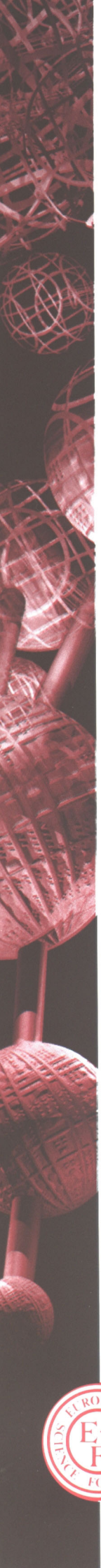

The meso-telencephalic dopamine consortium (DopaNet)

an ESF Scientific Network

Recent advances in our understanding of the chemistry and molecular biology of the synapse coupled with the availability of the underlying genomic sequences has created the potential for unravelling the complex processes of neuronal signalling. These processes involve too much detail for qualitative analysis, and so understanding them requires mathematical models using quantitative data regarding the identity, localisation and properties of the different molecules involved. The ultimate objective is to develop computational simulations that can be used to predict quantitatively the changes in behaviour of neuronal systems in response to perturbations in their genetic or biochemical environment. This would have numerous applications both in deepening our scientific understanding of neuronal processes and testing potential therapeutic drugs for conditions such as Parkinson's disease associated with neuronal malfunctions.

To meet this objective, it is necessary to integrate proliferating volumes of experimental data into databases and then analyse patterns via data mining in a consistent manner. These tasks are a major focus of this Network, which is establishing consistent standards both for obtaining the experimental measurements and performing the subsequent data mining.

This Network provides Europe with a great opportunity to catch up and even overtake the US in the critical field of neurotransmission modelling. Although several large proteomics projects (focusing on proteins and cellular mechanisms rather than genes and their transcription) are underway in the US following the launch of the Alliance for Cell Signalling, they mostly avoid neural systems. This is largely because the neuron is one of the most complex cells in the body, as a result of which neural transmission has so far been considered too difficult to simulate in detail.

However recent developments, notably the availability of complete genomic sequences, make it possible to transcribe all the genes involved in a particular neural pathway, and then localise the mRNA translation as a prelude to isolating and quantifying the proteins involved. These are the first tasks being undertaken by this Network focusing on the meso-telencephalic dopamine pathway.

Although meso-telencephalic dopamine is just one of many pathways, it involves three neurons that together are represented in almost all neurotransmitters and neuropeptides. Therefore the knowledge gained by this Network, although acquired through study of a specific neuronal system, will serve a wide scientific audience and be valuable for research into other neural pathways.

Furthermore the diversity of the meso-telencephalic dopamine pathway means it is involved in many cognitive and behavioural functions, and is implicated in a number of neuropathological conditions such as Parkinson's Disease, schizophrenia, and Huntingdon's chorea. On top of that the pathway is directly responsible for drug addiction. Opioids, cocaine, amphetamines, nicotine, and caffeine, all enhance the dopamine response at the striatal and mesencephalic levels. Alcohol may also affect the striato-nigral feedback. All these factors combined to make the meso-telencephalic dopamine pathway a starting point for neuronal modelling.

Following the localisation of proteins involved in the meso-telencephalic dopamine pathway, the Network will study the biochemistry of proteins quantitatively across all the principle modes of interaction, i.e. synthesis, modification, degradation, transport, assembly, and function. This will involve a major data mining effort lasting for three to five years.

This mining will yield information needed for the second phase of the project, to assemble the various protein molecules into supramolecular structures that perform various roles in the pathway. This second phase overlaps with the first, and is expected to take a similar time.

Finally quantitative models and simulations will be designed based on experimental data, in order to identify and understand precisely the mechanisms involved in neural signalling. In common with other proteomics projects and branches of systems biology, these models will then become the hub of an iterative refinement process whose ultimate goal in this case is realistic simulation of whole neurons. This will allow sets of interconnected neurons to be designed.

This iterative process will start with generation from the models of specific predictions of neuronal behaviour under varying conditions. These predictions will then be tested experimentally, and the resulting data used to refine the models, which in turn are used to make more predictions, hopefully more accurate than the preceding ones.

This project involves differing lines of experiment and data handling proceeding in parallel, and several technical sub-committees, meeting frequently, have been charged with ensuring that consistent measurements and data handling techniques are employed. The data will be stored on common computer platform holding the database and shared analysis tools, linked to various dedicated machines for data mining at the various member sites.

This Network was approved by the ESF Network Group in November 2002 for a three-year period

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