

# Brain-wide calcium imaging in zebrafish and generative network modelling reveal cell-level functional network properties of seizure susceptibility

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Epilepsy is a neurological disorder that causes recurrent seizures, but the underneath mechanisms are still unclear. Traditional methods, using data from humans, nonhuman primates, or rodents, have limitations in resolving the activity of single cells. An approach that captures the dynamics of individual neurons and their interactions within brain-wide networks could therefore be of great utility in understanding epilepsy. Zebrafish and calcium imaging offer such an approach, as they allow for simultaneous in-vivo recording of neuronal activity across the brain at cellular resolution.

Zebrafish share genetic and physiological similarities with humans and can exhibit seizure-like behaviours in response to various drugs. One such drug is Pentylentetrazol (PTZ), a pharmacological agent that blocks inhibitory GABAergic signalling, causing hyperexcitability and seizure-like activity. Additionally, mutations in the *scn1lab* gene, encoding a sodium channel, can also cause spontaneous seizures in

zebrafish. In this study, we used in-vivo light-sheet calcium imaging, brain-wide and at cellular resolution, on wildtype and *scn1lab*<sup>-/-</sup> mutant zebrafish larvae under baseline and post-PTZ conditions.

We utilised network analyses and computational modelling to statistically quantify differences in network topology and dynamics between two genotypes and conditions. Specifically, we examined the network of active neuronal cells involved in ictogenesis across microscopic to macroscopic scales. Our study reveals significant and consistent changes in brain network connectivity, indicating that *scn1lab*<sup>-/-</sup> mutations impact brain structure and functions. Additionally, we developed a generative network model (GNM) at the cellular level to explain the wiring principles governing the development of both genotypes and the effects of PTZ on the brain-wide functional network. This novel model highlights brain regions associated with genotype differences, seizure severity, and overall network excitability and synchronisation. Combining experimental data and mathematical modelling, our approach provides a novel perspective on the mechanisms of epileptogenesis at a breadth and resolution that traditional epilepsy studies cannot achieve.

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