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Computational biology of Alzheimer's disease: Modelling and investigation of NMDAR-mediated Ca^{2+} signalling at hippocampal dendritic spine in Alzheimer's disease

Alzheimer's disease (AD) is a devastating, incurable neurodegenerative disease affecting millions of people worldwide. Dysregulation of intracellular Ca2+ signalling has been observed as an early event, prior to the presence of clinical symptoms of AD and is believed to be a crucial factor contributing to its pathogenesis. Mathematical modelling and computational analyses offer great opportunities to overcome the experimental limitation to advance our understanding of Ca2+ dysregulations of AD. We developed a mathematical model of a CA1 pyramidal dendritic spine, integrating essential components and reactions related to N-methyl-D-aspartate (NMDAR)-mediated Ca2+ response in the dendritic spine. Using this model, computational experiments are conducted to mimic major alterations under AD conditions and these alterations in glutamate availability, as well as NMDAR availability and activity, are studied individually and globally. Through simulation, we investigate how they are involved in the Ca2+ dysregulation in the dendritic spine and predict the most sensitive factor of Aβ that affects the Ca2+ response. To further study the effects of alterations of NMDARs in their roles in downstream events, a CaMKII state transition model is added to the downstream of our Ca2+ model. CaMKII state transition is an important event in the early phase of long term potentiation (LTP), a critical process in memory formation. We investigate the internalisation of synaptic NMDAR on the CaMKII state transition to gain insights into the disturbances from alterations in synaptic NMDAR in the emergence of LTP in AD.

Recent Publications

1. Liang J, Kulasiri G D and Samarasinghe S (2017) Computational investigation of Amyloid-β-induced location- and subunit-specific disturbances of NMDAR at hippocampal dendritic spine in Alzheimer's disease. PLoS One 12(8):22.
2. Kulasiri D and He Y (2017) Computational systems biology of synaptic plasticity: modelling of biochemical pathways related to memory formation and impairment. London, UK: World Scientific Publishing Europe Ltd. doi: 10.1142/Q0097.
3. Kulasiri G D, Liang J, He Y and Samarasinghe S (2017) Global sensitivity analysis of a model related to memory formation in synapses: Model reduction based on epistemic parameter uncertainties and related issues. Journal of Theoretical Biology 419:116–136.
4. He Y, Kulasiri G D and Samarasinghe S (2016) Modelling bidirectional modulations in synaptic plasticity: a biochemical pathway model to understand the emergence of long term potentiation (LTP) and long term depression (LTD). Journal of Theoretical Biology 403:159–177.
5. Liang J, Kulasiri G D and Samarasinghe S (2015) Ca2+ dysregulation in the endoplasmic reticulum related to Alzheimer's disease: a review on experimental progress and computational modeling. BioSystems 134:1–15.

Biography

Don Kulasiri obtained his PhD in BioEngineering in 1990 at Virginia Tech, USA. He has been an Academic for 28 years at Lincoln University, New Zealand and a Chair Professor since 1999. He founded the Centre for Advanced Computational Solutions (C-fACS) in 1999 and currently leads the centre. He has been a Visiting Professor at Stanford University, Princeton University, USA, and has been a Visiting Scholar at the Mathematical Institute, Oxford University, UK since 2008. He has a large group of PhD students working on modelling of synaptic plasticity related to memory including its impairment under disease conditions.

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