**Project title**: Single particle divergences from pure diffusion: inference of Brownian motions.

*Background*: With the advent of single particle tracking (SPT) of single fluorescent molecules (10nm, ms resolution), it has been possible to directly see how proteins (and lipids) move in cell membranes. A diversity of behaviours have been reported, from trapped (corralled) motion, e.g. by cytoskeletal barriers, to heterogeneity in the environment, e.g. lipid rafts. Essentially, there is a hierarchy of ordering in the cell membrane from 10nm to microns that affect molecule diffusion, Lingwood & Simons, whilst different molecules may have specific interactions, possibly due to their function which will alter their motion. However, since this is a stochastic system, with short trajectories (due to bleaching), how can we ensure that the interpretation is robust? And can we use the trajectories to get a better idea of the underlying mechanisms?

*Objectives*: Develop a suite of models for diffusion of particles in 2D and algorithms for their inference using Bayesian techniques. Use model discrimination methods (such as AIC, BIC, evaluating Bayes factors) to determine which model best describes the data. Test algorithms on simulated data. Use algorithms on real data.

*Importance*: Understanding molecule motion in membranes is crucial to understanding transport processes in membranes and how interactions in the membrane affect their movement and their function.

*What the student will do*:

Learn about random walks, Brownian motion and diffusion processes (stochastic models). Learn about molecule diffusion on membranes and the hierarch of ordering processes in membranes (Kumsumi et al, Lingwood & Simons.).

Examine the existing analysis methods, including a hidden Markov model for molecule binding, Das et al.

Learn about model discrimination techniques in an MCMC sampler context and hierarchical modelling.

Design inference algorithms for a range of diffusion processes models within a Bayesian context. Essentially we will use a Brownian motion model for a diffusing particle in a variety of potentials and compute the posterior probability of the parameters given the data. Then we will be able to test if the criteria for free diffusion are satisfied, i.e. we test if particular divergences from free diffusion are present.

Develop and implement Markov chain Monte Carlo (MCMC) algorithms for these models. Test on simulated data.

Implement methods for model discrimination, i.e. determining which model fits the data best whilst allowing for model complexity. Test on simulated data and compare to existing methods for picking up confinement.

Using data on lipid movement in membranes (from Eggling lab, MPI, Eggeling et al.), determine whether lipids are undergoing free diffusion.

**Deliverables**: Code for simulating different diffusions. Code for inference of different diffusion models. Code to determine which models are best supported by particular data sets.

**Skills needed**. Good MatLab programming skills will be needed. An understanding of stochastic processes (Markov chains, random walks), Bayesian inference and MCMC in particular is essential.

**References**

1. Das et al. PLoS Comput Biol., 5:e1000556, 2009;
2. Eggeling et al. Nature, 457:1159;
3. Kumsumi et al. FEBS Letters, 584:1814;
4. Lingwood & Simons. Science 327, 46;

**Consumables budget**: £ 100

**Scope for a PhD**. This project could be extended to a PhD working with Christian Eggling (MPI) on either FCS analysis and extending the models to different types of heterogeneity. Ideally we would aim to integrate different data types (SPT and FCS) and thus achieve a better understanding of the divergences from Brownian motion across increasing spatial scales, perhaps finding signatures for rafts and corrals. Another direction would be to modelling of particles with drift, e.g. microtubule ends.