Modelling cerebrovascular pathology and amyloid beta spreading in Alzheimer's disease

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Alzheimer's disease (AD) is associated with the accumulation and dissemination of amyloid beta (Aβ) proteins in the brain, a process now known to be intimately linked with vascular dysfunction. Recent evidence demonstrates that Aβ oligomers cause contraction of microvascular mural cells, leading to capillary constriction and elevated flow resistance. In turn, this hypoperfusion enhances Aβ production and impairs its clearance, establishing a pathological positive feedback loop. In this talk, I will introduce a mathematical model that captures the interplay between Aβ dynamics and capillary function, incorporating both the local protein–vascular interactions and the prion-like propagation of Aβ. The model reveals a bistable regime in which both healthy and diseased states coexist stably, with a critical protein seed threshold required to initiate disease onset. We investigate how this bistability influences disease spread across the brain's structural connectome. Finally, we propose a novel mathematical formulation of the two-hit vascular hypothesis, showing how spatially localized perfusion deficits—such as those arising from embolic strokes or leptomeningeal atherosclerosis—can act as initiators of global disease progression.