



ULTRASOUND LOCALIZATION MICROSCOPY OF THE BRAIN: THE MISSING MICRO VASCULATURE

Stephen A Lee¹, Jonathan Poree¹, Alexis Leconte¹, Alice Wu¹, Samuel Michelic², Andreas Linnerger^{2,3}, Jean Provost^{1,4}

¹Department of Engineering Physics, Polytechnique Montreal, Canada

²Department of Biomedical Engineering, University of Illinois Chicago, United States

³Department of Neurosurgery, University of Illinois Chicago, Chicago, Illinois, USA

⁴Department of Cardiology, Montreal Heart Institute, Canada

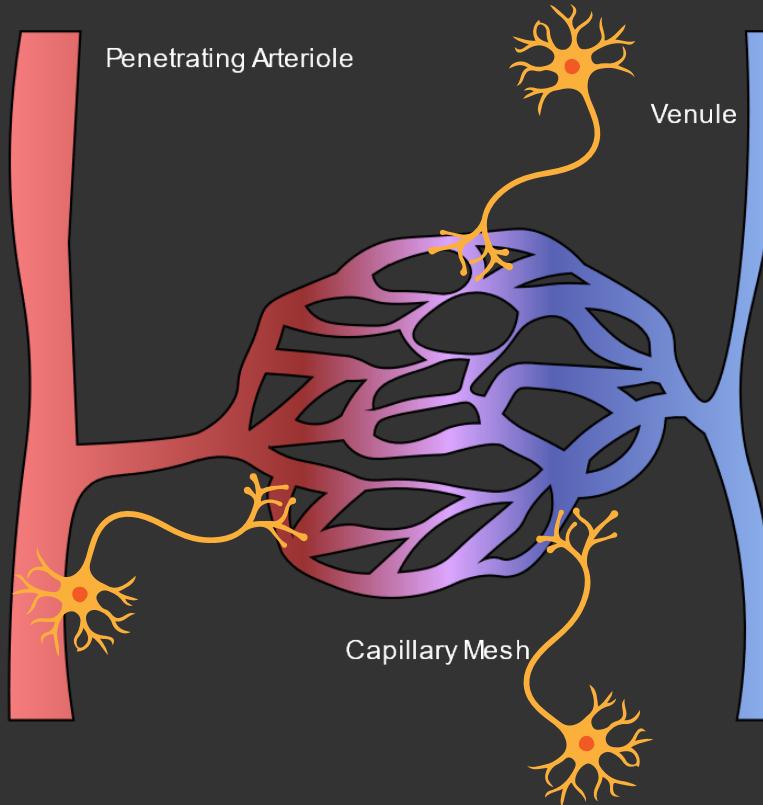
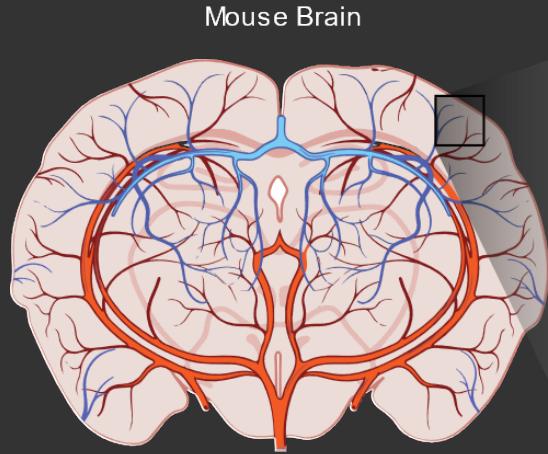
ISBI 2024 - Athens, Greece

Ultrasound Imaging

Wednesday, May 29th, 9:00 – 9:15



Healthy capillaries, healthy brain

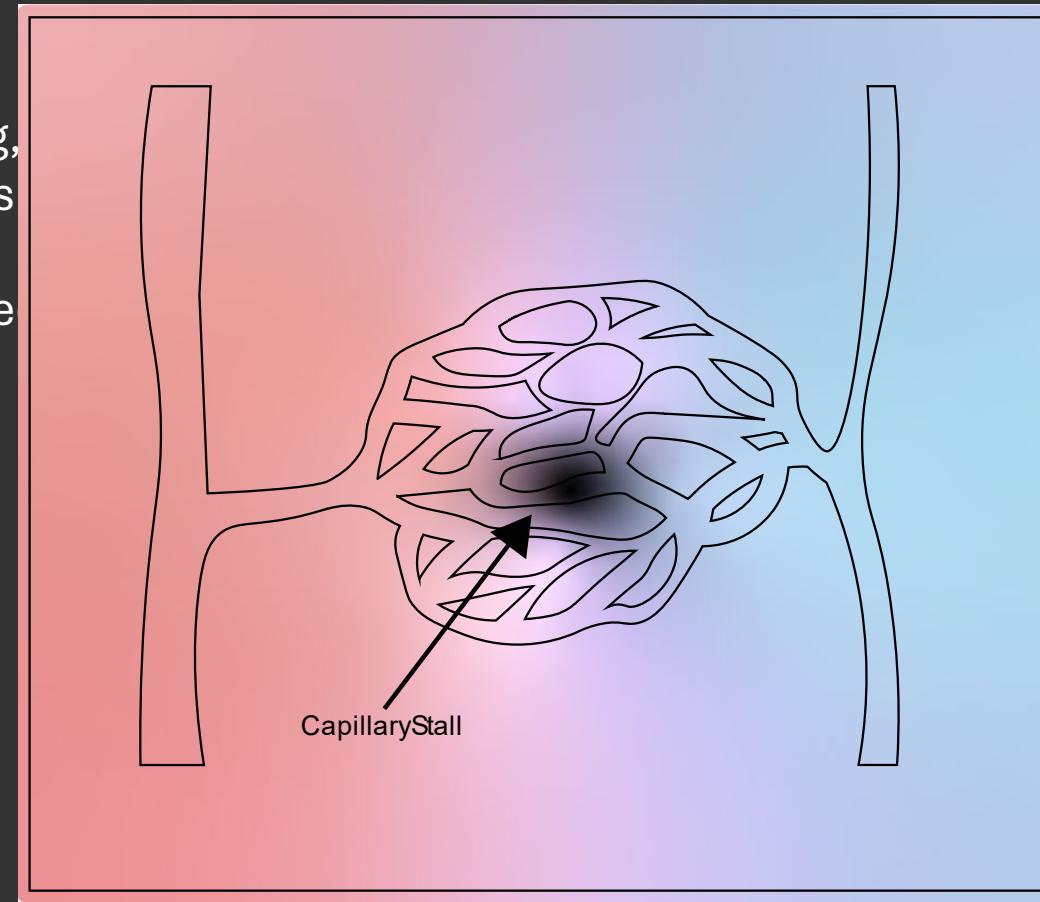


- The brain is a hungry organ, constantly consuming 20-25% of total oxygen and glucose¹
- Cerebral capillaries are involved in oxygen exchange, glucose delivery, and waste removal.²
- It is estimated that nearly each neuron has its own capillary supply.³

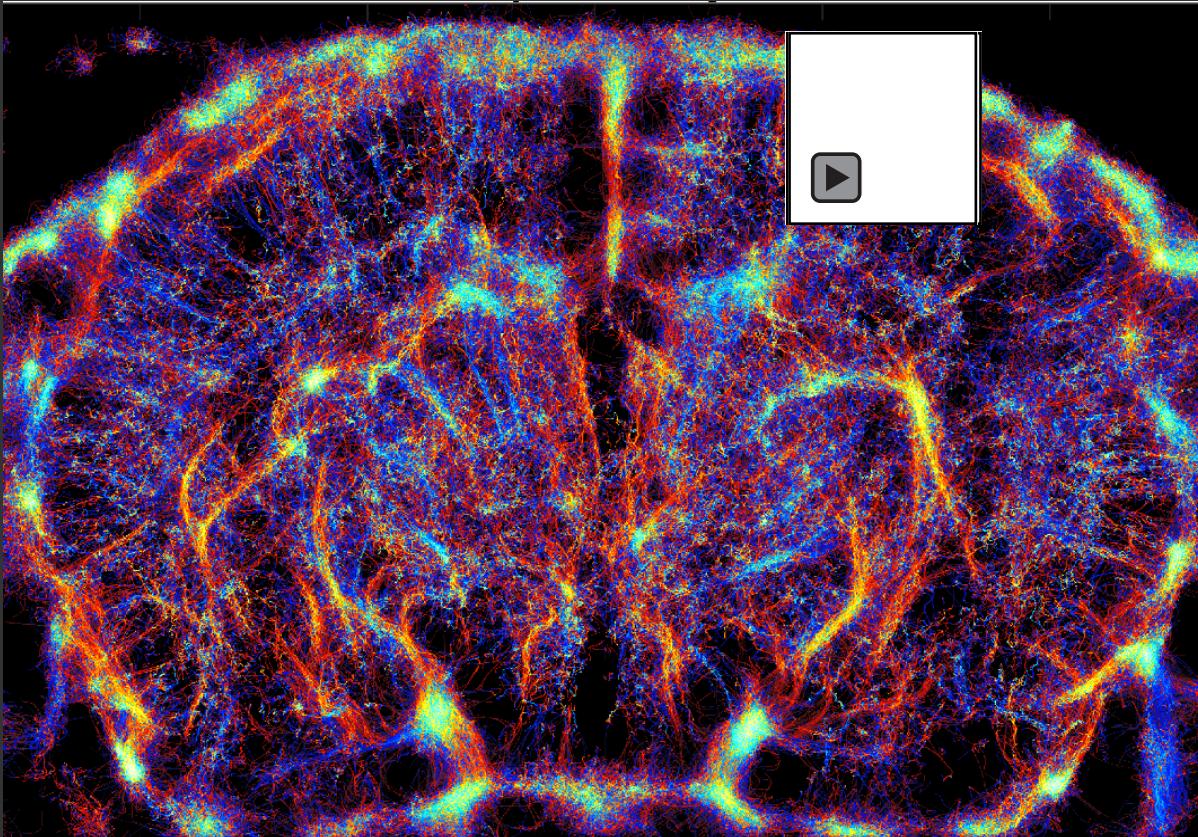
There is an intimate relationship between the brain and the microvasculature: the neurovascular unit (NVU)

Stalling at the capillary level can cascade throughout the brain

- Measurement of capillary function has large implications in stroke, aging, neurodegenerative diseases
- Age-loss density is correlate with impaired cognitive function¹

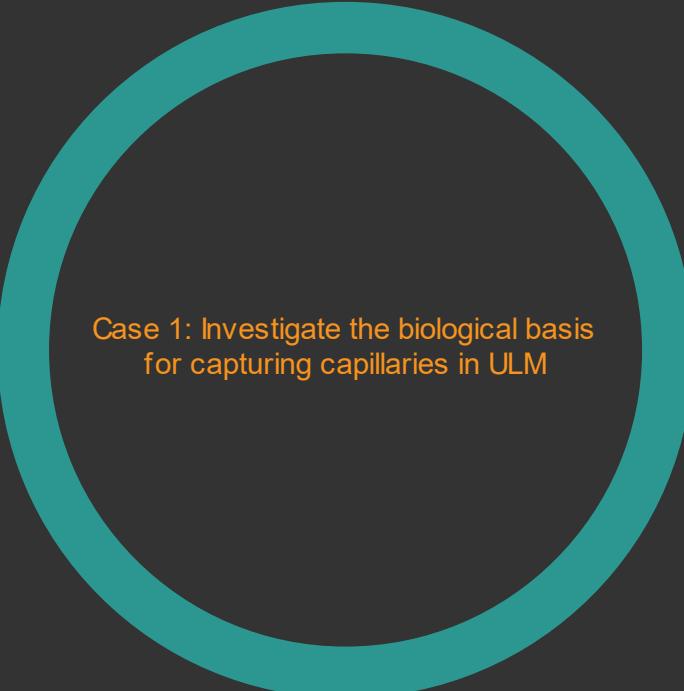


Ultrasound Localization Microscopy (ULM) can visualize most of brain microvasculature



The case of the missing microvasculature

Motivation: Is there a ULM paradigm that can recover single capillary structure and function?



Case 1: Investigate the biological basis
for capturing capillaries in ULM



Case 2: Identify computational limitations
and solutions for slow flow microbubbles

How long does it take to perfuse a cerebral capillary with microbubbles?

Method	Microbubble Concentration (MBs per mL blood)	Time to 90% MB perfusion (seconds)	MB perfusion time adjusted to common blood concentration (seconds)
Dencks <i>et al.</i> [12]	5.56×10^6	101	150
Christensen-Jeffries <i>et al.</i> [7]	5.56×10^6	139	206
Hingot <i>et al.</i> [6]	3.75×10^6	230.4	230.4
ULM CAM saturation	5.6×10^7	21.4	319
Confocal wash-in	5.6×10^7	13	193
Markov-chain (unweighted)	5.6×10^7	1.6	24.5
Markov-chain (distance-weighted)	5.6×10^7	3.5	51.8
Markov-chain (centroid-weighted)	5.6×10^7	5.9	88.3
Markov-chain (distance- and centroid-weighted)	5.6×10^7	12.2	182

1

CAM

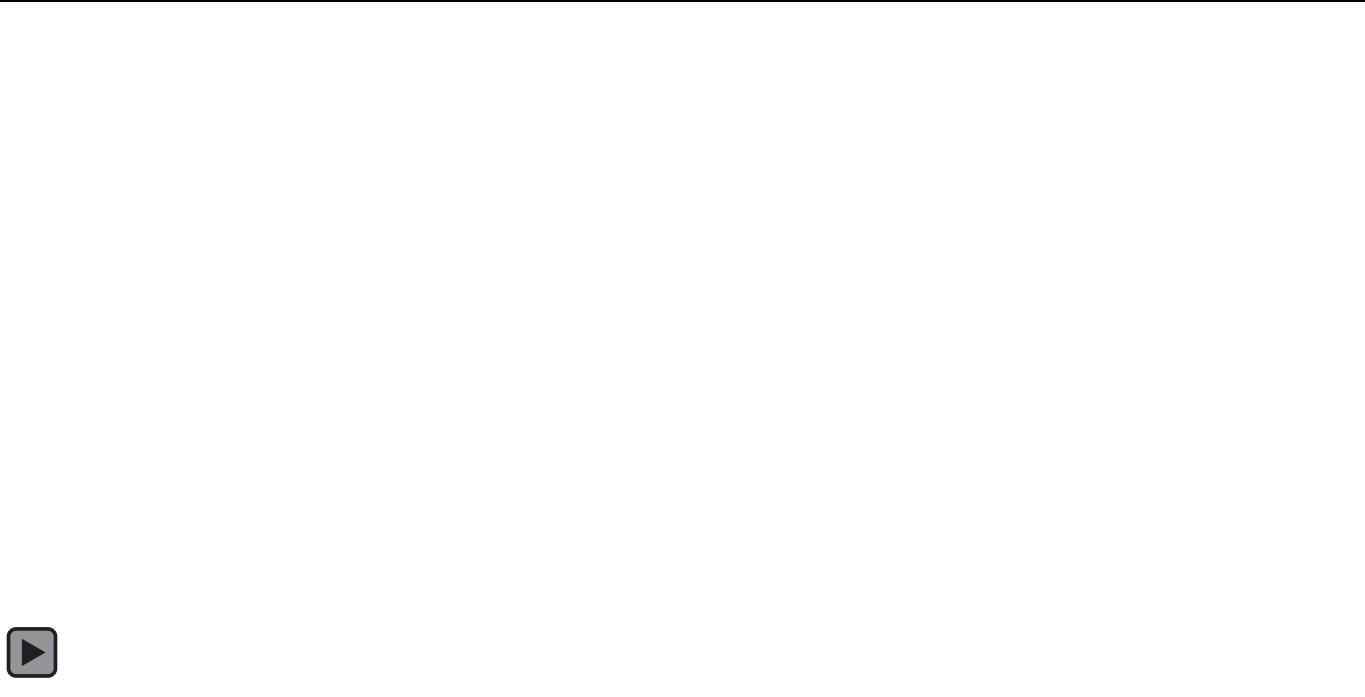
Mouse Tumor
Computational Model
Rat brain

“detecting all the smallest vessels, would take minutes to tens of minutes for capillaries”²

- How do microbubbles behave in capillaries?
- How can we identify vessels based not on a collective of microbubbles, but single microbubbles?



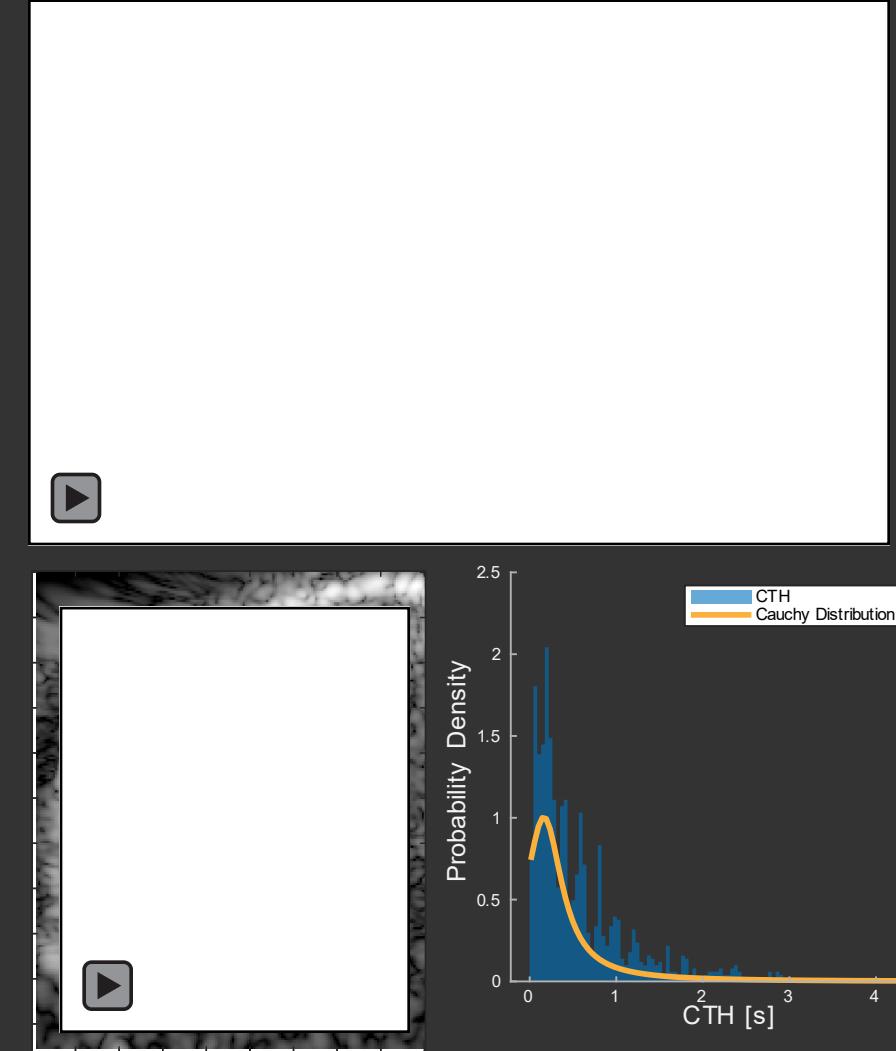
How long does it take to perfuse a cerebral capillary with microbubbles?



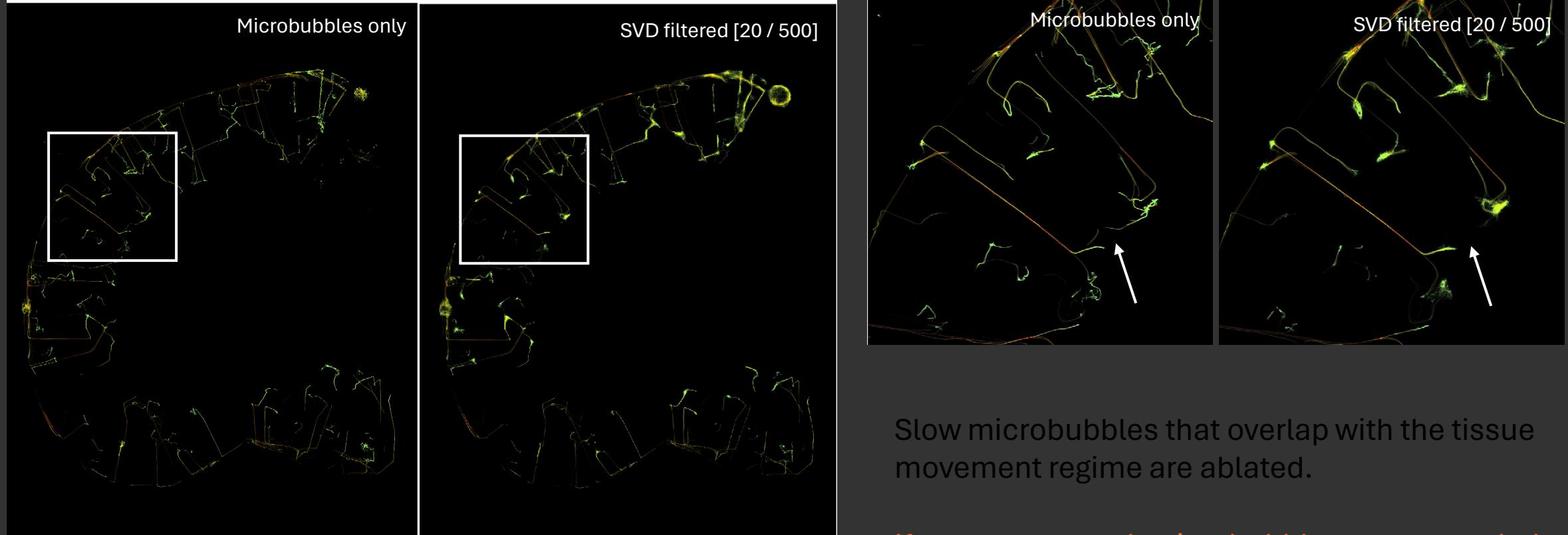
Computational hemodynamic modeling¹ of microbubble flow through the microvasculature reveals an **upper limit (4 s) of the capillary transit-time heterogeneity (CTH)**.

Popular acquisition schemes

- 500 Frames @ 1000 Hz = 0.5 s
- 750 Frames @ 500 Hz = 1.5 s



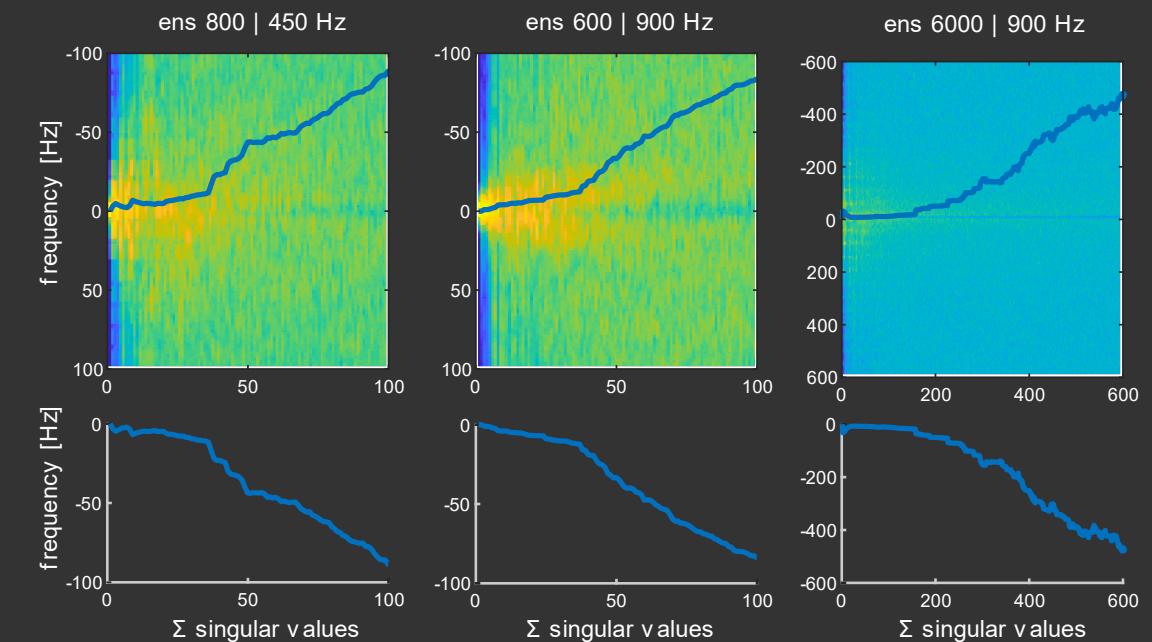
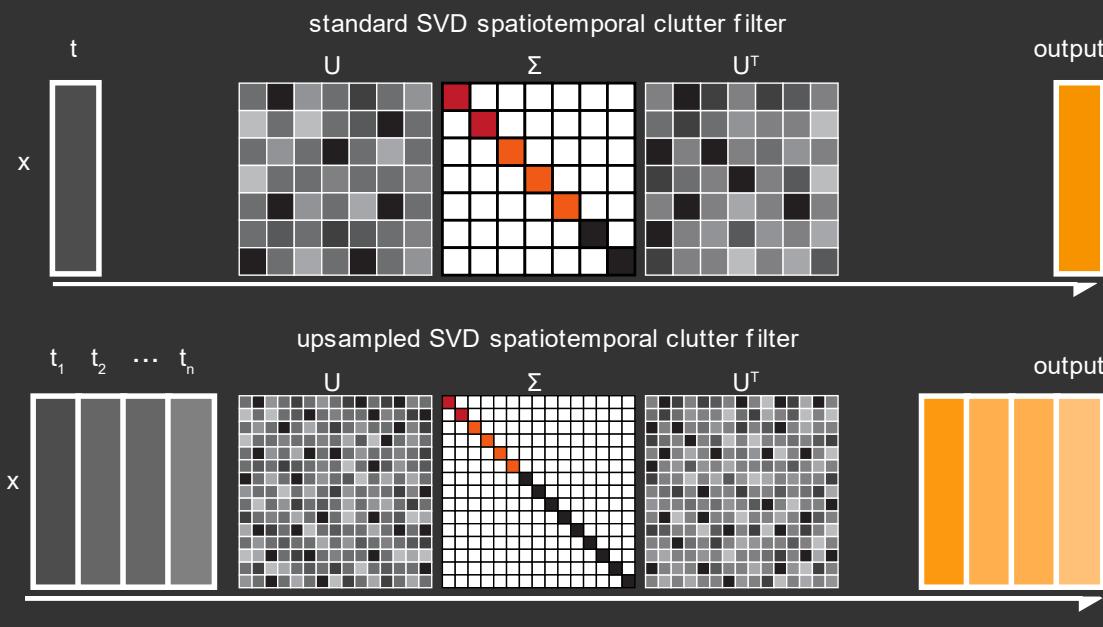
SVD removes tracks corresponding to capillaries



Slow microbubbles that overlap with the tissue movement regime are ablated.

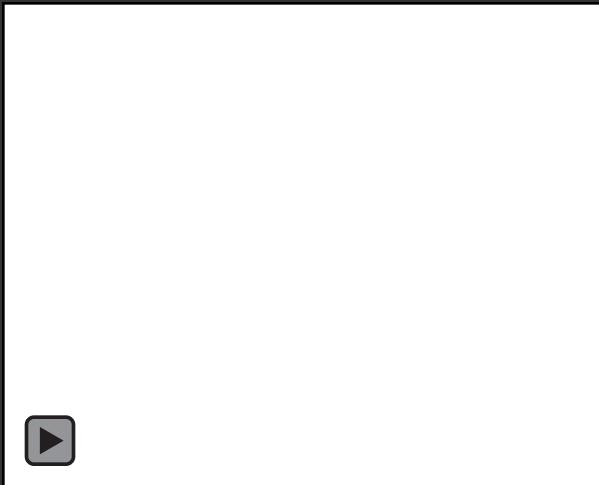
If we want to track microbubbles over extended periods of time, we need to recover slower flows.

We propose long-ensemble (LE)-SVD to recover slower microbubbles

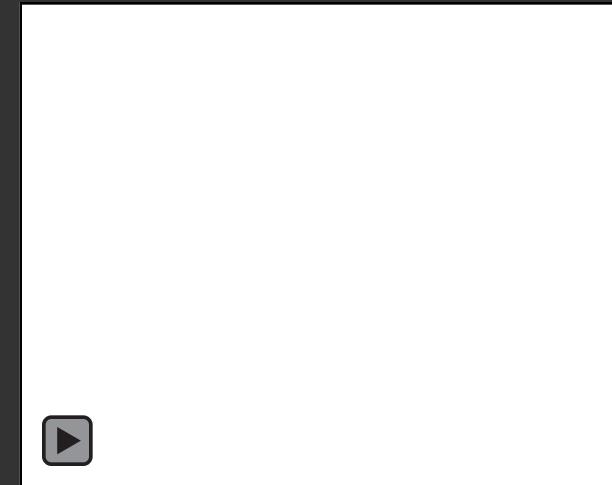


We propose long-ensemble (LE)-SVD to recover slower microbubbles

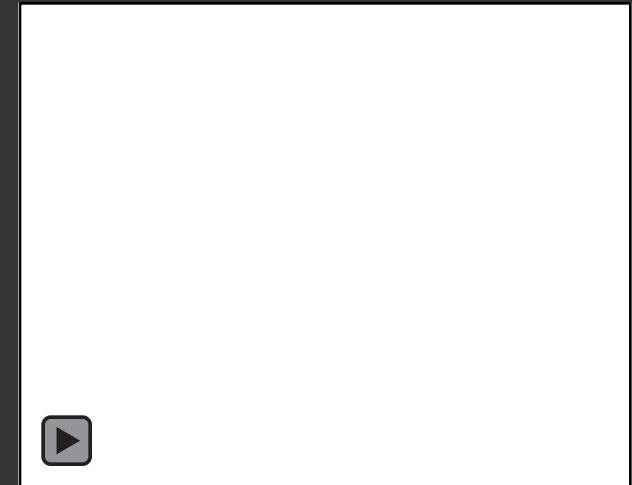
Ensemble 1000



Ensemble 3000



Ensemble 6000

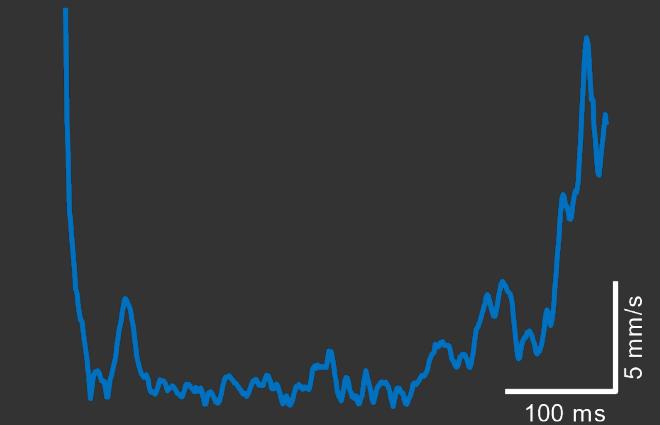


Trained Hidden Markov Models can identify single capillaries

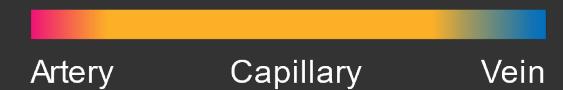
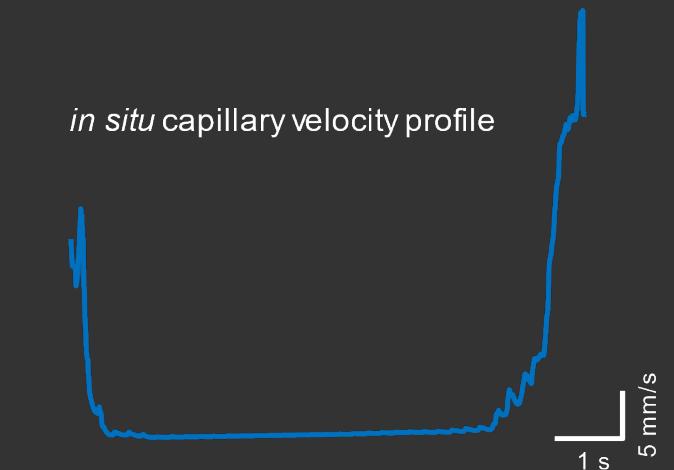
Single Capillary Reporter (SCaRe)



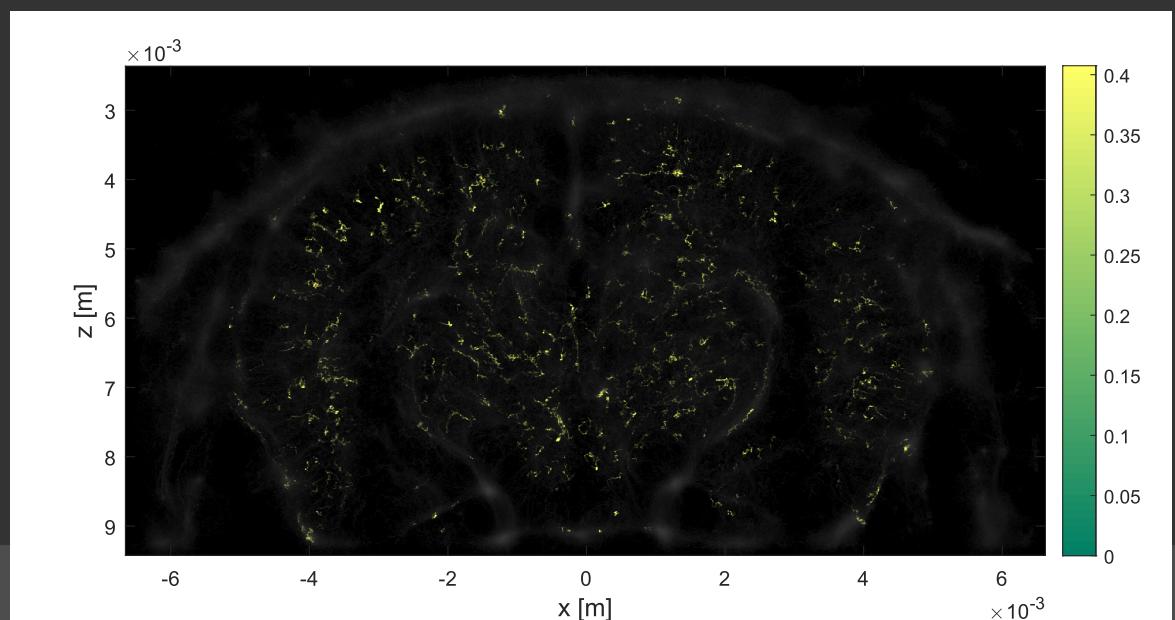
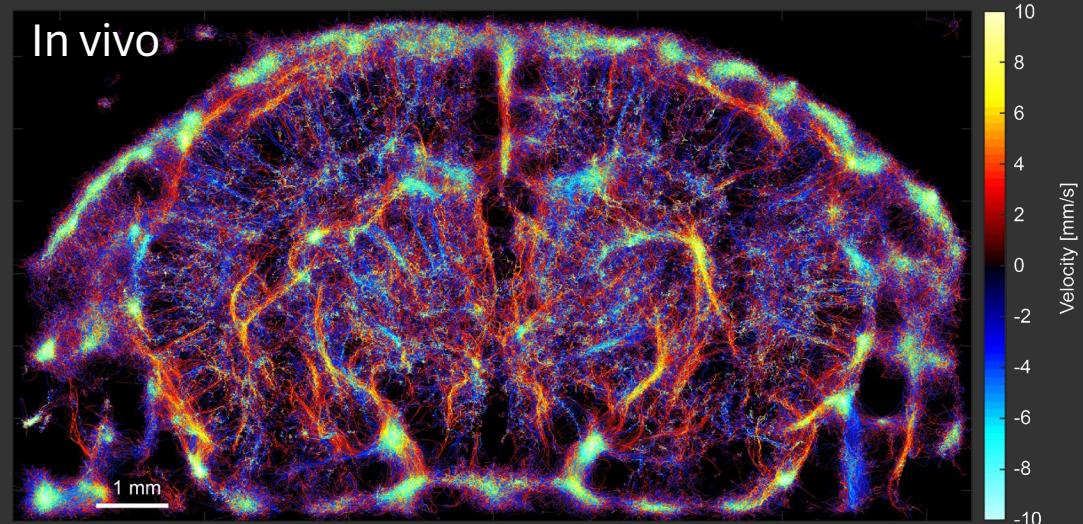
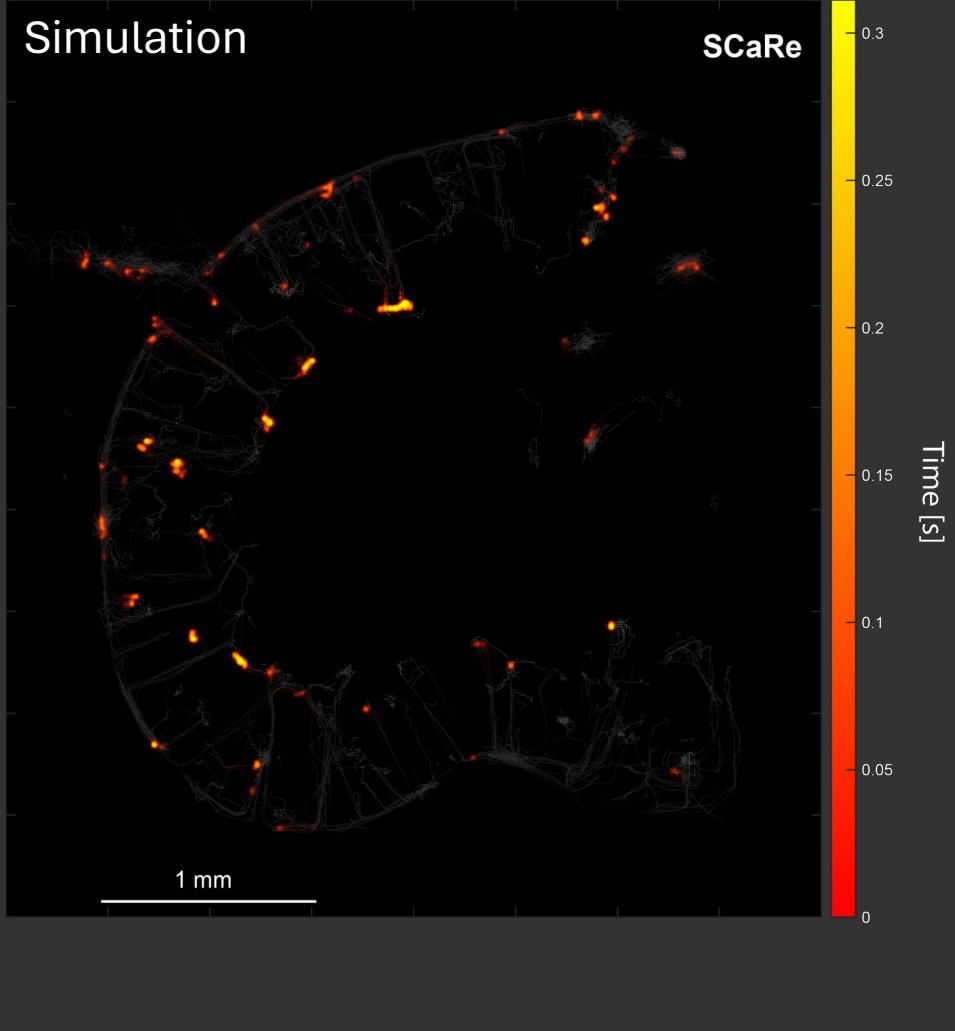
in vivo capillary velocity profiles



in situ capillary velocity profile



SCaRe-ULM maps capillaries throughout the whole brain



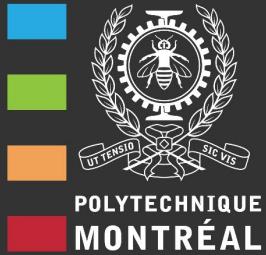
Conclusions

- Computational simulation of microbubble flow through a fully-enclosed microvasculature network indicates that conventional acquisition sequences under samples CTH
- Long ensemble SVD enables tracking microbubbles over 1 second
- SCaRe ULM can map singular capillaries without the need for multiple traversing microbubbles



Future Work

- Simulate microbubble flow in pathological synthetic models
- Devise new strategies to further push the length of our tracks
- Refine statistical determination of single capillaries and explore in pathological *in vivo* animal models



Provost Ultrasound Lab



Bourses postdoctorales
Banting
Postdoctoral Fellowships



INSTITUT DE
CARDIOLOGIE
DE MONTRÉAL



MONTRÉAL
TRANSMEDTECH
INSTITUT
LIVING LAB

LE-SVD leads to longer tracks and more capillaries

Type	Number of Tracks [N]	Max Track Length [s]	Number of Capillaries [N]	Mean CHT	STD CHT
SVD 20/1000, Ens 1000	143462	0.4189	3	0.1769	0.0312
SVD 20/1000, Ens 6000	222687	0.5148	8	0.1748	0.0423
SVD 20/1000, Ens 6000 Track-pairing	737837	0.643	91	0.2092	0.0557
SVD 20/6000, Ens 6000	352822	1.3589	118	0.1876	0.0842
SVD 20/6000, Ens 6000 Track-pairing	732669	1.3589	838	0.2422	0.1107