A critical transition from homeostasis to a self-propagating spread of neuronal damage induced by glia-neuron crosstalk in inflammation

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We study the role of the cross-talk between neurons and their supporting cells for the formation of areas of neuronal damage in inflamed tissue. This crosstalk can constitute a positive feedback loop leading to a critical transition from a homeostatic to an apoptotic state which can help understand the progression of lesions of neuronal damage in neurodegenerative diseases such as multiple sclerosis (MS), Alzheimer or Parkinson's disease. These diseases, which affect millions of people worldwide, have unique triggers and molecular processes, but share the common hallmark of chronic inflammation in the brain tissue.
Here, we single out the propagation of a lesion in spatially heterogeneous tissue in MS. Usually, MS starts with a relapse-remitting course. This disease course is thought to be mainly driven by immune cells which are activated in the periphery and then cross the blood-brain-barrier and cause demyelination and neuronal loss [1]. In the later progressive phase, the innate immune system of the brain tissue plays a more prominent role in the disease progression [2], possibly leading to a self-propagating feedback loop [3].
We identify two key candidates responsible for a self-propagating inflammatory spread of a lesion: spatially localised damaged neurons, and a network of supporting cells, namely microglia and astrocytes, spanning the whole brain tissue. In the healthy brain, neuronal damage activates microglia, which secrete targeted neuroprotective factors. In the inflamed tissue, microglia are in an overactivated state characterised by the secretion of toxic factors. This can set off a chain reaction, activating reactive highly neurotoxic astrocytes, which further damage neurons [4]. The balance between the strength of this dysfunctional neuron–glia–neuron interactions versus in-built homeostatic neuronal and glial effects can be decisive for the outcome of a lesion.
We propose a phenomenological reduced model with two variables: one field variable in space, representing the departure of glia from their beneficial homeostatic state and the corresponding release of neurotoxic factors. The second discrete set of variables represents the damage per neuron. The system contains two nonlinearities: First, the glial sensitivity increases with neuronal damage. Second, once the neurons exceed a threshold value of neuronal damage and become apoptotic, a predefined cell-debris clearance mode is activated.
We study the amount of overall neuronal damage per external perturbation (e.g. infiltration of immune cells) as a function of the connectivity of the tissue and the strength of the positive feedback loop. The critical transition between a parameter region in which neuronal damage is mainly caused by external perturbations, and a region in which the positive feedback loop leads to a self-propagating, expanding lesion, is presented. Propagation speeds are determined and three distinct regimes of inflammatory spread are identified: First, an increase in the local feedback loop or an increase in the diffusivity of neurotoxic factors leads to a spread fuelled by a high inflammation at the lesion rim. Second, impaired cell debris clearance allows for a very stable mode of slowly expanding lesions. Third, a baseline global insult to the system can lead to a destabilisation and a catastrophic accelerating lesion propagation.
Naturally, the brain tissue is a highly heterogeneous system, both across and within brain regions. We discuss the stability of the lesion propagation modes with respect to spatial heterogeneity, and implications for the phase diagram. Limitations imposed by the model assumptions, the transferability of the results to other neurodegenerative diseases, and similarities to other spreading critical transitions in biology and physics are discussed.

References

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