

## A reaction-diffusion model of the action of the neuromodulator adenosine

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**Background.** Neurons communicate using a variety of media such as fast synaptic neurotransmitters, direct electrical connections, electrical-field mediated coupling and the action of neuromodulators released into and diffusing through the extracellular space. Neuromodulators have been largely neglected by the modeling community; however, comprising compounds such as dopamine or acetylcholine, they can have powerful and long lasting effects. One important neuromodulator that protects the brain during periods of high activity is *adenosine*. This compound is released from networks and acts to weaken synapses and reduce the excitability of neurons. Recent work at Warwick Life Sciences using adenosine biosensors has demonstrated that after release adenosine is rapidly broken down by enzymes. This suggests that, though diffusive, its effect might be highly localized in time and space, contrary to the prevailing view on volume-mediated neuromodulators.

**The aim** is to develop computational and analytical models of the spatio-temporal dynamics of the release, diffusion and breakdown of adenosine in neocortical tissue informed by experimental data available from collaborators at Warwick. Of particular interest will be the effect of the tortuosity of the extracellular space, the distribution and density of the enzyme that breaks down adenosine, and the effect of spatial dimension in the resulting reaction-diffusion system - it is well known that predictions from the mean-field rate approaches are often incorrect as they ignore the build up of correlations (the classic example being  $A+A \rightarrow 0$  which has concentration scaling of  $1/\sqrt{t}$  in 1D rather than  $1/t$  as would be predicted by a rate equation).

**Techniques.** The computational approaches (low risk) will comprise (i) numerical solutions of mean-field rate-equation models in the 2D or 3D geometry of neural tissue and (ii) Monte-Carlo particle diffusion simulations. Analytical solutions to the mean-field models will also be sought that also take into account the presence of the biosensors used to measure the concentrations of adenosine. A field-theoretic approach is possible, but might be too ambitious for a mini-project (this would be dependent on the interests of the student).

**Deliverables and beneficiaries.** The direct beneficiaries are the experimental and theoretical modeling communities working on neuromodulators (particularly the world-leading adenosine research group at Warwick). Spatial effects in neural tissue have been neglected in previous treatments that have only considered the internal metric of the networks themselves. The role of diffusing neuromodulators is one area where a spatial approach is absolutely essential.

**Potential for a follow on PhD project.** The cross-talk between fast electrical activity in neural networks and diffusive neuromodulators is a rich area of research for modelers that has yet to be exploited. There is a wealth of unique experimental data at Warwick Life Sciences on the actions of adenosine that would provide an empirical basis for a more detailed project. Furthermore, the system is likely to be amenable to the field-theoretical renormalization group approach to reaction diffusion systems. I would be very interested in pursuing this angle if a student were interested.

**Reading material**