

The way of life: The network challenge of blood flow in the brain

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Few biological facts are as striking and counterintuitive as the brain's energy economy. Despite consuming more energy per unit mass than any other organ, the brain maintains only minimal energy reserves. It is exactly this mismatch that leaves brain function critically dependent on a continuous and precisely regulated blood supply. Consequently, deciphering how cerebral blood flow is controlled is central to understanding healthy brain function. This need is sharpened by the fact that neuronal activity can elicit rapid and highly localized surges in energy demand that must be met almost instantaneously. Ji et al. (1) elegantly combine theoretical analysis with in vivo data to show that flow regulation in the brain is a true network problem.

The process by which neuronal activity regulates cerebral blood flow is known as *neurovascular coupling* and has been the subject of sustained investigation since the late nineteenth century (2). Because this tight link between neural activity and local increases in perfusion is a defining feature of healthy brain function, it forms the physiological foundation of widely used imaging modalities, including BOLD fMRI and PET. Disruptions in neurovascular coupling and the resulting impairment in flow regulation have been reported

across many of the most prevalent neurological disorders (2), from Alzheimer's disease to poststroke pathology, making them an important biomarker for diagnosis and to monitor disease progression.

In the past years, substantial progress on some aspects relevant for neurovascular coupling has been made. For example, in identifying the capacity of different vascular mural cells in changing vessel diameters along the vascular path from artery to vein (3). Yet, a fundamental question remains: How can precise and reliable blood flow control emerge in a vascular network composed of millions of

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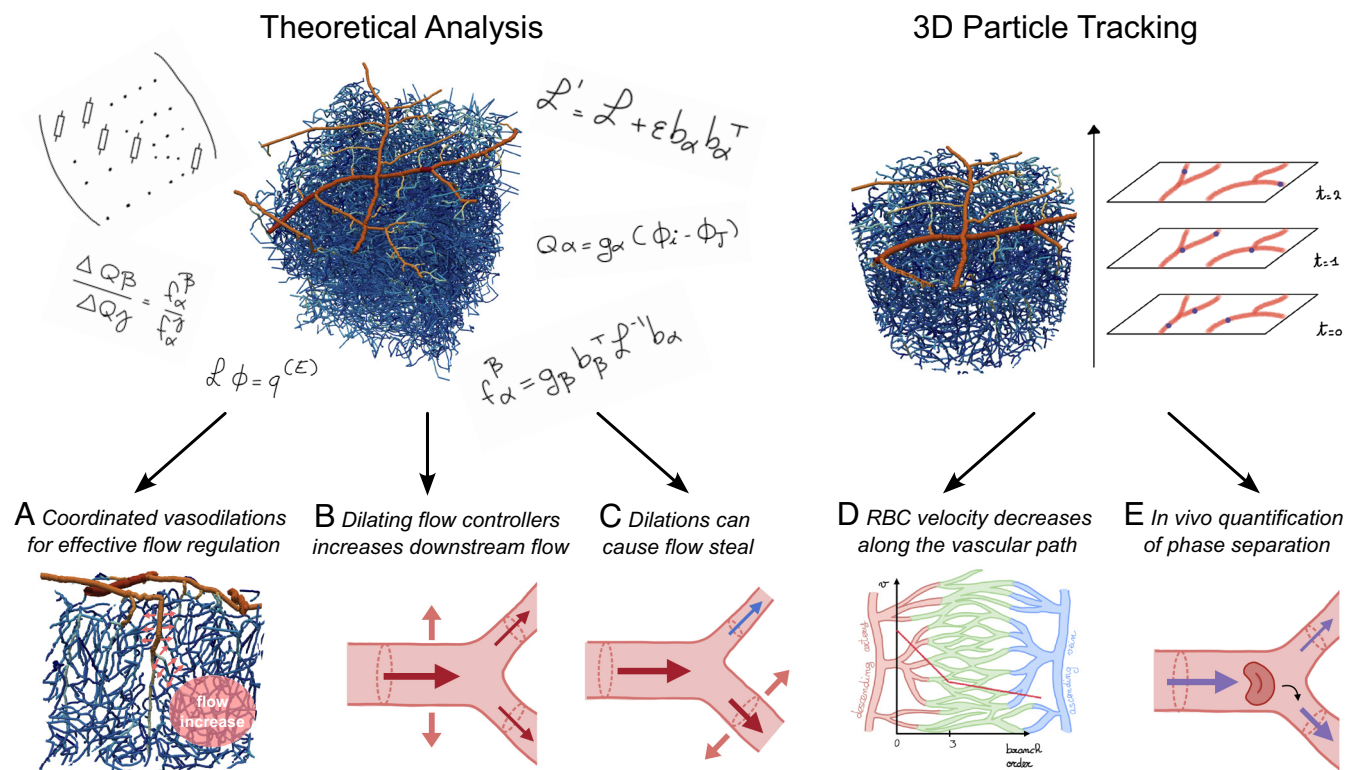


Fig. 1. Overview of the key conclusions obtained in the work of Ji et al. (1) based on theoretical analysis (A–C) and 3D in vivo particle tracking (D and E). The multi-part figure (Upper row) shows realistic microvascular networks that match datasets used for theoretical analysis and particle tracking in size but are based on data obtained in Blinder et al. (9).

interconnected vessels? Addressing this question is challenging for several reasons. First, the cerebral vasculature forms a dense and interconnected network spanning vessel diameters from only a few micrometers to more than one hundred (4). Second, blood flow itself is heterogeneous and fluctuating even at baseline (5, 6), which obscures the detection and interpretation of perfusion changes. Finally, vasodilatory responses are highly dynamic and often overlap across multiple vessels, making it difficult to disentangle cause and effect in vivo (2).

Ji et al. elegantly combine theoretical analysis with in vivo data to show that flow regulation in the brain is a true network problem.

Combining theoretical analysis with unprecedented in vivo imaging of microvascular perfusion, Ji et al. (1) directly confront these long-standing challenges. Central to their work is an innovative particle-tracking algorithm tailored to the unique features of microvascular blood flow, where both flow direction and velocity can change abruptly at vascular bifurcations. By iteratively integrating information from the vascular network topology with local velocity estimates, the authors are able to robustly identify and track fluorescently labeled red blood cells (RBCs) across the network. This strategy yields an exceptional dataset, with approximately 1.2 million RBCs tracked across more than 3,000 vessels within a sizable tissue volume of 800 μm in diameter and 550 μm in depth. Alternative techniques either provide larger fields of view but lack volumetric information (7) or require prohibitively long acquisition times (5, 8). Both points severely limit the ability to capture microvascular flow dynamics. By overcoming these limitations, Ji et al. achieve a unique combination of scale and speed that enables network perfusion to be studied, for the first time, in its characteristic heterogeneous and fluctuating state.

The cortical vasculature exhibits a hierarchical organization, where arteries and veins penetrate the cortex perpendicular to the surface and are connected by a mesh-like capillary bed (4). Leveraging their novel tracking algorithm, Ji et al. quantify flow speed and variability along the entire vascular trajectory from descending arterioles to ascending venules. Those recordings reveal a continuous decline in flow velocity that is most pronounced within the first few branches downstream of the arteriole (Fig. 1D). Interestingly, also velocity profiles along individual vessels can be resolved. The observed variations in flow speed within a single vessel likely reflect a combination of locally varying diameters, the averaging of discrete RBC trajectories along one vessel, and secondary effects arising from the particulate nature of blood itself. Together, these observations underscore the complexity and stochasticity of microvascular flow and raise the fundamental question to what extent single vessels measurement provide a representative picture of microvascular perfusion at the network level?

Combining information on vascular connectivity with branch-specific flow velocities also enables a quantitative analysis of how diverging and converging bifurcations are distributed along the vascular path. Consistent with previous

computational studies of cerebral blood flow (10), diverging bifurcations are found to preferentially cluster near arterial segments. Importantly, in combination with the authors' theoretical analysis, this topological trait takes on functional significance because divergent bifurcations emerge as *flow controllers* that are ideally suited to shape and regulate perfusion across the network.

The theoretical framework developed by Ji et al. rests on representing the microvascular network as a spatial graph, in which vessels form edges connecting branching points.

From vessel length and diameter, the flow resistance for each segment can be calculated. This allows the construction of a graph Laplacian, i.e., a compact mathematical description of how network structure constrains pressure and flow.

Within this formulation, the dilation of a single vessel corresponds to a rank-1 modification of the Laplacian enabling to analytically assess how a local resistance change redistributes flow throughout the network. Importantly, this approach is purely based on topological network characteristics and does not require knowledge of the baseline flow field, which would be necessary to predict absolute perfusion changes. Instead, it offers a principled way for uncovering how individual vessels shape blood distribution and for pinpointing vessels that exert control at the scale of the vascular network.

Based on this robust theoretical framework, Ji et al. (1) show that substantial increases in blood flow cannot be achieved through isolated vessel dilation but instead require coordinated vasodilatory responses across multiple segments of the network (Fig. 1A). In doing so, the work provides a theoretical basis for established experimental observations, such as the propagated vasodilation (2) to increase perfusion during neurovascular coupling. More broadly, the results challenge simplified models that treat vascular networks as collections of independent pipes, demonstrating instead that flow changes emerge from the collective properties of the interconnected network.

Focusing on perfusion changes in immediately adjacent vessels, the authors analytically demonstrate that dilation of the parent branch at a divergent bifurcation leads exclusively to increased flow in both downstream branches (Fig. 1B). This underscores the role of divergent bifurcations as primary *flow controllers* and fits well with their preferential position on the arterial side along the vascular path. In contrast, dilation of one daughter vessel at a divergent bifurcation induces a flow steal from the competing branch (Fig. 1C). Ji et al. provide rigorous analytical support for this behavior, consistent with previous in vivo and in silico observations at individual bifurcations (10, 11). These results challenge the common intuition that vasodilation invariably increases local perfusion. This further might imply that not all vasodilatory responses are aimed at increasing flow but that some may be required to limit flow steal from other regions. This characteristic behavior puts further emphasis on the need for targeted vasodilation to effectively regulate flow.

An interesting extension to this theoretical foundation would be to examine how these principles translate to the redistribution of RBCs. This is particularly relevant because, at the microvascular scale, blood behaves as a biphasic fluid

in which plasma flow and RBC dynamics directly influence each another. Precisely, each RBC increases the flow resistance of a vessel, and at divergent bifurcations, RBCs do not divide in proportion to bulk flow. Instead, the branch carrying the larger flow tends to attract a disproportionately large fraction of RBCs (*phase-separation effect*). Together, these RBC-related effects partially balance outflow velocities at divergent bifurcations (6). While such biphasic effects are not expected to alter the main conclusions of Ji et al., they likely add an additional layer of complexity to flow regulation on the network scale and may directly contribute to the observed spatiotemporal heterogeneity of microvascular flow.

Importantly, the work of Ji et al. also provides valuable insight into our fundamental understanding of biphasic microvascular perfusion dynamics. Although the phase-separation effect has been recognized for approximately five decades (12), its quantitative characterization has been limited to measurements at two-dimensional bifurcations in the rat mesentery (13) or to computationally costly simulations resolving RBC deformation (14). Further in vivo quantification has been hampered by the technical challenge of simultaneously measuring flow velocities in all branches of a bifurcation across many sites. The method presented by Ji et al., which enables the tracking of millions of RBCs, allows to conveniently close this gap. Thereby providing in vivo evidence for the unequal RBC partitioning at divergent bifurcations (Fig. 1E). Moreover, this data offers the opportunity to quantitatively refine existing empirical laws (15) describing the phase separation effect. These laws are an indispensable component across in silico models describing microvascular flow (16). A more accurate quantification

of this effect could consequently help to substantially improve the fidelity of in silico flow modelling. Given that phase separation depends on local vessel diameters and vessel-specific hematocrit, additional high-resolution measurements of vessel geometry at selected bifurcations could further support this effort.

Taken together, the work of Ji et al. represents a substantial advance in our understanding of microvascular flow and regulation on different ends. Their theoretical analysis highlights the intrinsic difficulty of controlling perfusion at the network level and emphasizes the necessity of coordinated vasodilatory responses to effectively increase and distribute blood flow. Complementing this, the large-scale 3D particle tracking provides a powerful foundation for a broad range of future investigations. This, for example, could include studies of how microvascular perfusion is altered during aging or under pathological conditions. The approach might further open the possibility of probing dynamic changes during neurovascular coupling, particularly given that related techniques have demonstrated sufficient temporal resolution (17). Altogether, this work not only advances our conceptual understanding of the mechanisms governing cerebral blood flow but perhaps even more importantly introduces a long-sought tool for studying microvascular perfusion at an appropriate scale that resolves large vascular networks with high temporal resolution. This capability holds promise for uncovering the full complexity, adaptability, and functional benefits of the brain's highly dynamic microcirculation.

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