

# Humans Have a Distributed, Molecular Long-Term Memory

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**Abstract.** Most memory research has assumed that our long-term memories are somehow retained in our brain, usually by modified synaptic connections. This paper proposes a very different scenario, in which the basic substrate of these memories are molecules which flow within a newly discovered circulatory system similar to our lymph system. Moreover, the information bearing molecules are postulated to be cyclic protein polymers similar to the proteins found in all cell membranes.

Two network algorithms are presented which convert networks to, and from, such cyclic structures and seem to mimic the psychological processes of consolidation, recall, and reconsolidation.

#### 1 Introduction

In 1968, Atkinson and Shiffrin [4] proposed a bipartite human memory consisting of short-term and long-term storage. This division has permeated current memory models because it is consistent with a considerable body of subsequent research. It is assumed that short-term memory is encoded by synaptic connections in the frontal lobe. But, the actual mechanism of long-term memory has never been very clear.

There is ample evidence that cognition and many memory processes occur within the neural network we call our "brain". The hippocampus seems to be particularly involved with memory encoding and recall [35]. So is it not surprising that it has been assumed that our long-term memories are stored within the brain itself. The plasticity of synaptic connections is often cited as the mechanism [32].

But does this make sense? Many unexpected long-term memories, such as "the color of our date's gown at the Junior prom" or "the nonsense words of the 'Jaberwocky' ", just seem to "flash back" unbidden. These are totally inconsequential (in a survival sense). Would an organism employ an expensive, high energy system such as our brain to actually store such data for many years? We think not.

In this paper we will propose a physically distributed, molecular long-term memory encoded as cyclic protein polymers. This is not an entirely new idea. Others have proposed molecular, non-neural, long-term memories e.g. [29], which are usually thought to be encoded by means of protein phosphorylation e.g. [13,14,27]. Similarly, the possibility that information might be distributed has

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S. Wang et al. (Eds.): BI 2018, LNAI 11309, pp. 87–98, 2018. https://doi.org/10.1007/978-3-030-05587-5\_9 been observed, particularly in experiments with *Planaria* flatworms e.g. [19]. But, we are unaware of any proposal that these all together could constitute human long-term memory.

To do this we will make 6 key points.

- Storage of long-term data in a neural system is simply too expensive.
- Plants and other organisms without neural systems have mechanisms that react to environmental change.
- Eposidic human information is initially represented, in some form, by neural networks.
- There exist well-defined procedures that convert networks into "chordless cycle" structures and back again.
- Chordless cycle structures abound in every cell of our bodies and illustrate properties normally associated with vectors in a vector space.
- There have recently been found physical systems of unknown function that could circulate information throughout our bodies.

We have addressed the first bullet above. Each of the latter 5 bullets will be described in more detail in the remainder of this paper.

# 2 Primitive Memory

It is difficult to imagine any organism without a neural system having a "memory". But there is ample evidence that plants, even one celled bacteria have a rudimentary form.

Perhaps the most obvious, and first to be seriously studied, is *phototropism* in which plants grow towards a light source. It was known to Darwin that the *colepotile* (growing tip) is the sensor, and later the hormone *auxin* was identified as having a role in transmitting this information to elongate the proper cells in the stem [14]. One might not call this "memory"; but it clearly illustrates a non-neural sensing and transmission of information.

It can be argued that any reaction to a changing environment at least requires the ability to compare two time dependent states to determine a gradient. Baluška and Levin [5] cite many examples. Stock and Zhang [31] give a very detailed description of the biochemistry of "the so-called nanobrain, a sensorymotor regulatory organelle located at one or both poles of the [*E. coli*] cell that functions as a molecular brain to control motor function". This mechanism controls the movement of flagellar filaments so as to follow a nutrient gradient. Gagliano *et al.* [11] describe a fascinating experiment in which pea seedlings appear to "remember" an association between wind direction and a light source.

Even in multi-celled organisms with neural systems all information need not be concentrated in the brain. *Planaria* (flat worms) with a neural system and centralized brain have been widely studied. Like many primitive organisms, *planaria* can reproduce by lateral division, giving half their body, brain and neural system to each of the progeny. But, if cut transversely, the head will regenerate a new tail and the tail will regenerate a *new head*. This might be attributed to DNA; but McConnell *et al.* [15] demonstrated that the tail "remembered" episodic information with which it had been conditioned. This research has been critized for a small sample size and primitive methodology. But more recently, Neuhof, Levin and Rechavi [19] have reported similar results.

That shows that information can be represented and stored independent of a neural network.

Plants, one celled Ecoli bacteria and other primitive organisms are capable of storing information and reacting to change in their environment. But, these processes are limited and relatively slow. The evolution of neural cells and neural networks that appeared in the Cambrian era support a much more rapid response to environmental change, and a significant competitive advantage [27]. Yet, evolution often retains vestigal organs and procedures. Mechanisms found in plants and *planaria* may well have been retained in our evolution as long term storage.

#### 3 Neural Systems

It is well established that the brain is the central organ by which we sense our environment, recognize change and, in general, "think". PET scans and other research has identified specific regions of the brain where various processes take place. For example, the prefrontal lobe of the hippocampus is associated with memory [6,35]; the visual cortex is known to be associated with that particular sense [28]. However, many finer details are still obscure. We do not know precisely how data is encoded; but it is assumed that its network structure is involved [9,30].



**Fig. 1.** A network graph  $\mathcal{G}$  that might possibly model a neural configuration.

Graphs, such as Fig. 1, provide a reasonable model of network structure, in which nodes correspond to neurons and edges (links) denote connections between them. (Seven of the 53 nodes have been labeled for later reference.) In this

network model, if x denotes a specific neuron, we let  $x.\eta$  denote its "neighbors", that is all neurons to which it is connected. We assume  $\eta$  is *reflexive*, so  $x \in x.\eta$ . In Fig. 1,  $x.\eta = \{v, w, x, y, z\}$  and  $w.\eta = \{v, w, x, y\}$ .

"Closure" is a mathematical concept that has proven useful in the analysis of a variety of network configurations [10]. We think closure is likely to be the basis of concept formation [22]. There are many different closure operators, which we generally denote by  $\varphi$ , but the one we use here is: "y is in the closure of x if all of y's neighbors are also neighbors of x". Or symbolically,  $y \in x.\varphi$  if  $y.\eta \subseteq x.\eta$ ." In Fig. 1, w is in x-closure because  $w.\eta \subseteq x.\eta$ . This is a very simple closure process; but one which has been shown able to extract blobs within the visual pathway [26].

### 4 Consolidation and Recall

It is generally thought that long-term memories undergo a process that is commonly called "consolidation" [18]. Assuming that episodic events and other thoughts are somehow encoded in a neural configuration that can be modeled as a graph, we coded the procedure  $\omega$  below to eliminate redundant elements and consolidate it into an irreducible form,  $\mathcal{I}$ .<sup>2</sup> A network is said to be irreducible if every node x is closed.

```
while there exist reducible nodes
{
  for_each x in G
    {
    get x.nbhd
    for_each y in x.nbhd - x
        {
        if (y.nbhd contained_in x.nbhd
            {
            remove y and its connections from network
            }
        }
    }
}
```

There is considerable indeterminism in this code; but we can prove that regardless of the order in which nodes are processed, every graph  $\mathcal{G}$  has a unique irreducible form  $\mathcal{I} = \mathcal{G}.\omega$ . Of course, two distinct, but similar, network graphs  $\mathcal{G}_1$  and  $\mathcal{G}_2$  may have the same irreducible form, that is  $\mathcal{G}_1.\omega = \mathcal{I} = \mathcal{G}_2.\omega$ .

Long-term memories have to be recalled. Many have observed that "recall" involves a measure of active processing in our mind and that the recalled memory need not be a faithful copy of the stored episodic event [12,17]. Details are often changed.

<sup>&</sup>lt;sup>1</sup> In mathematics,  $\in$  and  $\subseteq$  stand for "in" and "is a subset of" respectively.

 $<sup>^{2}</sup>$  C++ source code for the following algorithms is available from the author.

The following simple procedure,  $\varepsilon$ , accepts an irreducible graph  $\mathcal{I}$  and expands it. Given a node y, lines 6 and 7 choose a random subset of  $y, \eta$  to be the

```
for each y in I
{
    while (|y.beta| > 1)
        {
        create new node z;
        S = choose_random_in (y.nbhd);
        z.nbhd = S;
        add {z} to N;
        }
}
```

neighborhood of the new node z. (The operator  $y.\beta$  in this code determines how many nodes should be expanded near y. Its specification is irrelevant to this paper.) Fig. 2(a) illustrates the irreducible graph  $\mathcal{I}$  that results from applying the procedure  $\omega$  to the graph of Fig. 1, together with (b) which is an expanded version of  $\mathcal{I}$  which we might call  $\mathcal{G}'$ .  $\mathcal{G}'$  is somewhat similar to  $\mathcal{G}$ , but not the same. Both networks of Fig. 2(a) and (b) were computer generated from that of Fig. 1. Networks of several thousands of nodes have been reduced and reexpanded using these codes.



**Fig. 2.** (a) The irreducible consolidation,  $\mathcal{I} = \mathcal{G}.\omega$  of Fig. 1, (b) An expansion (or recall)  $\mathcal{G}'$ , given  $\mathcal{I}$ .

If we consolidate the graph of Fig. 2(b) again, we will once again get the irreducible graph of Fig. 2(b). Many memory experts believe that "reconsolidation" is a fundamental aspect of memory maintenance [2]. We believe these two computer procedures constitute a reasonable, if abstract, model of the memory process.

#### 5 Chordless Cycle Systems

The consolidation of the network of Fig. 1 which is shown in Fig. 2(a) consists of 6 cyclic structures, each a sequence of nodes, sometimes called a "path" which loops back to the starting node. This kind of cyclic structure, which we believe may be the basis of biological signaling and storage, needs more explanation.

A chord is a single edge, or link, that "short circuits" the cycle. If the dotted link between the nodes a and b were to exist, it would be a *chord*. The 6 cycles of Fig. 2(a) have no chords. It is a chordless cycle system. Chordal graphs, in which there are no chordless cycles, have been widely studied [16]; chordless cycle networks less so. It can be shown [23] that every node in an irreducible network,  $\mathcal{I}$ , must be a member of a chordless cycle of length  $\geq 4$ .

Chordless cycle systems have the unique property that no cycle (regarded as a set of nodes) can be contained in another. This is sometimes called the Sperner property. Because of it, we can define a cycle composition operator which is analogous to vector composition in a vector space [24]. Indeed, each chordless cycle system can be shown to be a "matroid", or generalized vector space. The cycle system (or matroid) of Fig. 2(a) has rank 6 because it has 6 independent (basis) cycles and 20 distinct simple cycles, each behaving as an individual vector.

Vectors are often used to represent physical properties, and other forms of information. Cyclic structures can as well. Moreover, such molecular networks can be found throughout our bodies.

"Membrane proteins" are found in the membranes of every cell, separating its interior from its exterior, and the nucleus of the cell from its cytoplasm (as well as other organelles). These membranes are host to a vast number of protein polymers. Almén *et al.* have identified at least 6,718 human membrane proteins [3]. Membrane proteins control the movement of other proteins across these cell membranes that enclose the nucleus and other organelles within the cell. Some transport, or block, the protein movement [20,33], others relay signals across the membrane. Figure 3 is a 2-D view of a membrane protein polymer, consisting of several chordless cycles, known as Gr4 that has been studied at John's Hopkins [1]. The numerous non-cyclic filaments suggest an expanded form. In effect, these protein structures "remember" what in the cell's environment is "good" for the cell and what is not. It is not hard to visualize a similar mechanism operating on a multi-cellular level.

The "shape" of information can be important. The memory of our species, that is our DNA, is tightly bound in a double helix. It is virtually a ROM (read only memory) which must be essentially flawless. It is. But, our long-term memories must be loose enough to be "writable", and need not be perfect—just good enough. Systems of chordless cycles provide this kind of shape.

#### 6 Mechanisms of Distributed Storage

Encoding information with an underlying cyclic structure seems plausible. The matroid properties ensure the expected mathematical richness; and the fact that



Fig. 3. A 2-dimensional rendition of the membrane protein polymer, Gr4.

biological versions exist in abundance provides further confirmation. It is the fact that the storage medium appears to be distributed (based on *planaria* and other studies) that has always seemed problematic.

That is why the recent paper by Benias, Wells, Carr-Locke, Theise, *et al.* [7] seems so important. The authors describe a new physiological system which is somewhat similar to our lymph system in that it is body-wide and flows by means of peristalsis. In their own words: "these anatomic structures may be important in cancer metastasis, edema, fibrosis and mechanical functioning of many or all tissues and organs. In sum, we describe the anatomy and histology of a previously unrecognized, though widespread, macroscopic, fluid-filled space within and between tissues, a novel expansion and specification of the concept of the human interstitium." Nowhere do the authors mention "memory"; but if their speculation regarding its possible role in cancer metastasis, then this unnamed structure is a conduit of protein information. It is reasonable to think that the hippocampus might be able to inject coded protein based information into this conduit, and later withdraw that information.

#### 7 Discussion

While each of the 6 bullets presented in Sect. 1 can individually be well documented, the conclusion that taken all together they indicate a distributed circulatory long-term information store seems rather startling. Yet, it can make sense.

We envision processes in the hippocampus consolidating episodic experiences into cyclic polymer structures for storage, and expanding (recalling) them by means of phosphorylation to a more useful active form. The probability of recall would then be based on traditional diffusion properties. Of course, recall expansion must be a neural process based on a molecular stimulation. Such a model is rather novel. But since the years spent searching for a storage mechanism, or "engram" have so far seemed to be futile [17,25], perhaps we should consider an altogether different model. This model has the advantage that it can be tested by mathematical considerations and by further physiological research. If it is confirmed, it would create a firm base for psychological investigation as well as a revised view of the cognitive structures of our body.

### 8 Appendix

Too much formal mathematics makes a paper hard to read. Yet, it is important to be able to check some of the statements regarding chordless cycles made in the body of the paper. In this appendix we provide a few propositions to formally prove some of our assertions. If you dislike mathematics, ignore this section. It is not essential.

The order in which nodes, or more accurately the singleton subsets, of  $\mathcal{N}$  are encountered can alter which points are subsumed and subsequently deleted. Nevertheless, we show below that the irreducible form  $\mathcal{I} = \mathcal{N}.\omega$  will be unique, up to isomorphism.

**Proposition 1.** Let  $\mathcal{I} = \mathcal{N}.\omega$  and  $\mathcal{I}' = \mathcal{N}.\omega'$  be irreducible subsets of a finite network  $\mathcal{N}$ , then  $\mathcal{I} \cong \mathcal{I}'$ .

*Proof.* Let  $y_0 \in \mathcal{I}$ ,  $y_0 \notin \mathcal{I}'$ . Then  $y_0$  can be subsumed by some point  $y_1$  in  $\mathcal{I}'$  and  $y_1 \notin \mathcal{I}$  else because  $y_0.\eta \subseteq y_1.\eta$  implies  $y_0 \in \{y_1\}.\varphi$  and  $\mathcal{I}$  would not be irreducible.

Similarly, since  $y_1 \in \mathcal{I}'$  and  $y_1 \notin \mathcal{I}$ , there exists  $y_2 \in \mathcal{I}$  such that  $y_1$  is subsumed by  $y_2$ . So,  $y_1.\eta \subseteq y_2.\eta$ .

Now we have two possible cases; either  $y_2 = y_0$ , or not.

Suppose  $y_2 = y_0$  (which is often the case), then  $y_0.\eta \subseteq y_1.\eta$  and  $y_1.\eta \subseteq y_2.\eta$ or  $y_0.\eta = y_1.\eta$ . Hence  $i(y_0) = y_1$  is part of the desired isometry, *i*.

Now suppose  $y_2 \neq y_0$ . There exists  $y_3 \neq y_1 \in \mathcal{I}'$  such that  $y_2.\eta \subseteq y_3.\eta$ , and so forth. Since  $\mathcal{I}$  is finite this construction must halt with some  $y_n$ . The points  $\{y_0, y_1, y_2, \ldots, y_n\}$  constitute a complete graph  $Y_n$  with  $\{y_i\}.\eta = Y_n.\eta$ , for  $i \in [0, n]$ . In any reduction all  $y_i \in Y_n$  reduce to a single point. All possibilities lead to mutually isomorphic maps.  $\Box$ 

In addition to  $\mathcal{N}.\omega$  being unique, we may observe that the transformation  $\omega$  is functional because we can have  $\{z\}.\omega = \emptyset$ , thus "deleting" z, so  $\omega$  maps every subset of N onto  $N_{\omega}$ , Similarly,  $\varepsilon$  is a function because  $\emptyset.\varepsilon = \{y\}$  provides for the inclusion of new elements. Both  $\omega$  and  $\varepsilon$  are monotone, if we only modify its definition to be  $X \subseteq Y$  implies  $X.\varepsilon \subseteq Y.\varepsilon$ , provided  $X \neq \emptyset$ .

The following proposition characterizes the structure of irreducible form.

**Proposition 2.** Let  $\mathcal{N}$  be a finite symmetric network with  $\mathcal{I} = \mathcal{N}.\omega$  being its irreducible form. If  $y \in \mathcal{I}$  is not an isolated point then either

- (1) there exists a chordless k-cycle  $C, k \ge 4$  such that  $y \in C$ , or
- (2) there exist chordless k-cycles  $C_1, C_2$  each of length  $\geq 4$  with  $x \in C_1$   $z \in C_2$ and y lies on a path from x to z.

*Proof.* (1) Let  $y \in \mathcal{I}$ . Since y is not isolated, we let  $y = y_0$  with  $y_1 \in y_0.\eta$ , so  $(y_0, y_1) \in E$ . Since  $y_1$  is not subsumed by  $y_0, \exists y_2 \in y_1.\eta, y_2 \notin y_0.\eta$ , and since  $y_2$  is not subsumed by  $y_1, \exists y_3 \in y_2.\eta, y_3 \notin y_1.\eta$ . Since  $y_2 \notin y_0.\eta, y_3 \neq y_0$ .

Suppose  $y_3 \in y_0.\eta$ , then  $\langle y_0, y_1, y_2, y_3, y_0 \rangle$  constitutes a k-cycle  $k \ge 4$ , and we are done.

Suppose  $y_3 \notin y_0.\eta$ . We repeat the same path extension.  $y_3.\eta \not\subseteq y_2.\eta$  implies  $\exists y_4 \in y_3.\eta, y_4 \notin y_2.\eta$ . If  $y_4 \in y_0.\eta$  or  $y_4 \in y_1.\eta$ , we have the desired cycle. If not  $\exists y_5, \ldots$  and so forth. Because  $\mathcal{N}$  is finite, this path extension must terminate with  $y_k \in y_i.\eta$ , where  $0 \leq i \leq n-3$ , n = |N|. Let  $x = y_0, z = y_k$ .

(2) follows naturally.

**Proposition 3.** Let  $\rho(x, z)$  denote a shortest path between x and z in  $\mathcal{N}$ . Then for all  $y \neq x, z, \in \rho(x, z)$ , if y can be subsumed by y', then there exists a shortest path  $\rho'(x, z)$  through y'.

*Proof.* We may assume without loss of generality that y is adjacent to z in  $\rho(x, z)$ .

Let  $\langle x, \ldots, x_n, y, z \rangle$  constitute  $\rho(x, z)$ . If y is subsumed by y', then  $y.\eta = \{x_n, y, z\} \subseteq y'.\eta$ . So we have  $\rho'(x, z) = \langle x, \ldots, x_n, y', z \rangle$  of equal length. (Also proven in [21].)

In other words, y can be removed from  $\mathcal{N}$  with the certainty that if there was a path from some node x to z through y, there will still exist a path of equal length from x to z after y's removal.

Figure 4 visually illustrates the situation described in Proposition 3, which we call a diamond. There may, or may not, be a connection between y and y'as indicated by the dashed line. If there is, as assumed in Proposition 3, then either y' subsumes y or vice versa, depending on the order in which y and y'are encountered by  $\omega$ . This provides one example of the isomorphism described in Proposition 1. If there is no connection between y and y' then we have two distinct paths between x and z of the same length.



Fig. 4. A network diamond

In the following, we merely sketch the steps needed to show that any collection of chordless cycles can be regarded as a "matroid", or the analog of a vector space.

The cycles,  $C_i, C_k$  of an irreducible form  $\mathcal{I}$  can be composed by retaining all links (edges) in either  $C_i$  or  $C_k$  but not both. It will be a new chordless cycle which we denote by  $C_i \circ C_k$ . Let Y be a collection  $\{C_i, \ldots, C_k, \ldots, C_n\}$ . By the span of Y, denoted  $Y.\sigma$ , we mean the collection of all possible cycles that can be generated by composition of some subset of the cycles in Y.

**Lemma 1.** If  $C_k = C_i \circ C_m$  then  $C_i = C_k \circ C_m$ .

*Proof.* Let  $C_k = C_i \circ C_m$ , then  $C_i = C_i \circ C_{\emptyset} = C_i \circ (C_m \circ C_m) = (C_i \circ C_m) \circ C_m = C_k \circ C_m$ 

In Proposition 4, we show that the spanning operator is a closure operator. This is a rather different form of closure than that in Sect. 3 created by the neighborhood operator,  $\eta$ .

**Proposition 4.** The spanning operator,  $\sigma$  is a closure operator over sets Y of cycles.

*Proof.* To show that  $\sigma$  is a closure operator, we need show that for all sets X, Y(a)  $Y \subseteq Y.\sigma$ , (b)  $X \subseteq Y$  implies  $X.\sigma \subseteq Y.\sigma$ , and (c)  $Y.\sigma.\sigma = Y.\sigma$ . It is evident that  $\sigma$  satisfies (a) and (b). Only (c) must be demonstrated.

Let Y be a set of cycles  $\{C_i\}$ . Suppose  $C_m \in Y.\sigma.\sigma$  implying that there exists some sequence  $1 \leq i \leq k$  such that  $C_m = C_1 \circ \ldots \circ C_i \circ \ldots \circ C_k$ , where  $C_i \in Y.\sigma, 1 \leq i \leq k$ . Hence  $C_i = C_{i_1} \circ \ldots \circ C_{i_n}$  where  $C_{i_j} \in Y$ . Thus, substituting for each i in the composition sequence for  $C_m$  above, we get  $C_m = (C_{1_1} \circ \ldots \circ C_{1_n}) \circ (C_{2_1} \circ \ldots \circ C_{2_n}) \circ \ldots \circ (C_{k_1} \circ \ldots \circ C_{k_n})$  implying  $C_m \in Y.\sigma$ .

A closure system is said to be a matroid if it satisfies the Steinitz-MacLane exchange axiom [8,34], that is: if  $x, y \notin Y.\sigma$  and  $y \in (Y \cup x).\sigma$  then  $x \in (Y \cup y).\sigma$ .

**Proposition 5.** Let C be a chordless cycle system and let  $\sigma$  be the spanning operator. The system  $(C, \sigma)$  satisfies the Steinitz-Maclane exchange axiom and is thus a matroid.

*Proof.* By Proposition 4,  $\sigma$  is a closure operator. Let  $C_i, C_k \not\subseteq Y.\sigma$  where  $Y = \{\ldots, C_j, \ldots\}$ . Suppose  $C_k \in (Y \cup C_i).\sigma$  implying that  $C_k = C_i \circ (\ldots C_j \ldots) = C_i \circ C_m$  where  $C_m \in Y.\sigma$ . Consequently, by Lemma 1 we have  $C_i = C_k \circ C_m$  and  $C_i \in (Y \cup C_k).\sigma$ .

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