How does general anaesthesia work? Although general anaesthetics are in use for over 150 years, the outlines of the answer began to emerge only in the last decades. There is now sufficient evidence that common general anaesthetics, such as propofol or isoflurane, are GABA_A receptor agonists, i.e., they act by potentiating inhibitory synapses throughout the central nervous system and in the cortex in particular. This understanding of the fundamental mechanism of general anaesthetics action does not however explain how they produce a stable state of sedation and unconsciousness. Examination of the neurophysiological effect of anaesthetics, using electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and recording of activity of individual neurons shows that under deep anaesthesia cortical activity is dominated by intervals of 1-4 seconds of complete silence (Down states), with active intervals of somewhat shorter duration in between (Up states). It is generally accepted that the reason for loss of consciousness in this condition are the Down states, and even more importantly the fact that Up and Down states happen in different times across the cortex, which means that different parts of the cortex are not active simultaneously and thus are unable to “talk” to each other.

Loss of consciousness, however, occurs also with more superficial level of anaesthesia, which does not produce the Up-and-Down regime of activity. The above explanation cannot therefore account for the loss of consciousness in this case. It is possible that complete cessation of neuronal activity, as observed in the Down states, is not actually necessary, and a reduction of firing rates of cortical neurons, which is achieved even under superficial anaesthesia, is sufficient to produce unconsciousness. An alternative hypothesis, backed by some recent studies and our preliminary data is that it is not the reduction in firing rates per se that causes the unconsciousness, but reorganisation of the patterns of cortical activity – i.e., the change in identity and order of spiking of neurons under anaesthesia vs wakefulness or sleep.

In this project we will address this question by performing in vivo recordings of the very same populations of cortical neurons across the three brain states of wakefulness, sleep and anaesthesia. Such experiments can be conducted in mice using high-density silicon probes chronically implanted into their cortex. Although an abundance of data exists on each of the three brain states individually, very little is
known about how the activities of a cortical neuronal population in these three states relate to each other at the single neuron resolution. In addition to testing the basic hypothesis of the existence of population activity reorganisation, we will ask whether this reorganisation is similar in different cortical areas. Based on the way sensory stimuli are processed under anaesthesia in primary sensory and higher association areas of the cortex, we will test the hypothesis that anaesthesia-induced reorganisation of population activity is qualitatively different in primary sensory areas when compared to frontal cortical areas. This hypothesis will be tested by performing the recordings in cortical areas of both kinds.

In order to better understand the mechanisms of reorganisation of population activity under the influence of anaesthetics, the in vivo experiments will be supplemented by in vitro recordings from cortical slices using multi-electrode arrays. In vitro experiments provide a highly controlled experimental conditions, suitable for example for elucidating the precise dependence of activity on drug concentration, or on combination of several anaesthetic drugs.

Techniques that will be undertaken during the project (  

A) In vivo population recordings using high density silicon probes (area of expertise of principal supervisor).

B) In vitro population recordings using high density multielectrode arrays (area of expertise of the co-supervisor).

C) Analysis of the highly dimensional datasets using Python and/or MATLAB software (area of expertise of the principal supervisor).