What lies underneath: Precise classification of brain states using time-dependent topological structure of dynamics

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Abstract

The self-organising global dynamics underlying brain states emerge from complex recursive nonlinear interactions between interconnected brain regions. Until now, all efforts of capturing the causal mechanistic generating principles have proven elusive, since they have been unable to describe the non-stationarity of brain dynamics, i.e. time-dependent changes. Here, we present a novel framework able to characterise brain states with high specificity, precisely by modelling the time-dependent dynamics. Through describing the topological structure of the brain at each moment in time

(its ‘information structure’), we are able to classify different brain states by using the statistics across time of these exact ‘information structures’ hitherto hidden in the neuroimaging dynamics. Proving the strong potential of this framework, we were able to classify the neuroimaging data from two classes of comatose patients (minimally conscious state and unresponsive wakefulness syndrome) compared with healthy controls with very high precision.

1 Introduction

Brain states such as wakefulness, sleep, and coma emerge through continuously evolving dynamics of self-organised whole-brain networks, which depending on the underlying condition, go through transient, “metastable”, arrangements [1]. The challenging question is to how best to describe them through disentangling the mechanisms underlying functional neuroimaging data capturing their whole-brain dynamics over time and space [2, 3, 4, 5]. Whole-brain models have been very successful in capturing many of the key features of brain dynamics including spatiotemporal aspects [2, 6], but they show stationarity of the underlying energy landscape which empirically has been shown not to be the case. In general, until now, it has proven very difficult to fully describe the principles generating the brain dynamics.

Here, the aim is to develop a mathematical formal framework able to characterise the dynamics of brain states with high specificity. Within the field of Dynamical Systems Theory, it has been shown that a coupled-system of differential equations has an associated Information Structure. This is given by a directed graph describing the structure of the global attractor which can be given in terms of invariant subsets (typically, stationary points or periodic orbits) and the trajectories in phase space connecting them [7]. Under some conditions, all invariant subsets of the global attractor can be ordered by their level of attraction or stability (energy levels [8]).

The Attractor Landscape (AL) analysis converts the behaviour of a dynamical system into a landscape of structures to which the system potentially tends to approach or move away. Every state of the system at a particular time is affected by the AL. This provides a number of topological measures in the structure of this attractor landscape, namely number of energy levels (NoEL), frondosity, criticality, synchronicity and cooperation (see Methods).

The information structure can be computed exactly when the number of dynamical variables is low. It has been shown that the information structure can be extracted by a Lotka-Volterra (LV) transformation procedure [9, 10]. This simple model matches the conditions so that the invariants can be ordered in energy levels, supports an algorithm of low computational complexity, and has well-known conditions for the existence and uniqueness of its global attractor, which can be characterized in detail.

We apply this precise mathematical framework to two empirical neuroimaging datasets including healthy controls (HC) and post-comatose patients with disorders of consciousness (DOC) after severe brain injury. This allows us to characterise the instantaneous information structure of the brain at each moment in time, for each measurement. Repeating this for all time points in the data provides statistics (i.e. the mean and variability of the information structure measures) which captures a brain state accurately, characterised by the exact “information structures” hitherto hidden in the neuroimaging dynamics.

To extract the attractor landscape at each instantaneous time point from empirical neu-

roimaging data, we apply the Lotka-Volterra Transform (LVT) [9, 10]. Similar to whole-brain models, this consists of coupling local dynamics with anatomical brain connectivity (Figure 1). However, different from whole-brain models, the Lotka-Volterra Transform is applied to each single time point to reveal the instantaneous information structure. The anatomical brain connectivity is estimated from the diffusion MRI using the Yeo parcellation [11], in order to allow for an exact and exhaustive description (Figure 2).

Demonstrating the power of this framework, we used it to characterise different conscious states, using two datasets (Liège and Paris) including healthy controls (HC) and two groups of disorders of consciousness (DOC) patients: minimally conscious state (MCS) and unresponsive wakefulness syndrome (UWS). Patients in MCS present some behaviour that may indicate awareness (i.e., visual pursuit, orientation to pain, or reproducible command following). Patients in UWS show arousal (eyes opening) but unresponsive (no response to simple commands) and without signs of awareness (never presenting non-reflex voluntary movements). We define several metrics of information structures (Figure 3) that characterise the brain activity of healthy subjects and differentiate it from DOC patients (Figures 4–6). Cooperation values are the most relevant of these metrics. They measure in several ways the degree to which a certain network is influenced by the action of others. The ones showing the most cooperative behaviour are frontoparietal and default mode networks. Cooperation in these networks is altered in MCS and practically disappears in UWS (Figure 7). Metrics on information structures significantly distinguish conscious states using the statistics of the time-varying information structures (Table 1). Furthermore, complementing this with a machine learning approach, we were able to classify the state of each subject with a precision of 95.6% for HC/DOC and 86.6% for MCS/UWS (Table 2).

2 Methods

We aim to characterise different consciousness states by looking at the evolution in time of the attractor underlying the brain dynamics. Lotka-Volterra cooperative systems are used, looking at several measures on the Information Structures (Figure 1 A) underlying the system dynamics. Supplementary material (see B) contains details about the used measures and their computation. Figure 3 contains an example of the calculation for a specific Information Structure (IS). In summary, the first of them, *Number of Energy Levels* (NoEL), measures the levels in the IS. *FronDOSITY* corresponds to the proportion of nodes in the IS with respect to a maximum depending on the NoEL. *Criticality* indicates the proximity of the system to a phase transition. *Synchronicity* is the ratio of ISs having either maximum or minimum NoEL value (all nodes of the system are together present or absent in the IS global stable point). The *Cooperation values* (a vector of three components) measure different aspects of the interactions between nodes of the dynamical system enabling the presence (value greater to 0) of one of them in some level of the IS thanks to the presence of some others in previous levels. Finally, the *Highest cooperation level* is the maximum level of the IS in which a cooperation (emergence of a new node thanks to some others) is produced.

Given a system like that in Figure 1.B with fixed connectivity and changing activity in the nodes, it is possible to look at the changes on the attractor governing the system behaviour by looking at the variability of the IS measures.

The methodology is depicted in Figure 2. We have applied it to data corresponding to 147 participants (81 from Liège and 66 from Paris) including 49 healthy controls (HC, 36

Figure 1: Information Structures and their dynamics. **A.** Left: Lotka-Volterra 7-nodes dynamical system. Relevant parameters are those affecting just one node (α_i) and those representing cooperation, given by the weighted links (γ_{ij}) between nodes (i and j). Right: Associated to each system (for given α_i and γ_{ij} parameters) there is an Information Structure (IS), containing the attractor landscape, that is, stable points of the system dynamics and the solutions linking them. Black nodes in the stable points represent a value greater than 0 of the corresponding node of the dynamical system. White nodes stand for 0 value of the corresponding node. Different γ_{ij} and α_i values produce different ISs in both the global stable point (the one in the bottom) and the nodes in the intermediate levels. The structure of the IS can be studied through several measures (see Fig. 3) depending not only on the number of levels and nodes (NoEL and Frondosity, respectively) but also on the interaction between nodes (Synchronicity, Criticality and Cooperation measures). **B.** For a dynamical system with fixed connectivity (γ_{ij} parameters) and changing activity among the nodes (α_i) it is possible to study the evolution of the IS measures. The top graphic represents the change in time of the α_i parameters in a Lotka-Volterra 7-nodes system with fixed connectivity γ_{ij} . Associated to each instant there is an IS with the structure of the attractor underlying the dynamics of the system. The evolution of the system dynamics can be characterised by looking at the mean and standard deviation across time of the IS measures. Several notions like metastability, cooperation or information integration can be interpreted in terms of these measures.

Figure 2: Measuring the changes in the ISs underlying brain activity. Yeo’s 7-network parcellation is used to map the brain activity registered through fMRI into seven brain networks. For each subject, given the timeseries of the activity and the structural connectivity matrix, Lotka-Volterra Transform produces the α_i values at each instant. This allows the study of the Information Structures evolution in time. Machine learning is used to train classifiers which identifies the state of each subject with a precision of 95.6% (HC/DOC) and 86.6% (MCS/UWS).

from Liège and 13 from Paris), 63 in minimally conscious state (MCS, 31 from Liège and 32 from Paris) and 35 in unresponsive wakefulness syndrome (UWS, 14 from Liège and 21 from Paris). These datasets have been previously described in [12, 13]. The diagnosis was conducted using CRS-R by trained clinicians, with some differences between both datasets. In case of Liège patients, the diagnosis was confirmed with Positron Emission Tomography (PET). Details on data acquisition and preprocessing are in Supplementary Material (see A). Brain activity is mapped into the 7 areas in the well-known Yeo parcellation atlas: (1) Visual, (2) Somatomotor, (3) Dorsal attention, (4) Ventral attention, (5) Limbic, (6) Frontoparietal, and (7) Default Mode Network [11]. Lotka-Volterra Transform (LVT, see B.7) produces the evolution in time of the α_i parameters given individual structural connectivity matrices. These α_i reproduce exactly the filtered empirical BOLD fMRI signals. In LVT, $h = 3.55 \times 10^{-4}$ was used for participants with data acquired with $TR = 2000$ ms (all participants from Liège and 32 from Paris: 21 MCS and 11 UWS). For the other 34 Paris participants with $TR = 2400$ ms. (13 HC, 11 MCS and 10 UWS) $h = 4.26 \times 10^{-4}$ was used. The average SC matrix of all Liège HC subjects multiplied by $g = 0.27$ was used for all participants. We computed GASS, NoEL, frondosity, criticality, synchronicity and cooperation of the corresponding IS at each time instant. Figure 3 introduces and illustrates these measures.

IS measures were then used as the input for machine learning classifiers. Class classification models were selected using Auto-WEKA, an automatic model selection and hyperparameter optimization tool implemented in WEKA [14].

3 Results

Given the α_i values returned by LVT and the structural connectivity matrix, the non-stationary attractor landscape is computed at every time instant registered for each subject. The values of the IS measures (Figure 3) can be compared between different groups using the Wilcoxon signed-rank test. Table 1 shows the p-values of the comparisons between groups for centrality (mean or median) and dispersion (standard deviation) of IS measures.

Figure 3: Measures of Information Structures. An information structure (IS) is shown on the left. It is determined by the structural connectivity matrix (fixed) and the α_i values (variable at each instant) for the 7 networks in Yeo's parcellation. The nodes of the information structure correspond to stable states of the system. Networks with a value greater than 0 are coloured. The IS can be studied through several measures. *NoEL* (number of energy levels) corresponds to the number of layers of the IS (levels 0 to 4). *Frondosity* is the ratio of nodes in the IS with respect to the maximum for its NoEL. Cooperation measures are applied on cooperative nodes, which are those (except for level 1) where a network that did not appear in previous levels is activated thanks to the activity of other networks. The *highest cooperation level* is given by the highest level at which a cooperative node appears. Cooperation values consider cooperative nodes in different ways. *Cooperation value A* counts all cooperative nodes, adding in each case the level of the node from which it proceeds. *Cooperation value B* considers only one level (the lowest) for each new network, and *cooperation value C* operates in the same way but by adding powers of 2. Other used measures are *criticality* and *synchronicity*. *Criticality* measures how close are the alpha values to a bifurcation point that modifies the globally stable node. Finally, *synchronicity* measures the ratio of IS of a subject (across time) in which all networks appear in the same state (active or inactive) in the globally stable solution.

Low p-values for the Wilcoxon test (<0.05) ensure that the measures are detecting relevant differences in the distributions.

Table 1: Wilcoxon Signed-Rank test for different IS measures. The mean (μ) and standard deviation (σ) of each measure across all IS of a subject are calculated. In the case of criticality, the median (M) is used instead of μ , as it is more stable. Synchronicity is just one value per subject, so there is no mean and standard deviation. The Wilcoxon test compares the distributions corresponding to two different groups of the measure indicated in each row. HC: Healthy Control subjects. MCS: Minimally Conscious State. UWS: Unresponsive Wakefulness Syndrome. DOC: Disorders of consciousness (both MCS and UWS patients). The All column includes all subjects from Liège and Paris. Low Wilcoxon test p-values (<0.05) ensure that the measures are detecting relevant differences in the distributions. Greater values are in red. Machine learning is used to search for classifiers discriminating between HC/DOC and MCS/UWS. Leave-one-out cross-validation was used to evaluate the classifiers. The %f columns indicates the percentage of folds in the cross-validation using each measure in the best found classifiers (Table 2).

		HC / DOC				MCS / UWS			
		All	Liège	Paris	%f	All	Liège	Paris	%f
NoEL	μ	$< 10^{-10}$	$< 10^{-6}$	$< 10^{-3}$	100	$< 10^{-4}$	0.003	0.002	0
	σ	$< 10^{-8}$	$< 10^{-5}$	0.002	0	$< 10^{-4}$	0.004	0.004	0
Frondosity	μ	$< 10^{-13}$	$< 10^{-11}$	0.005	95	$< 10^{-6}$	$< 10^{-3}$	$< 10^{-3}$	0
	σ	$< 10^{-12}$	$< 10^{-10}$	0.011	1	$< 10^{-6}$	$< 10^{-3}$	$< 10^{-3}$	1
Criticality	M	$< 10^{-13}$	$< 10^{-10}$	$< 10^{-3}$	100	$< 10^{-5}$	$< 10^{-3}$	0.001	94
	σ	0.144	0.134	0.393	0	$< 10^{-3}$	0.003	0.010	1
Synchronicity		$< 10^{-13}$	$< 10^{-9}$	$< 10^{-4}$	96	$< 10^{-4}$	0.002	0.002	0
Coop. Level	μ	$< 10^{-11}$	$< 10^{-10}$	0.005	0	$< 10^{-6}$	$< 10^{-4}$	0.001	0
	σ	$< 10^{-10}$	$< 10^{-10}$	0.025	0	$< 10^{-6}$	$< 10^{-4}$	$< 10^{-3}$	1
Coop. Val A	μ	$< 10^{-9}$	$< 10^{-7}$	0.010	1	$< 10^{-6}$	$< 10^{-4}$	$< 10^{-3}$	100
	σ	$< 10^{-4}$	0.001	0.025	0	$< 10^{-5}$	$< 10^{-3}$	0.003	100
Coop. Val B	μ	$< 10^{-12}$	$< 10^{-10}$	0.004	100	$< 10^{-6}$	$< 10^{-4}$	$< 10^{-3}$	0
	σ	$< 10^{-10}$	$< 10^{-10}$	0.051	0	$< 10^{-6}$	$< 10^{-3}$	$< 10^{-3}$	99
Coop. Val C	μ	$< 10^{-11}$	$< 10^{-10}$	0.024	1	$< 10^{-6}$	$< 10^{-4}$	$< 10^{-3}$	0
	σ	$< 10^{-9}$	$< 10^{-8}$	0.066	94	$< 10^{-6}$	$< 10^{-3}$	$< 10^{-3}$	82

Figures 4 and 5 show the distributions corresponding to NoEL, frondosity, criticality and synchronicity for the subjects in the three groups. Together with the distributions for all subjects in the same state (All), Liège and Paris participants are shown separately to highlight the similarity between groups of subjects sharing the same state of consciousness.

The interpretation of frondosity as a measure of the absence of integration would result in the integration being higher in the control group and reaching its lowest value in the unresponsive group. This coincides with other criteria for the measure of integration [6, 15]. The variability of the frondosity can be interpreted as a measure of complexity so that the greater functional complexity would correspond again to the control group and the lower to the unresponsive group.

The measure of criticality indicates that the control group is the one closest to bifurcation points, while the unresponsive group is the farthest, having more stable but trivial

Figure 4: Distributions of NoEL, Frondosity and Criticality. Each subject contributes with one value in the distributions (the mean or standard deviation of the corresponding measure across time). Standard deviation of NoEL can be considered a measure of metastability, since it reflects the tendency of the system to change the attractors. Frondosity is related to integration: ISs with low frondosity exhibit greater cooperative interactions between nodes (see the cooperation measures on Fig. 6). Mean frondosity values very close to 1 (like those of UWS patients) denote a trivial brain activity. Criticality indicates how close is the system to a major change on the attractor shape (affecting the globally stable state). The lower the criticality, the closer the system is to a bifurcation point and the easier it is for the IS to undergo large changes. The median criticality distributions show that the IS of healthy subjects move closer to bifurcation points.

Figure 5: Distributions of Synchronicity. This measure is not applied to individual ISs. It is the ratio of ISs having the global stable point with all nodes in the same state (either 0 or greater to 0). That is, the extreme values of NoEL. Subjects with low Synchronicity have information structures with more differentiated behaviour of the nodes. UWS patients have synchronicity values very close to 1, denoting trivial brain activity.

information structures. It agrees with the idea that phenomenal consciousness is realized by a particular level of brain configuration guided by criticality and self-organisation [16, 17].

Fig. 6 shows the distributions of the mean and standard deviation of both the highest cooperation level and the different cooperation values. These measures are of particular relevance for identifying the type of brain dynamics characterising conscious states, as shown in Figure 7. Healthy subjects have more cooperative interactions (mean) and higher variability across time (standard deviation). In contrast, UWS patients (and to a lesser degree also MCS) have high levels of NoEL and frondosity but the brain dynamics is almost trivial, as there is barely any cooperation among the different networks. The most relevant networks in terms of cooperation are DMN and frontoparietal. This is consistent with some results pointing to their key role in conscious activity [18].

Using the IS measures in Table 1, classifiers have been trained using Weka. Table 2 (top) shows the confusion matrices of the classifiers together with several performance measures. The precision of the classifiers is 95.6% for HC/DOC and 86.6% for MCS/UWS. The areas under the ROC and PRC curves are in all cases greater than 0.92.

4 Discussion

Information structures [19, 20] have been previously used to determine the level of integrated information for different states such as wakefulness and different stages of sleep [9]. Identifying attractors in phase space and transitions between attractors may serve as useful descriptors for global brain dynamics [21], as they can be seen as a proper mathematical framework describing the space-time flow of observed dynamics [22].

The *model transform* (MT) allows simple theoretical models to be applied to complex empirical systems (such as the human brain) in each short interval of time [10]. In [9] it is shown that the simplest model in which the attractor landscape can be determined at each time point is the Lotka-Volterra (LV) model. This simple model: a) matches the

Figure 6: Distributions of cooperation measures. These measures consider in different ways the cooperative relationships between different networks (Fig. 3). It can be observed that the higher the consciousness level, the more cooperation is in the IS (mean) and with a higher variability (standard deviation).

Table 2: Performance of the classifiers. Confusion matrices describing the performance of the Weka classifiers for HC/DOC (left) and MCS/UWS (right). Classifiers are trained with the 15 measures in Table 1 and validated using leave-one-out cross-validation. This strategy trains the classifier as many times (folds) as subjects are in the dataset, leaving one of them out of the training for validation. At each fold, Weka selects the most relevant measures to train the classifier and the training is validated with the patient that was left out. Table 1 (column %f) shows the percentage of folds in which each of the 15 measures was selected for training. The resulting classifiers (JRip and REPTree) were found by Auto-Weka, an automatic mode for model selection and hyperparameter optimization. Several performance metrics are shown in the bottom table for both classifiers, for each of the classes and the weighted average. The true positive (TP) rate (also called sensitivity) is the probability that a subject belonging to the class is correctly identified. The false positive (FP) rate is the probability that a subject not belonging to the class will be misclassified. Precision and recall are complementary accuracy measures. Precision is the proportion of positive predictions that actually belong to the class. Recall is the ratio of positive predictions to total positive cases in the dataset. The F-measure is an accuracy measure that is calculated as the harmonic mean of precision and recall. The Matthews Correlation Coefficient (MCC) is a correlation (between -1 and 1) between the observed and predicted values. Finally the areas under the ROC (Receiver Operating Characteristic) curve and PRC (Precision-Recall Curve) are widely used measures of classifier performance. These areas are 1 for perfect classifications and classifiers with a value above 0.9 are considered to perform very well.

Weka JRip			
True label	HC	42	7
	DOC	0	98
		HC	DOC
		Predicted label	

Weka REPTree			
True label	MCS	58	5
	UWS	8	27
		MCS	UWS
		Predicted label	

Classifier	Class	TP Rate	FP Rate	Precision	Recall	F-Measure	MCC	ROC Area	PRC Area
JRip	HC	0.857	0.000	1.000	0.857	0.923	0.894	0.929	0.905
	DOC	1.000	0.143	0.933	1.000	0.966	0.894	0.929	0.933
	Weighted Avg.	0.952	0.095	0.956	0.952	0.951	0.894	0.929	0.924
REPTree	MCS	0.921	0.229	0.879	0.921	0.899	0.707	0.938	0.953
	UWS	0.771	0.079	0.844	0.771	0.806	0.707	0.938	0.881
	Weighted Avg.	0.867	0.175	0.866	0.867	0.866	0.707	0.938	0.927

Figure 7: Presence of brain networks in the GASS and cooperative interactions. The proportion in which each network appears in the GASS is shown above. Values range from 0.8 to 1. The highest values appear in UWS patients, followed by MCS. This is due to higher values of NoEL and frondosity. However, this does not imply complex behaviour in brain dynamics. The proportion of occurrences of each network in the GASS due to cooperative interactions of other networks is shown below. The values are between 0 and 0.1. The greatest values belong to HC (the leading group in terms of cooperative measures, followed by MCS, see Fig. 6). A greater differentiation between networks is observed than when looking at the GASS alone. The highest values in all three groups correspond to DMN followed by frontoparietal.

conditions so that its invariants could be ordered in energy levels, b) supports an algorithm of low computational complexity, c) includes empirical information regarding the structural connectivity of the brain, d) and has well-known conditions for the existence and uniqueness of its global attractor. Lotka-Volterra Transform (LVT) is the particular case of the MT when the LV model is used. The LVT can also be seen as a mathematical operator defined to exactly reproduce the empirical signals by finding the growth rate function that tracks their evolution over time. However, their equations are used to identify the temporal evolution of the global attractor and the non-stationary attractor landscape, *not* to model the temporal evolution of the system itself.

Our approach wants to give a mathematical foundation to the existence of a flow of structures with causal power. Since, in addition to this solid mathematical framework [20, 19, 9], we can confront concepts with real data from human brain dynamics, we believe that we are facing a very deep framework that deserves further investigation. In summary, our approach uses a mathematical concept from Dynamical System Theory as a useful tool to discriminate subjects in different states of consciousness. We think this mathematical construction tells us something about the real underneath structure of the informational flow in the human brain dynamics. Among all measures on Table 1 we find particularly interesting the case of cooperation values. It is a notion that cannot be watched by looking only at the global stable point of the attractor, as most whole-brain models do. The relevance of cooperation in frontoparietal and default mode networks (Figure 7) can only be observed by looking underneath the globally stable solution (bottom row of the figure). The GASS is a very relevant point in the dynamics of the system but by itself does not inform how and

through which pathways it is reached. Notions like metastability, information integration, or criticality require to look at the whole information structure. LV dynamical systems is an ideal framework because, as mentioned above, it allows these structures to be built and studied in depth.

Our findings point to the significance of the time-dependent topological structure of brain dynamics and promote the clinical utility of the informational structure for single-patient diagnostics. In our proposal, functional MRI resting state data are the starting point, which do not require sophisticated setup and surpass the need for subjects' active participation. Furthermore, many of the measures of consciousness in the scientific literature are defined for theoretical systems but difficult to apply in practice. For example, Φ in IIT 3.0 is applicable only to discrete Markovian systems [23], and, even when proposals have been made to define the ON and OFF states of IIT 3.0 in terms of emergent properties of assemblies of neurons [24], simplifications in the theory must be assumed. On the contrary, our theoretical framework can be implemented without simplifying the theory. Other measures can be estimated from real data using empirical distributions only if stationarity can be assumed. Non-stationarity is a remaining important challenge in many practical scenarios. For long data segments, it can be unrealistic to assume that all the statistics are constant throughout, while for shorter data segments, one cannot be confident that the system has explored all the states [25]. However, our measures are designed to be applied directly to non-stationary empirical data. By simply measuring the BOLD signal of a DOC patient and calculating through our formalism the informational structure measures for a few minutes, we can predict its state of consciousness with high accuracy.

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Author contributions

Design of the methodology: FST, JAG, JAL, MLK, GD. Data acquisition: JDS, JA, OG, AT, RP, SL. Data preprocessing: AE, YSP, ALG. Data analysis: FST, JAG, FJE, JAL. Writing of the manuscript: FST, JAG, JAL, AE, MLK, GD. Revision and discussion of the manuscript: all authors. Funding acquisition: JAL.

Data availability

The datasets analyzed during the current study are not publicly available due to constraints imposed by the ethics approval but are available from the corresponding author on reasonable request. Custom-made scripts to calculate IS measures are available upon request.

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