Our research group develops and applies converging multi-scale multi-disciplinary methods to address some of the most fundamental questions in neuroscience and to contribute to drug design and discovery.

**Brain energetics and convergence of neurochemical and functional activity patterns in rodent brain:** fMRI is widely used to study the operational organisation of the brain. The exact relationship between the measured functional signal and the underlying neural activity, however, is yet unclear. Previous studies (Logothetis et al., 2001; Caesar et al., 2003) have already examined the relationship between large-scale electrical (in particular the local field potentials) and functional activity patterns. However, the large-scale neurochemical context, which is of utmost importance for drug design and development, has so far not been considered. This gap is most likely due to the experimental limitations of neurochemical measurement techniques by biosensors or in vivo microdialysis. While these methods allow the observation of local drug-induced alterations of extracellular neurotransmitter concentrations at a consistent spatiotemporal scale as fMRI studies, simultaneous observation of the drug effects on the entire brain is not possible, and as such global neurochemical activity patterns induced by drugs cannot be retrieved. To overcome this dilemma, we will utilise multi-scale mathematical/biophysical modelling and simulations as well as converging multimodal imaging and neurochemical measurement techniques. In particular, novel mathematical models using non-linear multi-dimensional network and functional analysis, infinite dimensional dynamical systems, algebraic and differential geometry and statistical mechanics will be developed, in order to study the convergence and robustness properties of neuronal energy functionals and thereby bridging the gap between neurochemical and functional observations.

**Atomistic understanding of ligand-receptor interactions, drug design and discovery:** Drug effects represent complex spatiotemporal multi-scale problems that are usually addressed by local nanoscopic investigation of drug-receptor interactions. Here, we take a different route, yet more accurate, and apply a converging combination of molecular dynamics simulations, docking, cellular single-channel recordings, generation of novel transgenic lines of animals, and behavioural experiments to investigate the consequences of molecular pro-
cesses on systems level. We have already validated this approach to shed light on the ef-
facts of drugs of abuse on neuromuscular processes and intend to continue this strategy to
improve treatment for rare congenital neuromuscular disorders.

**Disease dynamics and prediction of behavioural patterns:** Disease dynamics can be
characterised by features of complex systems such as critical phase transitions, but in the
biomedical field little evidence has been provided for this concept so far. Technological ad-
vancements are now making it possible to measure the intensive longitudinal data (ILD) nec-
essary to capture pathologically-relevant signal components exhibiting the multi-scale com-
plexity of disease dynamics. Using a well-established models of neuropsychiatric diseases in
rats as examples of disease onset and progression, we apply multi-scale computational ap-
proaches to extract dynamical characteristics of massive high-resolution measurements of
rat behaviour in 1+3 dimensions. We have been able to show a stage-by-stage dynamical
phase transition as a function of instability of drinking behaviour and circadian rhythms, and a
resultant increase in low frequency, ultradian rhythms and we will apply the approach to re-
verse engineer behavioural patterns causing disease onset.

**Nanotechnology and brain activity:** In the past few years, nanoparticles with unique physi-
cal properties have been developed that enable sensitive measurements of magnetic fields,
temperature, etc. We intend to investigate the potential of a specific category of such parti-
cles to probe brain function in vitro and in vivo.

**Membrane geometry and multi-scale dynamics:** Plasma membranes are self-assembled
highly flexible supra-molecular aggregates that are involved in various chemical reactions es-
sential to cellular function. These liquid crystalline structures also have the ability to undergo
an array of dynamical conformational transitions, which are vital to many biological pro-
cesses. An example of particular interest in neuroscience is the process of vesicular fusion
and formation at synaptic terminals. Following the influx of calcium ions into the neurons,
transmitter-containing lipid bilayer spheres of ~40 nm diameter diffuse within the intracellular
space and through a specialised machinery fuse with the presynaptic membrane. Recent
studies have suggested that this fusion process is triggered by extreme membrane curva-
ture. In order to maintain “equilibrium” i.e. the necessary reservoir for synaptic transmission,
the membranes subsequently form vesicles as a dynamical response to local perturbations.
Due to spatiotemporal limitations in describing membrane properties in terms of dynamics of
individual atoms, continuum models have been used commonly to characterise membrane-
related processes. These continuum models typically treat the bilayer as a two-dimensional
linear-elastic sheet with surface tension. Parameters like the bending modulus, the surface-
tension coefficient, and spontaneous curvature are typically used to characterise the membrane properties. Forces on the membrane are usually modelled as entropic forces that arise from proteins attached to the surface or as stochastic forces due to the Brownian fluctuations of the surrounding medium. However, because of the typical formulation of these models, only small displacements and small surface curvatures can be accurately modelled. Recently, mathematical models have been developed to describe the static and dynamic shape of these vesicles in fluids by energetic variation analysis and phase field Navier Stokes equations. Furthermore, reaction-diffusion partial differential equations have been utilised to simulate the diffusion of lipids on cell membranes. Yet, less attention has been paid so far to the multi-scale dynamics and geometrical aspects of the vesicle fusion and formation process. The process of bubbling and fusion of (2+1)-dimensional Riemannian manifolds in the (3+1)-space have already been thoroughly investigated in geometric analysis as well as string and d-brane theory in physics. However, the representation of the biological membranes in similar robust mathematical formalisms and the identification of relevant action functions (such as the entropy, energy, and curvature) responsible for vesicular processes is still missing. Approaches in this direction are challenging since they require a balance between abstract mathematical formalisms and biological relevance. Thereby, the outcome is not only critical for understanding the vesicular release process at synapses, but may further open novel perspectives for pharmacological treatment strategies.