simula

Kristian Augusts gate 23 | 0164 Oslo | Norway
post@simula.no

+47 67 82 82 00
simula.no

Oslo, Norway
March 5, 2025

Dear Editors,

On behalf of the authors, I write to submit the attached manuscript titled **In-silico molecular enrichment and clearance of the human intracranial space** by Marius Causemann, Miroslav Kuchta, Rami Masri, and Marie E. Rognes for consideration as an Article in Nature Communications.

How are waste products cleared from the brain and its environment? With the discovery of the glymphatic system in 2012[1] and meningeal lymphatic vessels in 2015[2], this question has reemerged as the subject of intense research over the last decade. What is clear is that blood vessel pulsatility as well as other pressure changes within the skull are crucial mechanisms driving these systems[3]. However, despite thousands of research articles on these topics, no study has been able to establish how sufficient pressure differences emerge nor explain the solute enrichment and clearance patterns observed in humans[4]. At the core of the matter is the problem that it is nearly impossible to understand this system by examining a single scale, for instance the surroundings of a single blood vessel, or even networks of blood vessels. Instead, there is a fundamental need to bridge the scales from the microscopic to the macroscopic, and to translate between theoretical, experimental, and clinical findings.

In our manuscript, we present a unique multiscale in-silico model of solute enrichment and clearance of the brain, allowing for precise predictions of the interplay between vascular pulsatility, brain fluid and pressure dynamics, and structural features. Our approach offers a groundbreaking opportunity to shed light on these crucial, yet poorly understood, physiological mechanisms by bridging scales – both in time (from vascular pulsations at a few Hz to enrichment patterns developing over hours and days) and space (from perivascular channels surrounding individual blood vessels to large scale clearance of the brain and its environment). By applying this model, we discover that the balance between fluid production and intracranial pulsatility plays a crucial role in shaping enrichment patterns; that low-frequency vasomotion in surface periarterial spaces is in fact sufficient to explain human perivascular enrichment patterns, even in the absence of structural compartmentalization; and that enlarged surface periarterial

[1] Iliff et al, "A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β", *Science Translational Medicine*, 2012.
[2] Louveau et al, "Structural and functional features of central nervous system lymphatic vessels", *Nature*, 2015; Aspelund et al. "A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules" *Journal of Experimental Medicine*, 2015.
[3] Mestre et al, "Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension", *Nature Communications*, 2018.
[4] Eide and Ringstad, "Functional analysis of the human perivascular subarachnoid space", *Nature Communications*, 2024.

simula

Kristian Augusts gate 23 | 0164 Oslo | Norway
post@simula.no

+47 67 82 82 00
simula.no

spaces directly impair enrichment and clearance. Crucially, this openly available modelling platform lays a new foundation for in-silico predictions of tailored drug delivery to the brain and for early diagnostics of impaired brain clearance in neurodegenerative diseases.

In summary, we consider this manuscript to be appropriate for Nature Communications because it represents a multidisciplinary breakthrough – a decisive advance both within computational mathematics and the neurosciences – that defines a new technological route towards predicting molecular enrichment and clearance of the human brain.

All authors have approved the manuscript for submission. The manuscript has not been published or submitted for publication elsewhere[5], and we declare that we have no competing interests.

Yours sincerely,

Marie E. Rognes, PhD
meg@simula.no
https://orcid.org/0000-0002-6872-3710

Chief Research Scientist
Department of Numerical Analysis and Scientific Computing
Simula Research Laboratory

Deputy Director
K. G. Jebsen Centre for Brain Fluid Research

[5] A version of the manuscript has been deposited at the public preprint server bioRxiv: https://doi.org/10.1101/2025.01.30.635680