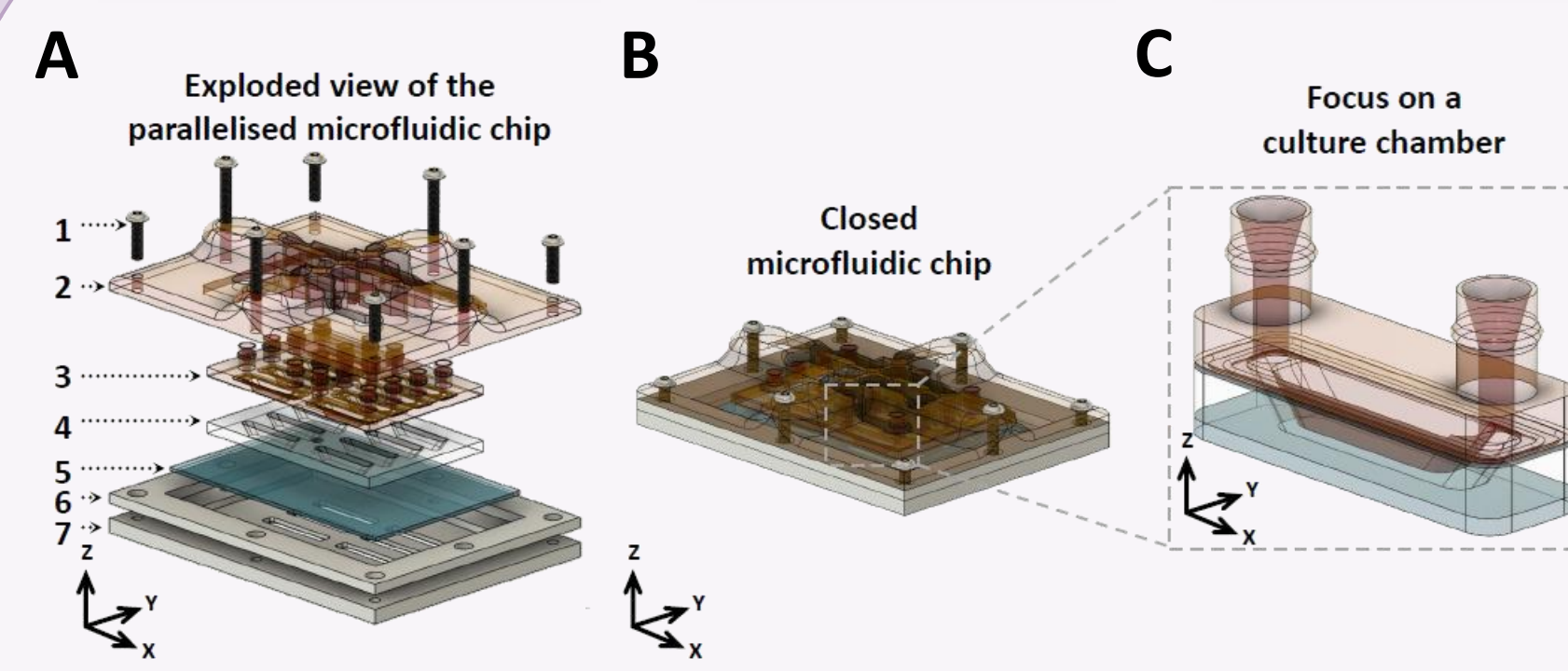
Evaluation of cytotoxicity and autofluorescence of the device, with and without surface treatments. (A) Fluorescence microscopy and (B) Cell viability (measured by Resazurin assay) of HPAC-eGFP cells after 48 hours of culture in contact with various resins. (C) Surface treatments with Sudan Black B and parylene C applied to BioMed Clear resin to reduce autofluorescence and improve biocompatibility. (D) Emission spectrum of BioMed Clear resin after Sudan Black B treatment. (E) Fluorescence microscopy and (F) Viability of HPAC-eGFP cells after 48 hours of culture in contact with the treated resins.



Surface treatments with Sudan Black B and parylene C effectively reduced both autofluorescence and cytotoxicity of the resins used in the system.

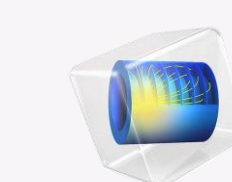
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Development of a Microfluidic Device for Applying Mechanical Stress



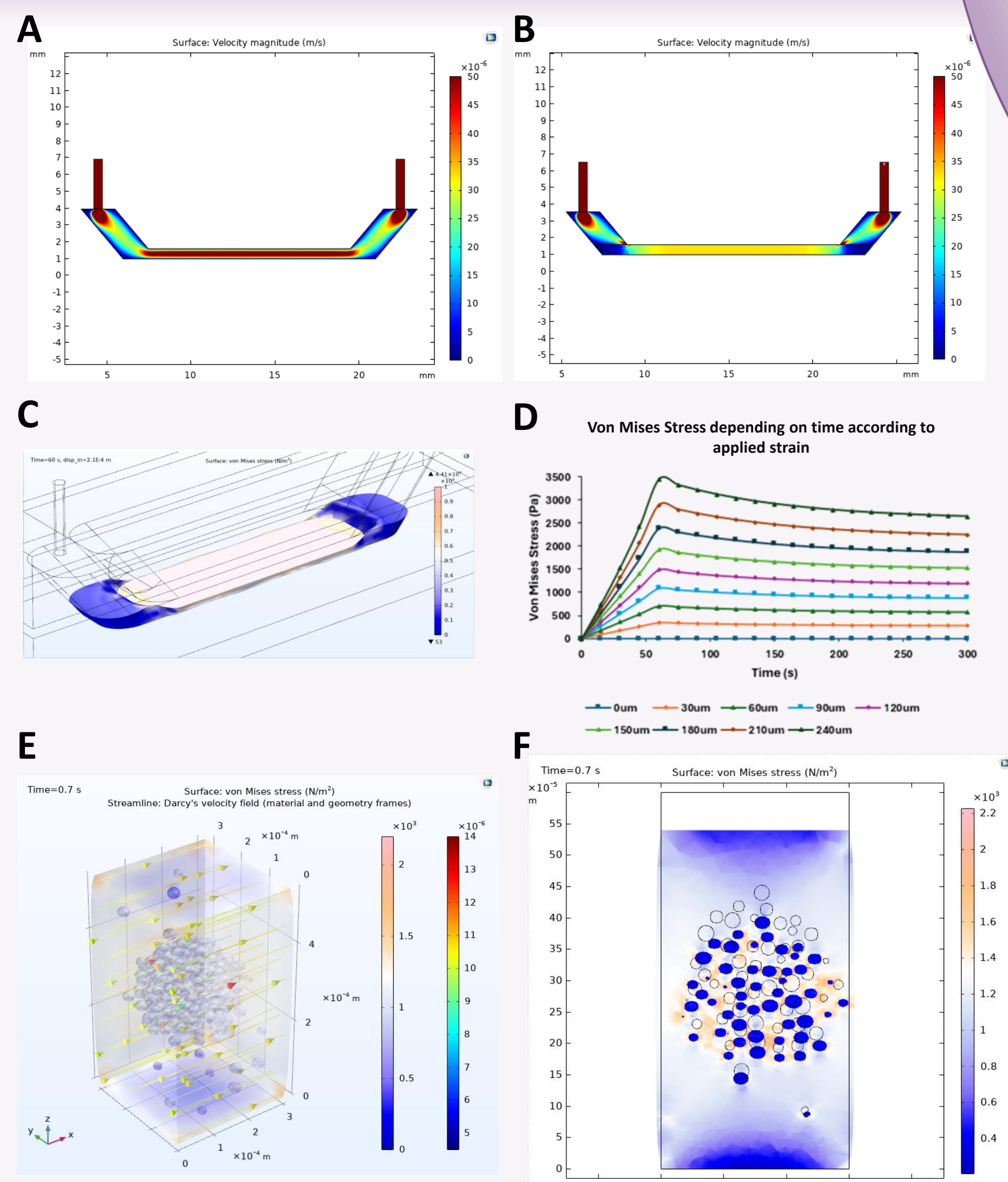
(A) Exploded view of the system showing the 7 parts composing the microfluidic chip: 1: M3x10.8 and M3x17.8 closure screws 2: 3D printed upper closure plate 3: 3D printed resin cap 4: PDMS bottom made from 3D printed mold 5: glass substrate 6: aluminium wedge for closure precision 7: aluminium lower closure plate. (B) Illustration of the closed chip. (C) One culture chamber formed by inserting the cap part. The microfluidic chip consists of eight individual culture chambers

Using the computer-aided design software Fusion 360®, we developed a microfluidic device primarily manufactured via 3D printing. The device consists of two distinct parts, allowing easy access to the biological sample at any point during the culture process.



(A) Flow velocity profile in the empty device at an inlet flow rate of 3.74 µL/min, without extracellular matrix. (B) Flow velocity profile with an extracellular matrix (no cells). (C) 3D view of the mechanical stress distribution within the extracellular matrix under 40% applied compression/deformation. (D) Stress-strain curves in the matrix for increasing deformation from 0% (0 µm) to 40% (240 µm), highlighting the viscoelastic behavior of the material. (E) Development of a microscale model (full channel cross-section) to numerically study the effects of flow and compression on cellular aggregates. (F) Cross-sectional view of mechanical stress localized at the core of a cell aggregate under 10% (60 µm) compression.

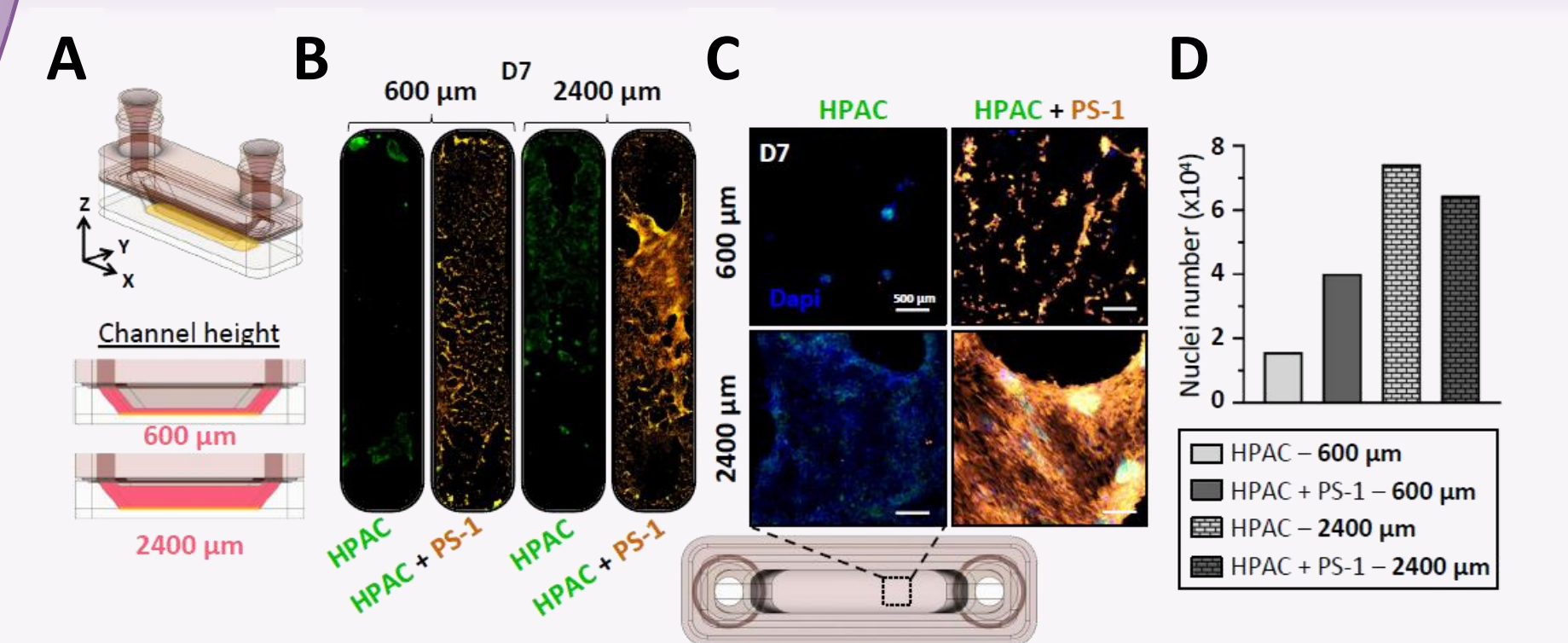
3 Multiscale Simulation of Mechanical Stress in the Tumor Microenvironment



The extracellular matrix significantly alters fluid flow dynamics in the microfluidic device, highlighting its crucial role in shaping the mechanical microenvironment. Mechanical stress is heterogeneously distributed within the matrix and increases proportionally with applied deformation. This uneven loading may contribute to phenotypic heterogeneity among tumor cells, affecting their behavior and treatment response.

At the cellular scale, simulations reveal pronounced stress heterogeneity, with stress concentrated in specific microregions. Importantly, the stress experienced by individual cells or aggregates is substantially lower than the overall matrix stress, underscoring the role of microenvironmental shielding and mechanical filtering in 3D culture models.

4 Biological Tests in the Microfluidic Chip under Two Flow Conditions

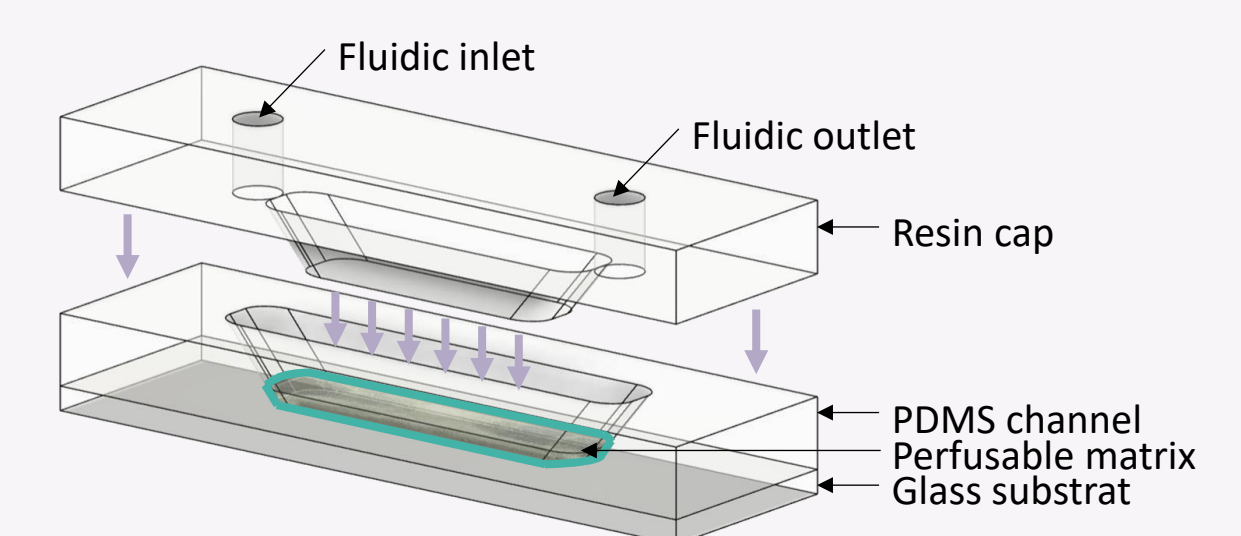


Validation of the feasibility of (co-)culture within the device and demonstration of the impact of fluid flow on tumor development.

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Conclusion and perspectives

Development and characterization of a dynamic culture system enabling the application of controlled mechanical constraints on 3D cell cultures embedded in an extracellular matrix.



- Investigation of the effects of three types of mechanical stress on ion channel signaling, highlighting their distinct roles in promoting tumor progression.
- Calibration of applied mechanical constraints using simulation models to closely mimic the physiological conditions of the pancreatic tumor microenvironment.

Acknowledgments

