The CoCoMac project in the context of European neuroinformatics initiatives.

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Abstract. The importance of neuroinformatics to improve and organize the flow of increasing amounts of neuroscience data and to develop an adequate infrastructure is increasingly being recognized also in Europe. Current progress is made either through individual research grants (often in coordination with US groups) or in the course of national efforts to implement the recommendations of the Organization for Economic Cooperation and Development (OECD) Working Group on Neuroinformatics. The 6th Framework Programme of the European Union (EU) in its Life Science priority with the 3rd call in 2004 limits the opportunities largely to the subcellular level; therefore it will be important to broaden the spectrum for the 4th call in 2005. The overall picture of European activities reflects the diversity of preferences and funding among heterogeneous groups of scientists and nations.

One specific topic where Europe has particular needs, expertise and opportunities is brain connectivity and the question why real brain networks are so enormously powerful and versatile in solving a multitude of complex problems. Such a project would address brain connectivity at all levels from neurons to large-scale systems, and from structural, functional as well as inferential points of view.

In the context of connectivity, the CoCoMac project (Collations of Connectivity data on the Macaque brain) is an example of a mature database that provides access to primary data from the literature, processed connectivity data and extensive mapping information based on 390 publications with a focus on the cerebral cortex of adult macaques. Since the first steps in 1997 to collate data, constrain data representation and implement quality assessment the project has developed to provide interfaces for automated online query and XML-formatted output for further processing. Current work extends the database to subcortical structures, provides tools for visualization and analysis, and investigates links between structural and functional connectivity. Major future directions include interoperability with other data resources including ontologies and coordinate-based atlases, extensions to additional data modalities, such as receptor and microcircuitry data, and the application of connectivity data to computer simulations and systems analyses, particularly in the context of functional imaging data.

1. European Neuroinformatics initiatives

Europe has a longstanding history of research in the field of neuroinformatics / computational neuroscience, although this field had different names and flavors in different European countries (see e.g. Kötter 1999). For about a decade we have seen initiatives on a European level mainly addressing issues of coordination, visibility, funding of workshops, scholarships and training programs. Among the best known of these initiatives is the EU Advanced Course in Computational Neuroscience, which started 1996 in Crete and has since moved on in a

triennial rhythm to Trieste, Obidos and Archachon. Other initiatives include the summer symposia supported by the European Science Foundation (ESF) and the Thematic Network "Computational Neuroscience and Neuroinformatics" funded by the 5th Framework Program of the European Union (see http://www.neuroinf.org).

Much of the biomedical focus of the EU 6th Framework programme appears to have been inspired by the rise of biotechnology and the prospect of an ageing population. Combining these two thrusts it appeared feasible to use high-throughput genomic and proteomic approaches, which would allow us to identify and manipulate the factors that cause degenerative diseases of the various body systems including the brain. While an unprecedented flow of molecular data has provided many new and sometimes surprising findings it was almost ignored that other research approaches, for example in systems neuroscience, had considered the complexity of biological systems and developed methods suitable to analyze their organizational principles. Increasingly it is also being recognized that connecting the genomic and the behavioral level has to explicitly address also the cellular and systems levels, which were often short-circuited. In a recent issue on "systems biology" of Nature Biotechnology (Vol. 22, No. 10, October 2004) several authors lucidly recall the origin of this term and its re-definition in the context of genomics approaches and subcellular processing. The emergence of the "new" field of systems biology constitutes a paradigm shift for molecular biology, which had often focused on reductionist thinking. This should be a good message for the field of neuroinformatics / computational neuroscience since it is well equipped using computational approaches to study the complex systems without the need to re-invent itself as an extension of bioinformatics.

The following is a list of current calls for project proposals in the priority 1: Life Sciences, Genomics and Biotechnology for Health to be funded by the European Union that have at least a vague relevance to neuroinformatics.

LSH-2004-1.1.0-2: Coordination Action (CA) proposals should aim at: - developing a coherent strategy for the maintenance and sustainability of essential European database resources for all model organisms important in functional genomics research, - or structuring systems biology research in Europe with particular emphasis on the collaboration between different expertises in life sciences research, - or developing a European public-private partnership to solve current bottlenecks in the production of eukaryotic proteins in quantities and quality required by structural genomics and proteomics programmes, - or improving European coordination of efforts to develop NMR methods for structural genomics, - collaboration between human sample biobanks in epidemiological research.

LSH-2004-1.1.4-1: Development of a European-wide package for creating and integrating relevant databases and analysis software to enable systems-level interpretation of complex experimental data in functional genomic

LSH-2004-2.1.3-1: Neural molecular mechanisms of synaptic information processing

LSH-2004-2.1.3-5: Strengthening neuroscience research in Europe

LSH-2004-2.1.3-6: Workshop on neuroimaging in brain research

LSH-2004-2.1.3-7: Organisation of a workshop on databasing the brain

LSH-2004-2.1.3-8: Consensus document on future European brain research

Some additional relevant initiatives can be found in the priority 2: Information Society Technologies (IST), including Future and Emerging Technologies (FET), and in the activity called "New and Emerging Science and Technology" (NEST). The priority 2 FET currently provides funding for an extended Network of Excellence entitled "Neuro-IT" (for more information see http://www.neuro-it.net).

Altogether, the current level of specifically European initiatives in computational neuroscience/ neuroinformatics is rather disappointing given the previous level of organization and the perceived importance of the field. While many groups are successful in attracting other sources of funding for their research work in the field, the coordination and integration of this work in view of the increasing challenges of the production, classification and use of neuroscience data will require grant support for an initiative in coordinating neuroinformatics activities. Such an initiative could lead up to and support the activities of the proposed International Neuroinformatics Coordinating Facility (INCF) (http://www.oecd.org/document/15/0,2340,en_2649_201185_25998799_1_1_1_1,00.html, Annex 4) on a European level. Even if the INCF should be established by then, a specific support action will still be critical to formulate a European perspective that can answer the thrust of the Human Brain Project and identify areas of particular significance within Europe where they differ from or depend on the developments in the US and Japan.

2. Connectivity as a European neuroinformatics research opportunity

One particular topic that constitutes a particular opportunity for European neuroinformatics research with an already strong position in theory and application is the study of brain connectivity and why real brain networks are so enormously powerful and versatile in solving a multitude of complex problems. This topic entails connectivity of real brains at all levels from neurons to large-scale systems, and from structural, functional as well as inferential points of view. A particularly important component will be to advance the theory of connectivity with a view to understand the principles of neural organization and its expression in brain functions. This includes the study of the rules of network development from simpler to more complex brains during phylogeny and ontogenesis, the types of network elements and the specificity of their interactions, the hierarchical structure of local and global connectivity levels, the computational power of identified circuits, and the experimental methods to probe complex network function including, e.g., multi-site stimulation and recording as well as structural and functional imaging methods. In this context it will be important to establish how methods and theories that were developed and employed in a specific field or at one scale of investigation can inform and be applied to other scales. Further activities include the coordination of collation and integration of data from specific levels of investigation and organisms (e.g. microcircuitry, invasive neuronal recordings and tracing studies, in vivo functional connectivity measurements), and the development of advanced computational methods for their analysis including graph-theoretical, machine-learning, multi-variate statistical, and computational modelling approaches.

Here is an outline of how the topic of connectivity could be structured:

Theory and inference of connectivity

Theory of Connectivity

Descriptive organisation of large-scale connectivity (e.g. hierarchies, streams, loops, motifs and other measures)

Development, growth, lesions and degeneration of connectivity patterns

Forward modelling of neural dynamics based on anatomical connectivity and neural dynamics

Dynamics arising from specific structural connectivity patterns

Information on microcircuitry

Database of neuronal cell types and their interconnections with anatomical, physiological and biochemical properties

Activity propagation in local microcircuits

Functional organisation of layers, columns etc.

Relations across multiple scales of connectivity

Connectivity and brain theories of learning and inference

Approaches from information theory

Machine learning approaches

Predictive coding and generative models

Hierarchical Bayesian Modelling

Methods for inference of connectivity

Developing the frameworks of Dynamic Causal Modelling and Structural Equation Modelling

Non-linear SEM using the specific constraints from neural architectures

Fusion of spatial and temporal information

Interfaces with connectivity databases (where necessary also addressing homology issues)

Lesion contribution analysis

Validation of concepts and models against empirical data

Anatomical Connectivity

What do we know about anatomical connectivity of the human brain?

Probabilistic atlas of white matter tracts in the human brain

Data from post-mortem fibre tracing

Documenting the ontogenetic development of white matter

Anatomical "ground truth" in model brains

Database of primate brain connectivity

Database of macaque brain connectivity from publications

Archives of detailed experimental tracing and mapping data

Volume-based electronic 3D macaque monkey brain atlas

Tools for mapping between parcellation-based and coordinate-based data

Experimental studies of conceptually important issues

3D course of fibre tracts and single fibres (e.g.: Is the arrangement of reciprocal connections intermingled or side-by-side?)

Composition of fibre tracts (e.g.: What are the number and geometrical properties of the constituent fibres of defined tracts?)

Investigation of critical unknown or controversial projections (e.g.: Is there a direct projection from somatosensory area 3b to primary motor cortical areas 4a or 4p?))

What is the homogeneity of the sources and targets of inter-area projections (Can we resolve remaining hierarchy issues, e.g. of area FST?)

Inter-individual variability of fibre tracts

Transsynaptic tracing (e.g.: How many consecutive synapses are between the input and output cells of an area?)

Development of complex connected structures (e.g.: How is the inter-area cortical network generated?)

In vivo measurements of connectivity

Diffusion weighted magnetic resonance imaging (dMRI)

Database of dMRI and white matter measures in humans (adult and ontogenesis)

Methodological developments

Tractography

Parcellation through dMRI measures

Validation of dMRI and paramagnetic tracers against classical tracing in primates

Functional connectivity measures

Informing correlation measures through anatomical priors

Perturbation studies

TMS

Database of functional impact of lesions (from stroke patients)

Electrophysiological studies of conceptually important issues

Conduction velocities in forward and backward projections and correlations with the number and types of fibres

Pathways leading to short-latency activation of the frontal eye field (FEF)

Relationship between activation and synchronisation

Application of results

Application of connectivity theory to complex networks in general (e.g. metabolic, social, and technological networks)

Application of connectivity information to other research questions, e.g. in combination with fMRI

Development of software for clinical use in diagnosis

Development of concepts for brain-like software and hardware

Brain interfaces for readout or intervention

Interfaces to other relevant neuroscience data and tools creating an integrated neuroscience portal

Dissemination of results, advice and teaching

Web resources (internal and external)

Peer-reviewed publications

Workshops, Courses

Exchange and training of students

Liaison with other specialists (e.g. clinicians, engineers)

Informing the public

Controlling and Administration

Finances

Project coordination, organisation (e.g. executive coordination committee of core group partners)

External Advisory Board and project monitoring

Internal quality assurance, policies, standards

Maintenance, outsourcing, marketing

Infrastructure and policy making

Infrastructure for theory (e.g. who are the key people, where are the labs, what key concepts are missing?)

Infrastructure for applications (e.g. data standards, databases, visualisation, data analysis, computational modelling)

Infrastructure for experiments (e.g. availability of anatomical techniques, imaging centres, animal facilities)

Infrastructure for dissemination, advice and teaching (e.g. web services, conference facilities, public relations, design)

Infrastructure for project coordination and controlling (e.g. management and EU experience, efficient administration)

Funding agencies (e.g. who is funding related projects, how big is the investment, coordination of funding, what parts are difficult to fund?)

Levels and hierarchies of funding institutions, identification of institutions in European countries including key people at comparative and adequate levels

Network steering committee

Coordination meetings

Overview documents (e.g. political roadmap, extracts of national programmes in English for other national agencies, activities outside the EU: OECD, INCF, IBRO, SfN-NIC, Human Brain Project)

3. The CoCoMac Project

Information on anatomical connections between brain regions has become a highly valued resource in systems neuroscience since this information is useful to put constraints on possible interpretations of functional data as obtained from multi-site recording or neuroimaging techniques. Models based on detailed anatomical data, for example, make better predictions of topographical activation patterns than those based on general assumptions of regular neighbourhood or random connectivity (Kötter & Sommer, 2000); also anatomical models provide a basis for structural equation modelling and its extensions to infer the causal effects underlying correlated functional signals (McIntosh & Gonzales-Lima, 1994; Büchel & Friston, 1997; Friston et al., 2003). In particular, as the conceptual emphasis is shifting from spatially segregated to interactive and integrative processing (Friston, 1995; Kötter & Stephan, 2003) knowledge of the anatomical routes of information transfer is of paramount importance.

Obtaining the necessary information at the required level of detail is still a complicated and tedious process. The most extensive and detailed information on regional interconnections has been obtained from tracing studies in the brains of mammals, in particular rats, cats and monkeys. Due to the invasive and time-consuming experimental procedures, however, the results are gathered incrementally and scattered across hundreds of separate research publications from the second half of the 20th century. Over this period the available techniques have improved to deliver more specific, more detailed and more complete results. In addition, the partitioning of

brain regions has become more sophisticated and diverse as many different subjective criteria are being applied. Finally, the correspondence between microstructurally identified brain regions and gross anatomical landmarks holds only at a coarse level (e.g. Amunts et al., 1999) leading to uncertainties when comparing individual maps or idealized schemes from tracing studies with the voxel-based data sets obtained by neuroimaging.

All these complicating issues need to be addressed by compilations of connectivity data. Whereas the first comprehensive literature reviews published in the 1990es already focussed on well defined species (Felleman & Van Essen, 1991; Young, 1993; Scannell et al., 1995, 1999; Burns & Young, 2000) the more intricate complications could only be efficiently addressed with the development of advanced neuroinformatics tools and algorithms (Stephan et al., 2000; Stephan et al., 2001; Burns, 2001; Kötter, 2001) that allowed us to keep track of thousands of heterogeneous details and still extract the gist of characteristic features in a transparent, reproducible and flexible way. We face further challenges, however, when trying to reconcile 1) the anatomist's distinguishing of microscopic details with the imager's need for less finely grained, but accurate information, 2) the comprehensiveness of textual lists with the intuitiveness of images and 3D representations, and 3) the notation in microstructural partitioning schemes with the application to spatial coordinate systems (tracing data have only in rare cases been referenced to the latter, e.g. Bjaalie et al., 2000; representations of data from Lewis & Van Essen, 2000b in Caret framework).

The CoCoMac database has gradually developed since 1997 with the aim to obtain an overview of the large-scale wiring of the primate cerebral cortex that could be used for systems analysis and computational modelling. This information is in principle available from experimental tracing studies, but the data are scattered across hundreds of individual research reports. By contrast, recent advances, such as spatially registered tracing and diffusion-weighted imaging data, have not yet generated comparable amounts of data. Therefore, CoCoMac was designed as a literature database to organize the wealth of published tracing data on the macaque monkey brain in an objective, detailed and coherent fashion. Building on experiences with previous data collections (Felleman & Essen, 1991; Young, 1993; Scannell, 1995; Burns, 1997) we realized very early that such a database had to provide full transparency all the way from the published datum to the final retrieved output if it was to stand the scrutiny of neuroanatomists and to survive the requirements of incremental data acquisition and the changing views on cortical partitioning schemes (Stephan et al., 2001). The adherence to the transparency principle is a particular advantage of CoCoMac. It had us a face major challenges, however, concerning the integration of redundant or contradictory published (primary) data, and the transformation of the integrated primary data from various partitioning schemes into a coherent brain map. Integration and transformation are effected by several methods, including the ORT (Objective Relational Translation) procedure, which is presented in detail elsewhere (Stephan & Kötter, 1998; Stephan et al., 2000).

CoCoMac has a clear focus on connectivity data from the brains of adult primates of the genus macaca. The most prominent member of this genus is the species Rhesus monkey (Macaca mulatta), but other frequently investigated species are the closely related Cynomolgus monkey (Macaca fascicularis), the pig-tailed macaque (Macaca nemestrina) and the Japanese macaque (Macaca fuscata). Data collation is carried out by a group of highly trained and closely interacting individuals in the course of their research projects. It progresses by functionally related regions and comprises already most of the cerebral cortex as well as its thalamic and amygdalar afferents.

Over the last years we have developed an online-interface for the CoCoMac database, which provides public access to large parts of the CoCoMac database (for a first introduction to the retrieval of literature data see Kamper et al., 2002). Access is gained via the internet at http://www.cocomac.org, is free of charge but requires registration. The registration information helps us to keep track of the user community, which is useful to prioritize further steps of data collation and software development. After successful login the home page offers a quick and simple keyword search as well as essential information on the main menu. The simple keyword search facility is a combined shortcut to the keywords searches in each of the three data categories literature, mapping or connectivity. The menu buttons are self-explanatory and include an INFO button, which delivers basic information to orient the novice user.

There is more content in the CoCoMac database than can be retrieved through the online interface despite the already extensive information provided. Interesting aspects are, for example, the method used for delineation of BrainSites, details on radioactive tracers employed, and quantitative data on connection densities, such as total number of labelled neurons in a BrainSite or the percentage of labelled cells in a BrainSite with respect to the total number of labelled neurons resulting from that injection. Since fewer than 5% of collated articles provide quantitative data, the implementation of a user interface for these data had low priority. Further information of interest includes visual representations of brain maps, and some of these are being re-drawn for representation in Catacomb and CARET (see section Graphical display of connectivity data).

The main menu of the online interface, however, contains further items that list changes to the contents or design of the database with time stamps so that recent additions can be monitored. Users are encouraged to add comments to all database output so that the community can benefit from external opinions on the representation or interpretation of the data (see the concept of the "Faculty of 1000" at PubMedCentral). Comments added to specific items are available whenever the item is retrieved again choosing the Display option “user comments”. Independent of specific contents, feedback - including bug reports and suggestions - is most welcome and can be given through the corresponding menu item.

Every version of the CoCoMac database is archived. Although older database versions are not available online anymore it is in principle possible to reconstruct any query results if the date and time of retrieval is known. Thus, it is recommended that users note the date of database upload shown on the login page and the search string that produced the results that they want to refer to. The contents of the search strings is listed at the top of each OutputList, and the full query can be referenced and bookmarked after clicking “Show URL” from the OutputList. When using data from the CoCoMac database then it would be adequate to reference the source referring to http://www.cocomac.org or Kötter 2004.

The online interface is conceptually a separate entity from the database and the query engine. It has two functions in interfacing with the user:

- to aid the user in constructing the desired search query, which is then passed on to the query engine, and
- to display the retrieved data in the form of textual output lists.

Both functions, query construction and display of results, can alternatively be carried out by other means including automatic generation of query strings and further processing of the returned results. This opens up many opportunities for interactions with other databases, visualization and modelling tools.

Query construction is a relatively straightforward process: Every query constructed in the online interface (and additional queries) can be expressed as a parameterized URL string that is a concatenation of the address of the server site, the search engine, a list of parameters, and the actual search string. If the output is HTML directed to the browser then the only differences to the manual output are the absence of the menu on the left and the additional CoCoMac login button, which allows the user to continue with a manual search under his own login. Alternatively, XML output can be obtained that is formatted according to the CoCoMac XML schema, which is available for inspection, download, and validation of XML files at http://www.cocomac.org/cocomac.xsd.

The full syntax of these http strings is documented at http://www.cocomac.org/cocomac_URLsearch.html.

4. Graphical display of connectivity data

As soon as large numbers of connections between several areas are listed as text it would be far more intuitive and convenient if these could be displayed graphically. Since the spatial position and course of the fibres is not documented we have two basic options to display the connections:

- We can follow the anatomical images, which show the label obtained from a specific tracer injection in sections or in a surface projection on a schematic brain.
- We can draw oriented lines that link source areas with target areas in an idealized non-spatial manner.

Both options have been implemented: The first is available as part of the Caret software developed by the Van Essen lab (http://brainmap.wustl.edu/vanessen.html) and highlights the areas that are connected to a chosen area in the map of Felleman & Van Essen (1991) both in the flat map and in the fiducial surface representation of the macaque cerebral cortex.

The second option has been developed in collaboration with Robert Cannon as part of his Catacomb Workspace (Cannon et al., 2003; download from http://askja.bu.edu/catacomb/unstable/). This JAVA-based tool was designed as a simulator of integrate-and-fire models with many extensions including a CoCoMac-specific part consisting of a map, a connector and a server accessor. The server accessor generates a URL search as described above, parses the retrieved XML output and displays the connectivity information superimposed on maps that are drawn using the built-in map maker. Information and example maps can be downloaded from http://www.cocomac.org/catacomb.

The main advantage of the display option implemented in the Catacomb Workspace is that it can present the connections between multiple areas simultaneously. The particular set of areas can be selected by mouse clicks, for example, in accordance with the mapping of significantly activated areas in functional imaging experiments. Depending on whether PrimaryProjections or IntegratedPrimaryProjections are retrieved the representation will show all available data including redundant and contradictory information or only one projection that represents the most precise among the available data. Further options include the display of all afferents and/ or all efferents of the selected area(s) and the display of six-tiered colour bars representing the density values for each isocortical layer at the source and target of each connection.

5. Conclusions and Perspectives

Information about the large-scale connectivity between brain regions is a valuable resource both for top-down descriptive modelling of functional data, such as those obtained with functional imaging techniques, and for bottom-up mechanistic modelling that constructs more complex models from detailed anatomical, biochemical, and physiological information. Such connectivity data are in principle available, but they are dispersed across hundreds of experimental reports whose interpretation requires neuroanatomical background knowledge and has a limited spatial resolution due to the lack of coordinate notations and the subjectivity of microstructural delineations. The CoCoMac database contains most of the published material on intra-cortical connectivity and presents it in a systematic and precise fashion. Remaining limitations result mainly from the confusing number of brain maps and the varying nomenclature of brain structures. As a consequence of the simultaneous collation of mapping information these problems are now systematically being addressed and have already led to the development of algorithmic transformation procedures, such as ORT (Stephan et al., 2000). Although this transformation process is fully documented and controlled by user-defined parameters, it is a complex multi-stage procedure whose understanding requires considerable familiarity with details of neuroanatomical data and their representation in the database. To complement older brain maps with controversial partitioning schemes and recent brain maps that are mostly limited to particular cortex regions we are taking steps to provide data in the comprehensive map of the first stereotaxic macaque atlas that comprises a cortex parcellation (Paxinos et al., 2000) and in an abstract map that refers to relatively large but less controversial topographic brain regions ("Regional Map") that will also facilitate cross-species comparisons. For retrieval purposes it would further be useful to link all BrainSites to a widely used ontology of macaque brain structures, such as the NeuroNames nomenclature (Bowden & Dubach, 2002), which has its conceptual counterpart in the implementation of a “General Map” in the CoCoMac system. Still the calculation of comprehensive connectivity matrices and the optimization of free-text interfaces is a time-consuming and tedious task that would benefit from dedicated software engineering work but is outside the scope and funding for scientific research projects. In the meantime, it seems important to convey the essential database concepts and retrieval options to make the search for relevant connectivity data more efficient, more versatile, and more rewarding.

As a result of the data collation for the CoCoMac database some surprising omissions became evident in the published data, which could be easily mended by attentive experimenters, referees and journal editors: In particular, essential descriptive information on the number and gender of investigated animals and the identity of the right or left hemisphere is frequently missing even in contemporary reports published in highly respected journals. From the viewpoint of the computational modeller it would be desirable to have more quantitative statements on the number of axons, their length and diameter, as well as the size of the connected brain structures to be able to constrain models in more detail and to test specific hypotheses of area interactions. For the purpose of interindividual and cross-species comparisons the time consuming and technically demanding process of three-dimensional registration of tracing data including the course of the fibre pathways will be essential. In this context, the validation of diffusion-weighted imaging (dMRI) data on the macaque brain against the battery of tracing data contained in a connectivity database, such as CoCoMac, could lead to a much better understanding of the conclusions that can be drawn from these convenient and non-invasive imaging methods. Finally, the spatial

comparison of connectivity data with a wealth of other structural as well as functional data (as started with the CARET software) will open up rational ways of addressing questions of brain structure-function relationships. Already at the current level of detail connectivity databases provide for far more systematic and exhaustive ways of specifying the anatomical basis of functional activations than the apparently haphazard references commonly encountered in the specification of anatomical models for Structural Equation Modelling.

Given the conceptual importance of connectivity data it is likely that more accurate data and better tools will soon be created to register spatially and to compare connectivity data, and that connectivity data can be displayed, analyzed, and integrated with other data modalities using a variety of add-on tools and compatible software. Particularly promising fields include the systematic selection of connectivity data for the construction of descriptive and mechanistic models that will help to explain the spatial and temporal properties of large-scale activation patterns in the brain.

Acknowledgements

The online text interface to the CoCoMac database was created with the aid of a grant by the German Research Council (DFG LIS 4-554 92 (2) Düsseldorf), implemented by Stefan Küppers at mon.de, Düsseldorf, and tested by Ina Gerken, Andreas Geißler, Jürgen Maier and Konrad Rybacki. Klaas Stephan and Konrad Rybacki wrote the XML schema. I thank Douglas Bowden and Gully Burns for feedback on the online interface, and David Van Essen and Robert Cannon for their support to interface CoCoMac with Caret and Catacomb, respectively. An extended version of the part explaining the CoCoMac project has been published as Kötter 2004.

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