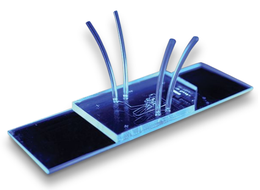
SynBBB™: AI/ML-Enhanced Standardization and Predictive Monitoring of Human-Relevant Blood-Brain Barrier-on-Chip for CNS Drug Discovery



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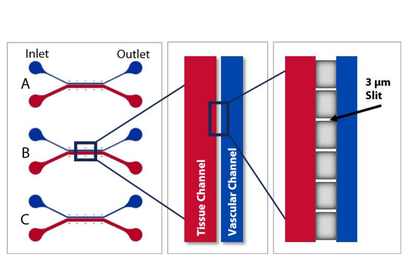
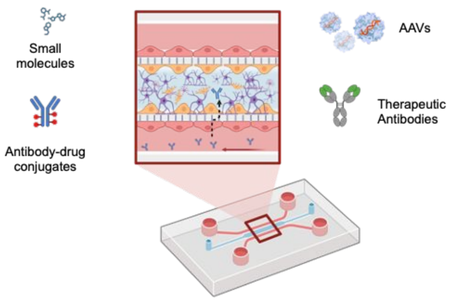
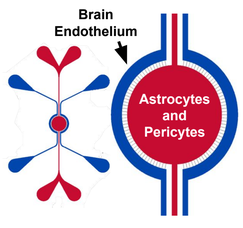
Background & Motivation

Conventional blood-brain barrier (BBB) models lack physiological relevance and reproducibility. **SynBBB™** model **is an advanced organ-on-chip model designed to study drug transport, toxicity and efficacy of compounds.** It recreates a human-relevant, vascularized BBB by co-culturing endothelial cells, astrocytes, and pericytes under controlled **fluid shear stress** to promote **complete lumen formation** and **robust barrier integrity**.

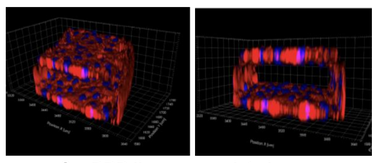


SynBBB Linear Design

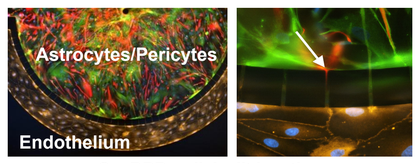




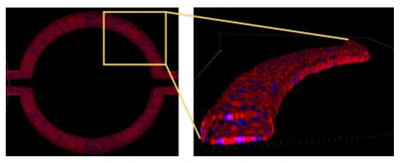
SynBBB Radial Design



SynBBB linear, complete lumen

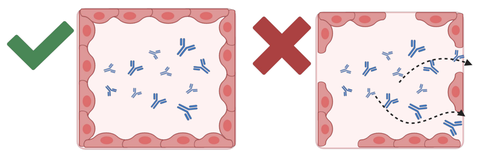


SynBBB radial, slit location



SynBBB radial, complete lumen

A complete lumen indicates strong barrier integrity and a good permeability performance which is physiologically relevant to a BBB *in vivo*. To ensure consistent performance and predictive value across studies, we introduced **AI/ML-based quality gating and monitoring**, making BBB assays more **standardized, reproducible, and translationally meaningful** for CNS drug discovery.



Good complete lumen | Bad incomplete lumen

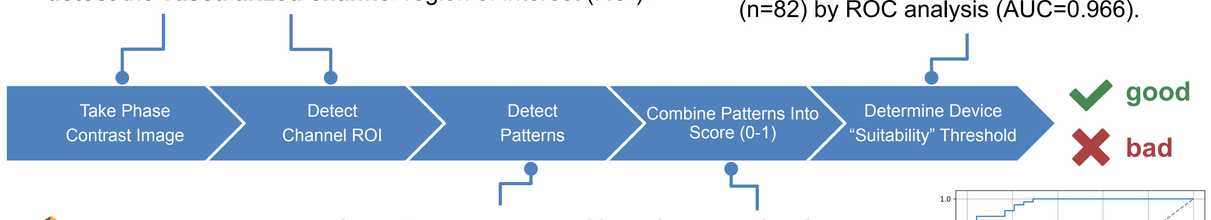
At a Glance

Challenge	Conventional BBB models lack physiological realism, resulting in poor translation to human outcomes.
Our contribution	SynBBB™ recreates vascularized human BBB-on-chip with AI-enhanced quality gating and predictive monitoring. High precision for intact BBBs and strong sensitivity for defective ones, ensuring reliable identification of both high-quality and compromised models.
Impact	Delivers standardized, reproducible, and human-relevant data for CNS drug discovery - with less variability and fewer animal tests.

Automated AI/ML-based Suitability Scoring

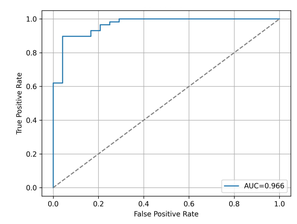
Phase-contrast images were analyzed on the IKOSA platform, where a **deep learning AI model was trained** to **detect** the **vascularized channel** region of interest (ROI).

The final classifier is based on a score threshold learned from the validation dataset (n=82) by ROC analysis (AUC=0.966).



IKOSA

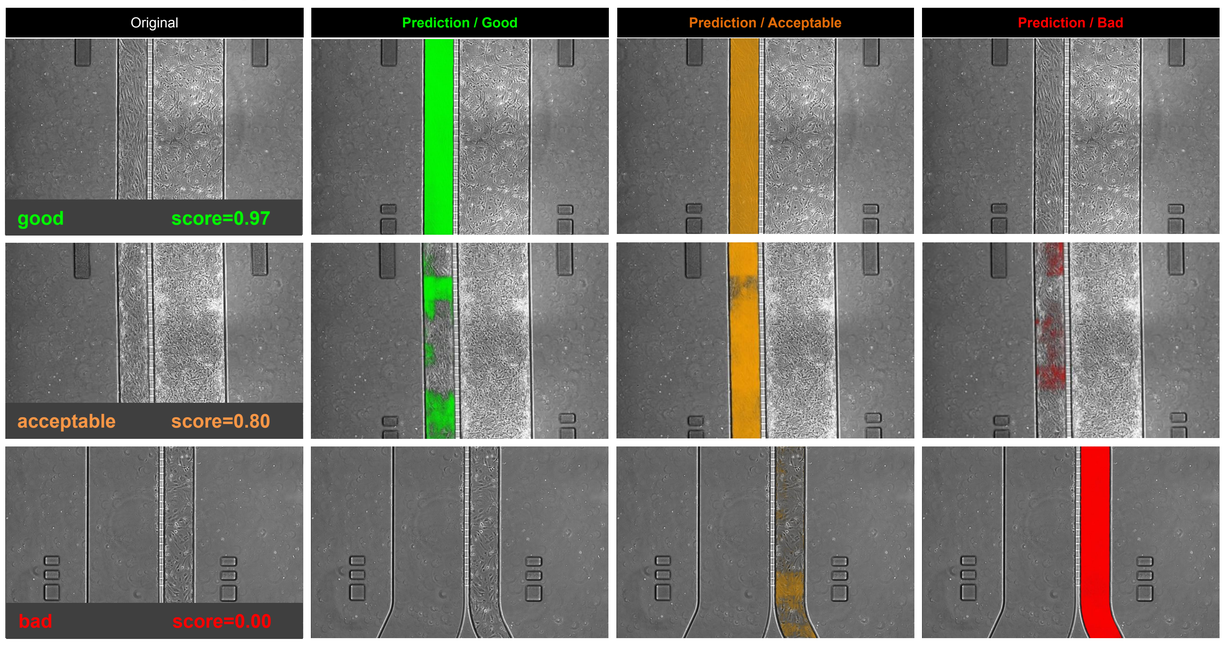
Lumen quality patterns are learned by a deep learning **AI model** as **good, acceptable, or bad** (n=327). Predictions are combined into a suitability score (0-1). Penalizing poor image features favors a high score for good devices, and a low score for bad devices. We applied a 5-fold cross-validation to assess AI model generalizability and compared to a standard method.



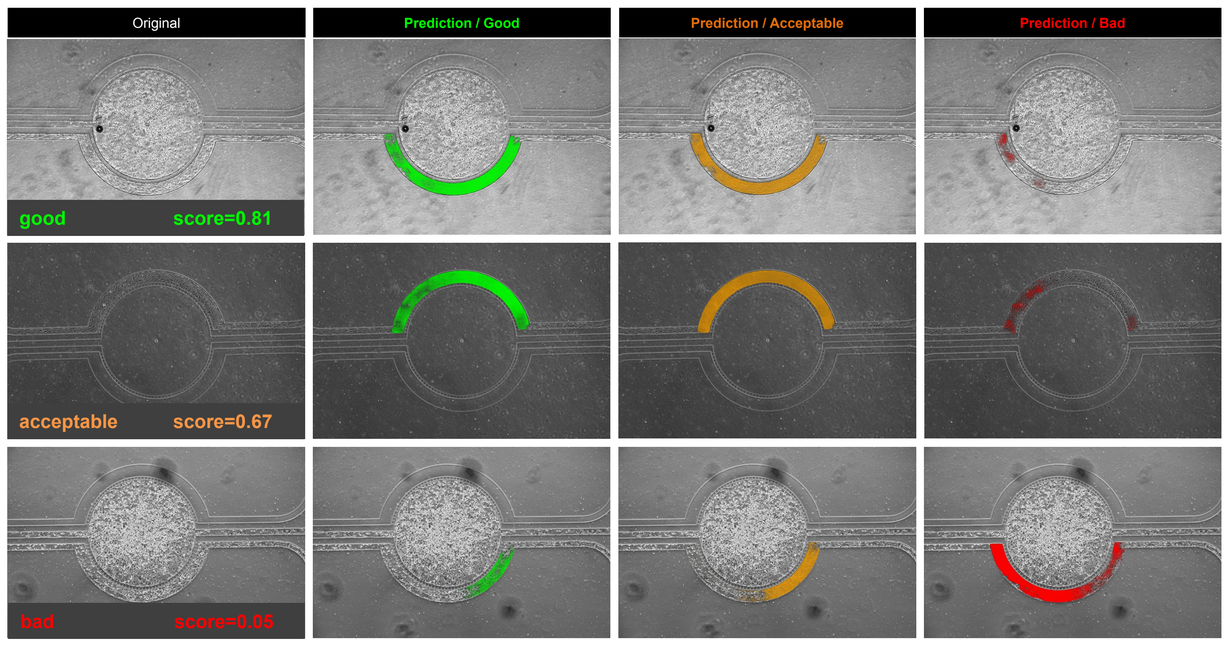
Results

Device suitability classification (test dataset, n=45)

SynBBB linear design



SynBBB radial design



Classifier performance metrics, **overall accuracy 88.9%** (test dataset, n=45)

Class	Sensitivity / Recall	Precision	Specificity
good	87.9%	96.7%	91.7%
bad	91.7%	73.3%	87.9%

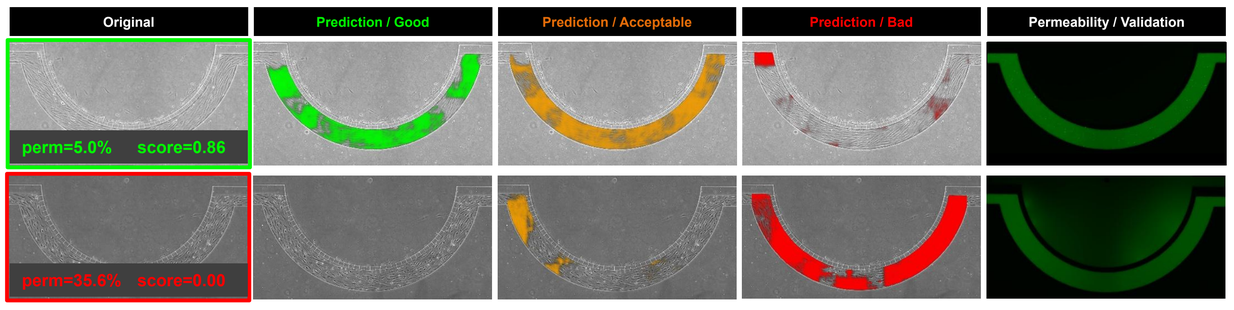
Q: *"How reliably does the model recognize intact, functional BBBs?"*
A: Sensitivity / Recall for "good" = 87.9%
Useful when you care about keeping **high-quality samples** in downstream analysis.

Q: *"How well does the model exclude leaky or incomplete barriers?"*
A: Specificity for "bad" = 87.9%
You care about this because **excluding poor models** improves assay reproducibility.

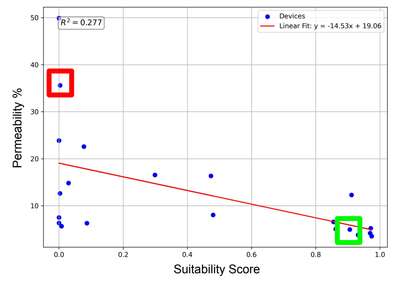
Q: *"When the model says 'good,' how often is it truly good?"*
A: Precision for "good" = 96.7%
Relevant if you want to **trust model-based quality gating** before experiments.

FAQ

Permeability analysis comparison experiment (test dataset, n=17)

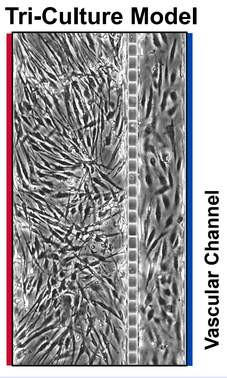


Higher scores correlate with lower permeability

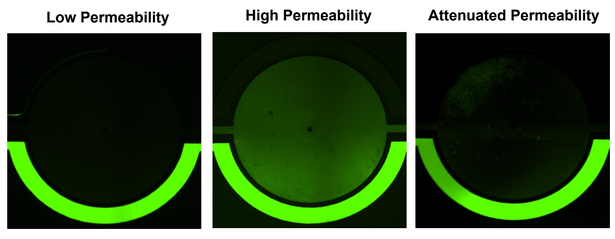


SynBBB Assays For BBB Therapeutic Analysis

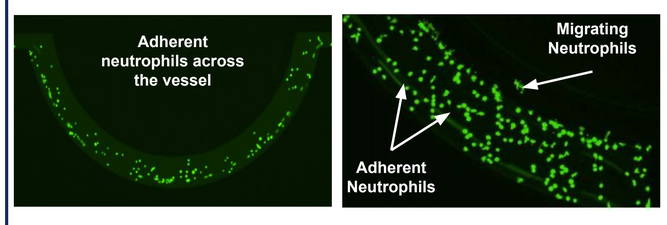
SynBBB Functionalized Tri-Culture Model



Barrier Integrity Assays for Drug Safety and Efficacy Testing

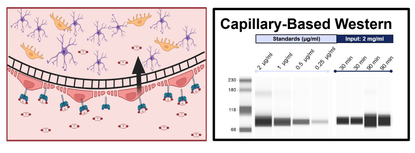


Leukocyte Adhesion Assay To Detect Inflammation



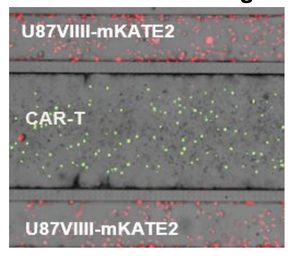
Quantifiable Neutrophil Rolling, Adhesion, and Migration

Drug Permeability and Receptor-Mediated Transcytosis: From Small Molecules to Antibodies and AAV Viruses



SynBBB allows collection and quantification of transcytosed compounds across the BBB via automated WES and qPCR

CAR-T Screening



SynBBB allows visualization of CAR-T cell extravasation across blood-brain tumor barrier

Key Takeaways & Conclusions

Reproducible and standardized BBB modeling	SynBBB™ provides a consistent, human-relevant in vitro BBB platform validated across transport, safety, and efficacy studies.
Predictive and non-invasive	Scoring can be reapplied post-dosing to detect drug-induced barrier disruption, enables continuous label-free monitoring over time.
AI-enhanced data integrity	Integrated quality gating and predictive monitoring improve experimental reliability and reduce variability. Stable performance across a 5-fold cross-validation, the model generalizes beyond single splits of the dataset.
Translational and ethical impact	SynBBB™ supports more predictive CNS drug discovery while minimizing reliance on animal testing.
Scalable, data-driven quality control	Fully data-driven AI pipeline that can be easily retrained for other microphysiological systems or assay types, enabling broad reuse and rapid adaptation across applications.

Contacts

IKOSA

Sign-up for your IKOSA AI free trial
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References

1. Charlebois C, Huang J, Sodja C, Ribecco-Lutkiewicz M, Baumann E, Stanimirovic DB, Jezierski A. Development of a Blood-Brain Barrier Permeability Assay Using Human Induced Pluripotent Stem Cell Derived Brain Endothelial Cells. Methods Mol Biol. 2022;2454:397-410. PMID: 33881753.
2. Sade H, Baumgartner C, Hugenmatter A, Moessner E, Freskgård PO, Niewoehner J. A human blood-brain barrier transcytosis assay reveals antibody transcytosis influenced by pH-dependent receptor binding. PLoS One. 2014 Apr 30;9(4):e96340. PMID: 24788759; PMCID: PMC4005765.