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The history of CoCoMac

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ABSTRACT

CoCoMac, the "Collation of Connectivity Data for the Macaque" is a relational database system which presently constitutes the largest electronic repository of published neuroanatomical connectivity data. Developed since 1996, CoCoMac comprises approximately 40,000 experimental findings on anatomical connections in the macaque brain, as derived from neuroanatomical tract tracing studies. In this historical review, I describe the origin and the history of CoCoMac from a personal perspective, illustrate the principles of its structure and outline the impact it has had on systems neuroscience, in particular as a prelude to the "Human Connectome" research programme.

Introduction: The origin of CoCoMac

The history of CoCoMac dates back to 1996 when I started as doctoral student of Rolf Kötter and Karl Zilles in the C. & O. Vogt Institute for Brain Research at the Heinrich-Heine-University of Düsseldorf. Rolf and I had met two years earlier, in autumn 1994, in the human anatomy dissection course of the university's medical curriculum. Rolf was a young lecturer in anatomy at the time and had recently returned from Dunedin, New Zealand, where he had trained in computational neuroscience, a field that was still rather new and not widely recognised in the early 1990s. In the dissection course, he supervised eight medical students who, over the course of six months, jointly dissected a whole corpse. During this slow and at times almost meditative process, we had ample opportunity to talk and soon discovered similarities in thinking and perspectives. In particular, both of us had a background in computer science and shared the strong belief that many aspects of brain function could only be understood properly on the basis of mathematically formal and biophysically plausible system models. One difference was that Rolf had a very general, almost philosophical, interest in understanding how the brain works. In contrast, my motivation was more strongly driven by clinical questions. In particular, I was under the (slightly delusional) belief that the anatomical and physiological properties of single neurons and neuronal populations were sufficiently well known that all that remained to do in order to understand complex brain functions and their alterations in disease was to model a sufficiently large number of neuronal units and study the behaviour that would emerge from their interactions. My dream was that such a model would eventually comprise the whole brain and enable a quantitative and formal characterisation of the mechanisms underlying complex brain diseases which had so far escaped our understanding.

Following the dissection course, Rolf and I started working together informally (on historical and conceptual aspects of the "limbic system"; (Kötter and Stephan, 1997)), until I started officially as doctoral student under his and Karl Zilles' supervision in April 1996. (In the German system, it is quite common to complete a dissertation in parallel to one's medical studies or during an intermediate break). The initial goal of my dissertation was to construct a large-scale model of the spread of activity during photosensitive epilepsy. This particular type of epilepsy arises in predisposed individuals after prolonged exposure to flickering light stimuli (typically around 10 Hz). It had been studied in great detail in a baboon model, with the interesting finding that the earliest epileptiform activity appeared in motor cortex, preceding epileptic responses in other parts of the brain (Menini and Silva-Barrat, 1998; Silva-Barrat et al., 1988). One possible explanation rested on the connectivity of the system, assuming a confluence of cortical and subcortical visual inputs in motor cortex with catastrophic resonance effects that would eventually lead to local runaway excitation and its subsequent spread, via long-distance connections, to the rest of the brain. To demonstrate the plausibility of this putative mechanism, I wanted to construct a large-scale model of interacting neuronal

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populations whose local dynamics was governed by established biophysical equations (e.g., the Hodgkin–Huxley formalism) and which interacted according to the anatomical long-distance connections between the different regions involved. In other words, the hope was that the large number of published neuroanatomical tract tracing studies in the monkey would enable me to build a realistic whole-brain network into which I simply had to plug in conventional biophysical models of neuronal populations. I thus turned my attention to the neuroanatomical connectivity databases for the macaque monkey which were available at the time.

The first database of this kind had become available in 1991. This was the pioneering work by Felleman and Van Essen (1991) who had collected data from numerous tract tracing studies in the visual system of the macaque. Their approach was straightforward and pragmatic: they listed their interpretations of the findings from the tract tracing literature in an Excel spreadsheet, providing a condensed summary of data distributed across hundreds of published studies. Although methodologically based on a simple approach, this initial database enabled statistical analyses of the macaque brain's connectivity layout, such as the hierarchical arrangement of areas in the visual system, which had previously not been possible and which had tremendous impact on neuroscience (as demonstrated by thousands of citations). This work was extended by the group of Malcolm Young at Newcastle who applied additional analyses to the Felleman & Van Essen database (Hilgetag et al., 1996; Young, 1992) and added macaque connectivity data from outside the visual system (Young, 1993). Furthermore, they established connectivity data repositories in other species, such as the rat (Burns and Young, 2000) and the cat (Scannell et al., 1995, 1999).

However, all of these early neuroanatomical connectivity databases suffered from a severe methodological limitation in how the original experimental findings were represented. The problem was that neuroanatomical tract tracing studies do not usually describe their data (i.e., the location of injections and labelled cell bodies and/or terminals) in spatial coordinates but refer to the absence or presence of injections or label within the areas defined by a particular parcellation scheme ("brain map"). Unfortunately, a large number of different parcellation schemes have been proposed over the last few decades, based on different microstructural (e.g., cytoarchitectonic, myeloarchitectonic, chemoarchitectonic) or functional criteria (e.g., neuronal response properties). Since each author chooses his/her favourite (combination of) parcellation scheme(s), a truly Babylonic confusion has arisen in the neuroanatomical literature over the last decades: often the same acronym is used to refer to areas that differ in the definition of the boundaries, e.g. they only partially overlap; more frequently still, different acronyms are used to refer to identically defined areas. Given this problem and the lack of systematic and global attempts in "translating" these different maps, the early connectivity databases by Felleman & van Essen and by the Newcastle group sensibly adopted a pragmatic approach: they chose one particular "reference map" to which they manually translated all original findings from the published literature. This resulted in a compact summary that could be compiled and searched reasonably quickly. However, the disadvantage was that these databases only contained the final results of an opaque transformation that rested on the subjective criteria and judgement of the database creators. This made it impossible to uncover the original data from the database entries and prohibited remapping the original findings into a different parcellation scheme, which was necessary, for example, when the "reference" map was suboptimal for the particular application of the user. Also, the various inconsistencies and contradictions across studies that are prevalent throughout the literature were no longer visible in these databases, making it difficult to judge how one should integrate new data that had arisen since the original publications.

These limitations suggested the creation of an entirely new type of connectivity database: a database that would store the published findings from each paper, described in terms of the parcellation scheme originally used by the authors, and which was equipped with analysis tools that would enable the user to transform the original data into any particular parcellation scheme while leaving the original data completely untouched. From a computer science perspective, this strict division into data representation and data interpretation seemed a natural, and indeed a mandatory, step. I suggested this to Rolf who was initially very sceptical. While I, in my youthful optimism, was convinced that this would be an exercise of at most a few months of hard work, Rolf feared that this methodological challenge would be much harder than I imagined and would distract me from my original goal of building a large-scale system model of photosensitive epilepsy. Of course, he was absolutely right. It took me almost three years to fully develop the theoretical foundations and implement the database structure and algorithms of what came to be known as CoCoMac.

Principles and implementation of CoCoMac

In designing the new database, we started with five general principles; for details, see Stephan et al. (2001). First, objectivity: each entry should be represented in its original nomenclature, with a precise reference to its publication and a citation of the original description. Second, reproducibility: transforming data from one parcellation scheme to another should be based on mathematical algorithms. Third, transparency: not only should the mapping process be fully documented and accessible, but also all inconsistencies and contradictions in the original data should be preserved in the raw data representation. Fourth, flexibility: the user should have the choice of converting the raw data into any chosen target map. And finally, we demanded simplicity: the new database should be able to deal with the existing data in the literature, despite their various shortcomings such as the lack of spatial coordinates.

The algorithmic framework developed on the basis of these five principles was called objective relational transformation (ORT; (Stephan and Kotter, 1999; Stephan et al., 2000b)). ORT consisted of three main components. First, it introduced three classifications: (i) the *Extension Codes* (EC) which described the spatial extent of experimental findings (i.e., the spread of injection or label within an area); (ii) the *Relation Codes* (RC) which comprised all possible logical relations that areas from two different brain maps could have; and (iii) the *Precision of Description Codes* (PDC) which reported the precision by which experimental findings were described in the original literature, thus supporting algorithmic resolution of contradictory or inconsistent cases. Second, these classifications formed the basis for an algebra of transformation, i.e., a set of rules formally stating whether and how a particular experimental finding (described in terms of EC) could be mapped from one parcellation scheme to another (given their logical relations encoded by RC), and how the result of this mapping would be integrated with the conversion of other original findings in literature, based on their relative precision of description (PDC). Third, one major problem was that for the large majority of parcellation schemes the original literature did not contain any statement on their logical relations to other parcellation schemes. Given that we did not wish to introduce our own judgement and only refer to what original authors had stated in the literature, another component was added to ORT. This was a collection of graph-theoretical methods that combined formal languages and shortest-path-all-pairs algorithms (adapted from the original algorithm by Floyd (1962)) in order to deduce logically valid transformation paths between any given pair of brain maps via a set of intermediate known relations (Stephan et al., 2000b). Since its introduction, these three components of ORT have been adopted by other neuroanatomical database projects (e.g., Bota and Arbib, 2004; Burns et al., 2003) and have been further refined (e.g., Bezgin et al., 2008).

I worked out most of the theory of ORT and CoCoMac during a stay of several months in Malcolm Young's group at Newcastle in 1997. As mentioned earlier, this was one of the leading groups in neuroanatomical databasing in the late 1990s, bringing together people like Gully Burns, Claus Hilgetag and Jack Scannell who created

neuroanatomical connectivity databases for various species (Burns and Young, 2000; Scannell et al., 1995) and developed new analysis strategies for large connectivity data sets, including the use of multidimensional scaling (Young, 1992; Young et al., 1995; see also the criticism by Goodhill et al., 1995) and genetic algorithms, such as optimal set analysis (Hilgetag et al., 2000). Malcolm and Rolf had been awarded a collaboration grant from the Wellcome Trust, which not only paid for my stay at Newcastle but also for a personal laptop — a huge help given that I did not have my own computer at the Düsseldorf lab and had to use whichever lab computer was temporarily available.

Being immersed in the Newcastle group provided me with an inspiring environment for laying the foundations of ORT and CoCoMac. After several months at Newcastle, I returned to Düsseldorf, bringing home a first functional version, implemented as a relational database system under Microsoft Access and Visual Basic code libraries. In fact, I had started building two complementary versions of CoCoMac, one anatomical and one functional connectivity database of the macaque monkey. The functional connectivity data were obtained from "strychnine neuronography" studies, describing correlated epileptiform activity between spatially remote patches of the macaque cortex that had been elicited by local application of strychnine. As established in pioneering physiological studies in the early 20th century (Dusser de Barenne and McCulloch, 1938, 1939; McCulloch, 1944), the local application of strychnine, an antagonist of $GABA_A$ and glycine receptors, leads to local disinhibition and ensuing epileptiform activity which propagates via association fibres to remote areas of the brain. It was Rolf's idea to harvest and re-use these data which were fairly old (mostly recorded in the 1930s and 1940s) and had largely been forgotten about. Over the course of a few months, I entered about 4000 published experimental findings from approximately 250 experiments into an early version of CoCoMac called "CoCoMac-Stry". Despite their age, these data constituted a unique collection of whole-brain functional connectivity and turned out to be surprisingly useful for statistical analyses. Initially, we used ORT to map these data into two classical maps of macaque cortex (Von Bonin and Bailey, 1947; Walker, 1940). Subsequent analyses of the resulting adjacency matrix of functional interactions, conducted in close collaboration with Claus Hilgetag, Gully Burns and Malcolm Young, led to two major findings (Stephan et al., 2000a). First, we found that the functional interaction patterns defined clearly distinguishable clusters of areas, suggesting a division of primate cortex into visual, orbito-temporal-insular and somatomotor systems. Motor and somatosensory areas were inseparably linked, while the visual system showed a clear differentiation into ventral and dorsal streams. Second, and perhaps more importantly, we showed that the macaque's functional connectivity network exhibited a clear "small world" structure. At the time, this was very exciting, given that Watts and Strogatz (1998) had recently published their seminal paper on "small world" properties of various networks and had hypothesised that the primate brain should exhibit such small world features, too. Together with Olaf Sporns and colleagues, who published similar conclusions using the data by Felleman and Van Essen (1991) at the same time (Sporns et al., 2000), we were the first to provide empirical evidence for this hypothesis. In retrospect, I have to smile a little at our excitement back then, given that it has since emerged that "small worldness" is an extremely common property of networks, and from today's perspective it would have been more intriguing had we failed to find evidence for small word structure.

This application of CoCoMac-Stry was important because it demonstrated the functionality of the five database principles described above and the underlying algorithmic machinery, including ORT. From a data collection perspective, however, it was still a comparatively moderate exercise, even though it contained thousands of entries. Its sister database containing anatomical tract tracing data (which we initially called "CoCoMac-Tracer" in order to distinguish it from CoCoMac-Stry) grew to contain an order of magnitude more data than CoCoMac-Stry. This was only possible because several additional students joined Rolf's team from 1998 onwards (see http://cocomac.org/WWW/contacts.htm). Each of these students would systematically collect tract tracing data for a particular division of the brain, such as the amygdala and hippocampus (Ahmed Bozkurt), thalamus (Lars Kamper), interhemispheric connections (Jürgen Maier), sensorimotor cortex (Andreas Geissler), auditory system (Konrad Rybacki) or the visual system (Ina Gerken). Collectively, this team entered almost 40,000 experimental tests of individual connections and thousands of statements on inter-map relations from the published literature into CoCoMac-Tracer (which gradually was referred to only as "CoCoMac"). To guide this process by strictly defined rules, I wrote a manual (see http://cocomac.org/WWW/manual_dataEntry_cocomac.pdf) which operationalised each aspect of data representation in CoCoMac and standardised data collection. The process of entering data from the primary literature into CoCoMac was tedious and rather dull but necessary because we could not find a satisfying way of automatically extracting the data from the literature. Rolf tried to convince colleagues from neuroanatomy who had published some of the key papers to engage in the data collection process and make these data available in a format readable be CoCoMac. Unfortunately, these attempts were unsuccessful, mainly because there were no real incentives for the experimentalists to engage in this tedious process. These challenges of extracting published information automatically and of motivating experimental scientists to upload their data into electronic repositories still exist in many domains of neuroscience today, not only with regard to connectivity data (Bakker et al., 2012; Russ et al., 2011) but also, for example, in functional neuroimaging (Van Horn and Gazzaniga, in press).

From network analyses to effective connectivity

By 1999, CoCoMac had reached a level of technical maturation and included enough anatomical connectivity data that serious applications were becoming feasible (see Fig. 1 for an overview of the analysis stream from data in the original literature via ORT to network analyses and simulations). For example, we had a sufficiently complete representation of prefrontal connectivity that we could examine, using multivariate techniques, the cluster structure of prefrontal areas based on their connectivity and describe putative differences between medial and lateral prefrontal areas (Northoff et al., 2000; Stephan et al., 2001).

It was at this point that I finally felt ready to return to the original question that had triggered my interest in developing a connectivity database in the first place, i.e., the construction of a large-scale and biophysically realistic model of the spread of excitation during photosensitive epilepsy. However, when I started to work on the implementation of this model, using a set of "cortical regions" (consisting of small populations of Hodgkin–Huxley units) that were wired together according to the connectivity information from CoCoMac, I quickly encountered a major problem: my model had so many degrees of freedom that it easily produced extremely different types of behaviour. This diversity partly arose when varying the parameters of the biophysical equations within ranges deemed plausible by the literature. More critical, however, was the influence of long-range connectivity. Even though the anatomical connectivity layout of the large-scale network was fixed, as prescribed by the structural information in CoCoMac, the functional strength of each individual connection, i.e. the effective connectivity, was unknown and had to be assumed arbitrarily. Altering the effective connectivity throughout the network resulted in vastly different large-scale dynamics, from regular firing via complicated burst patterns to rapid runaway excitation and whole-brain epilepsy.

At the time, I did not see how one could decide between different parameter settings and accept one as more plausible than another in explaining the empirically measured spread of excitation during photosensitive epilepsy. It seemed that even under a fixed anatomical connectivity pattern the unknown coupling strengths made my model so indeterminate that variations in the inter-regional connectivity

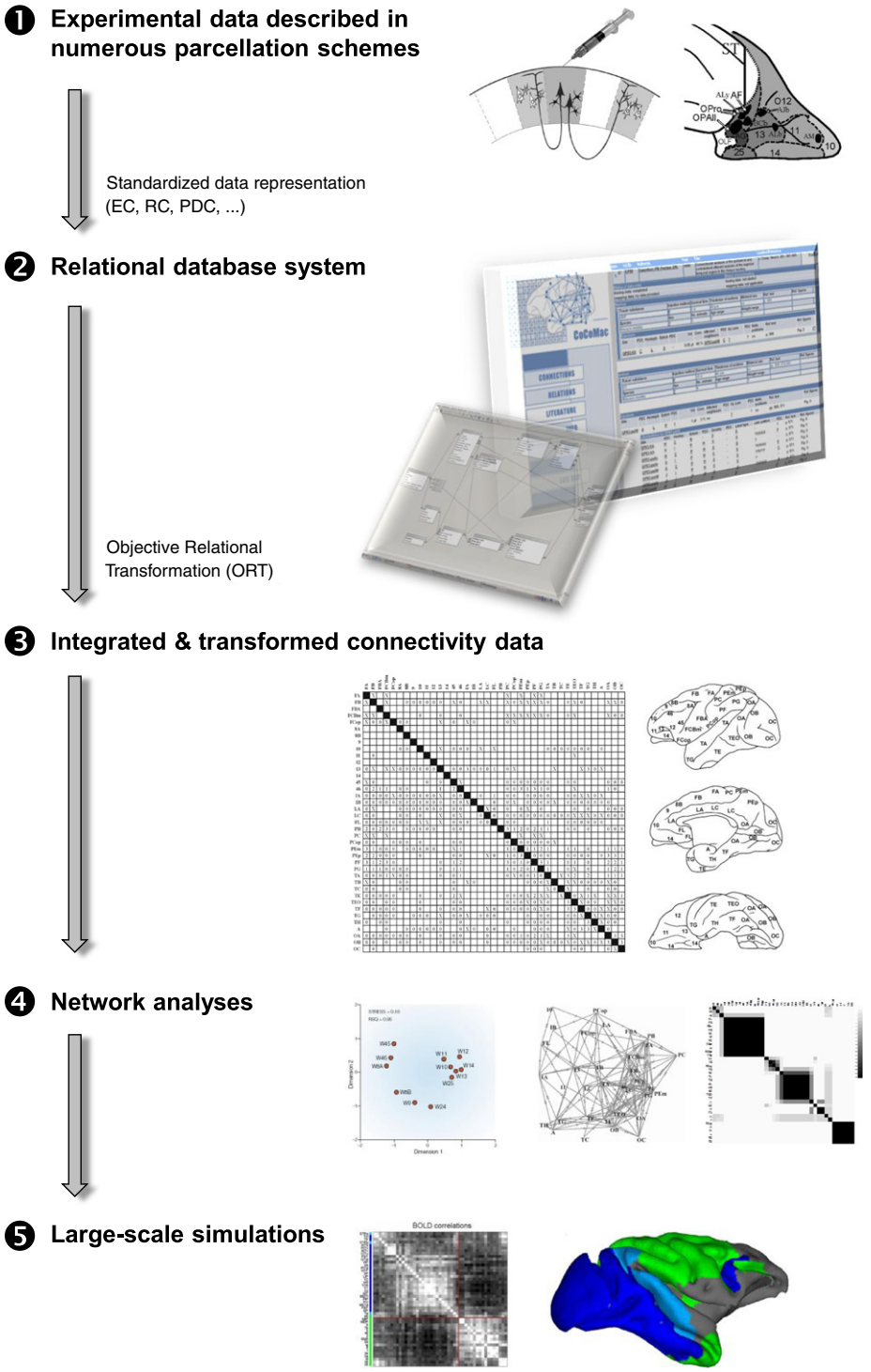

Fig. 1. This figure provides a summary of the data analysis stream in CoCoMac. The published experimental data, described in reference to numerous different parcellation schemes, are represented within a relational database system, using their original nomenclature and standardised coding schemes for the spatial extent of tracer, logical relation of brain maps, precision of description, etc. The original connectivity data across all publications stored in CoCoMac can then be integrated and mapped to a user-chosen parcellation scheme using ORT. This results in a connectivity matrix which serves as the basis for subsequent analyses. These may include, for example, multivariate or graph-theoretical analyses of network structure, or large-scale simulations of brain dynamics that use this connectivity matrix as an "anatomical skeleton". Please note that this figure combines and adapts figures from previous publications (Barbas et al., 2005; Honey et al., 2007; Passingham et al., 2002; Stephan et al., 2000a) which are reproduced here with permission by the copyright holders.

parameters could lead to almost any dynamics. As my model seemed too complex for fitting it to the empirical data, I had no criterion by which I could decide which of these parameter settings was more meaningful. As a consequence, I became doubtful whether this bottom-up approach to modelling, which rested on generating predictions about neuronal dynamics from the anatomy and physiology of network components, was at all a promising approach to obtain my goal of determining mechanisms of brain disease. I was deeply dissatisfied by the

uncertainty of how to choose parameter values within physiologically plausible ranges and by the qualitative nature of comparing the model's predictions to published data.

At this point, my attention was drawn to a different approach which inferred parameters of effective connectivity from empirical measurements of brain activity. This included techniques such as structural equation modelling (SEM) (Buchel and Friston, 1997; Horwitz et al., 1999; McIntosh and Gonzales-Lima, 1994) or time series analyses (Buchel and Friston, 1998; Friston and Buchel, 2000) that could be applied to non-invasive measurements of human brain activity with positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). I was fascinated by these approaches. These models were considerably less sophisticated and allowed for biophysically far less fine-grained interpretations than the one I had toyed with. However, while the representation of physiological mechanisms was coarse, it was possible to estimate these from the data. This possibility of inferring upon the strength of specific network connections from empirical measurements started to look much more relevant for my goal of elucidating disease mechanisms than bottom-up modelling approaches.

CoCoMac online

Influenced by these thoughts and experiences, I started to slowly disengage from the CoCoMac project. Until 2000, the conceptual and technical development of CoCoMac had been entirely in my hands. Now, as I was approaching the end of my dissertation in medicine, I started to look for labs abroad where I hoped to obtain training in methods for inferring effective connectivity from neuroimaging data. While I still remained involved in some aspects of database and code development from a distance until 2004, my engagement slowly faded out and Rolf was increasingly required to take over the actual development process of CoCoMac. Over these years, he initiated some important developments which enabled CoCoMac to become the widely used database it is today. Clearly, the most important decision Rolf made was to develop an online version of CoCoMac (www.cocomac.org) that gave free access to the community. Over the years, CoCoMac online slowly grew in functionality and offered increasingly flexible access to the entire contents in CoCoMac (Kötter, 2004).

The process of making CoCoMac available online revealed that some of its design features created practical obstacles for external users. In particular, the philosophy of representing only original statements, in the very same description and nomenclature as used by the original authors, was conceptually well-motivated but made it difficult for users not deeply familiar with the multitude of brain maps to extract the data they needed. To overcome this problem and facilitate access, Rolf engaged in two main initiatives. First, he collaborated with colleagues like David van Essen, Robert Cannon and George Paxinos in order to establish interfaces between CoCoMac and graphical software, such as Caret (Van Essen, 2002) or Catacomb (Cannon et al., 2003), and link it to anatomical atlases (Bezgin et al., 2009). Secondly, he took up an idea from my earlier work which I had not fully brought to completion. To facilitate data queries and enhance the graph-theoretical optimization of transformation paths, I had previously envisaged the creation of "synthetic" brain maps referred to as *Acronym Map* and *General Map*, respectively (see http://cocomac.org/WWW/manual_dataEntry_cocomac.pdf). The concept of these synthetic maps was eventually published by Kötter and Wanke (2005), together with the definition of a so-called *Regional Map* which consisted of topographically defined regions across the whole cortex. The macroanatomical definition of these areas was sufficiently specific for addressing concrete neuroscientific questions, yet sufficiently broad that they would absorb uncertainty about the exact boundaries and that they could be determined in different species. This facilitated comparisons between the primate and human literature and constituted an important step forward, given that despite all advances of diffusion weighted imaging we still lack methods for obtaining very high resolution measurements of directed connectivity in the human brain, and primate tract tracing data still represent the gold standard to inform anatomically grounded models of human brain function. The connectivity matrix derived by mapping the contents of CoCoMac, via ORT, to the *Regional Map* defined in (Kötter and Wanke, 2005) has subsequently been used in numerous modelling studies, as described in the next section.

The impact of CoCoMac on systems and computational neuroscience

Before it became publically available online, CoCoMac had already enabled several novel analyses of principles underlying the brain's structural and functional organization, such as the small world analyses based on neuronographic data (Stephan et al., 2000a). Another important example was the idea of "connectional fingerprints", i.e., the notion that the functional profile of a given cortical area is critically determined by the anatomical pattern of its afferent and efferent connections. This idea, which was introduced in Passingham et al. (2002) and illustrated by juxtaposing anatomical data from CoCoMac and electrophysiological recordings, became an influential concept. Motivated by the connectional fingerprint idea, in vivo parcellation methods of the human brain, based on diffusion weighted imaging have been developed. Specifically, several studies used tractography-derived connectivity profiles to determine boundaries between neighbouring areas, e.g., between motor areas (Klein et al., 2007; Tomassini et al., 2007), or between speech-relevant areas in inferior frontal cortex (Klein et al., 2007). It was also used to define subdivisions of Broca's area (Anwander et al., 2007) and cingulate cortex (Beckmann et al., 2009), respectively, showing a good correspondence with parcellations suggested on functional grounds. The connectional fingerprint concept also contributed to the development of methods for formally integrating structural connectivity information into models of effective connectivity, e.g., tractography-based priors for dynamic causal models of fMRI data (Stephan et al., 2009). Finally, an elegant experimental validation of this concept was provided by a recent human diffusion weighted imaging study, showing that the individual anatomical connectivity patterns predicted face selectivity in the fusiform gyrus (Saygin et al., 2012).

The online tools for searching and extracting data from CoCoMac were crucial in making it a popular tool for studies modelling large-scale neuronal systems. These studies can be classified broadly into two groups, those concerned with characteristics and principles of the brain's structural network, and those using data from CoCoMac to define an anatomical "skeleton" for large-scale models of neuronal dynamics (cf. Fig. 1). Concerning the first group of studies, numerous papers have used CoCoMac for sophisticated statistical analyses of neuroanatomical network properties. For example, data from CoCoMac were used to quantify the statistical properties of large-scale connectivity patterns in the primate brain (Averbeck and Seo, 2008; Bezgin et al., 2012; Kötter et al., 2001; Modha and Singh, 2010), to characterise the distribution of structural network motifs (Sporns and Kötter, 2004), to examine the potential processing roles of individual areas in the cortical network with graph-theoretical methods (Kötter and Stephan, 2003; Kötter et al., 2007; Sporns et al., 2007), to revisit the long-standing question whether and which hierarchies can be defined between cortical regions on the basis of the laminar specificity of cortical connections (Goulas et al., in press; Krumnack et al., 2010; Reid et al., 2009), or to demonstrate that the design of the global wiring layout is not exclusively driven, as previously suggested (Cherniak, 1994), by the need to minimize wiring length, but are shaped by functional constraints such as the minimization of processing steps (Kaiser and Hilgetag, 2006).

Beyond structural analyses, CoCoMac has also enabled major progress in building anatomically plausible large-scale dynamic system models for investigating structure–function relationships. This has resulted in important insights into the mechanisms underlying, for

example, functional connectivity during "rest", in particular with regard to how time delays and noise shape dynamics at multiple time scales; e.g., Deco et al. (2009), Ghosh et al. (2008a, b), Hlinka and Coombes (2012), Honey et al. (2007), Knock et al. (2009), Rho et al. (2011), and Shen et al. (2012). Other notable work has used CoCoMac to show that seemingly inconsistent relations between structural connectivity hierarchies and visual response latencies can be explained by subcortical–cortical connections (Capalbo et al., 2008). Finally, CoCoMac is used within the "Virtual Brain" project which aims at using simulation-based predictions for clinical purposes, e.g., concerning epilepsy and stroke (http://www.thevirtualbrain.org).

When reviewing the continuously growing literature on applications of CoCoMac for constructing large-scale dynamic system models, and noting the intentions of the Virtual Brain project, it was extremely pleasing to see that, with respect to its original motivation and goal, the construction of CoCoMac had not been in vain. In exploiting the detailed anatomical connectivity information in CoCoMac for constructing useful large-scale dynamical system models, others have clearly succeeded where I had failed.

The future of CoCoMac

The application examples described above may illustrate that CoCoMac has established itself as an important neuroinformatics tool for the computational and systems neuroscience community. Following Rolf's tragic death in 2010 there was great concern that this resource could decay. Fortunately, several colleagues have stepped forward, taking initiative and responsibility to maintain and further develop CoCoMac as an open resource for the community. Their ideas on the future of CoCoMac are described in a recent paper (Bakker et al., 2012) and include, for example, the transfer of CoCoMac to a more efficient database engine, computationally more powerful implementations of ORT, and new online tools for data entry and graphical display. These extensions, which they refer to as "CoCoMac 2.0" and whose development is illustrated at www.cocomac.g-node.org, will undoubtedly be instrumental in maintaining, and further enhancing, the utility of CoCoMac for future applications.

From today's perspective, CoCoMac has made three major contributions to enabling structure–function analyses of the brain. First, it has developed a novel methodological framework which has enabled previously infeasible computational treatments of the vast amounts of available tract tracing data and which has provided techniques such as ORT of which derivatives can now be found in most other neuroanatomical databases. Second, it has enabled a wealth of studies examining principles of network structure and structure–function relationships in the primate brain through graph-theoretical analyses and dynamic system modelling. These have led to important insights, e.g., concerning "connectional fingerprints" of brain areas, fundamental properties of structural network organization in the primate brain, and the crucial role of noise and delays in shaping large-scale brain dynamics. And finally, and perhaps most importantly in the context of the specific special issue in which this paper appears, the experiences with CoCoMac led Rolf to write a paper, jointly with Olaf Sporns and Giulio Tononi, which was fundamentally important for initiating the research programme on the "human connectome" (Sporns et al., 2005). In this paper, Olaf, Giulio and Rolf argue that a quantitative database of the anatomical connectivity of the human brain will be crucial for developing a formal understanding of human brain function. I could not agree more and suspect that by now many colleagues in neuroscience feel the same — which is perhaps the reason why you are presently reading the special issue in which this paper appeared.

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Conflict of interest statement

The author has no conflict of interest to report.

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