The Molecular Basis of Memory. Part 2: Chemistry of the Tripartite Mechanism

Gerard Marx*

MX Biotech Ltd., Jerusalem, Israel

Chaim Gilon*

Institute of Chemistry, Hebrew University, Jerusalem, Israel

ABSTRACT: We propose a tripartite mechanism to describe the processing of cognitive information (cog-info), comprising the (1) neuron, (2) surrounding neural extracellular matrix (nECM), and (3) numerous "trace" metals distributed therein. The neuron is encased in a polyanionic nECM lattice doped with metals (>10), wherein it processes (computes) and stores cog-info. Each [nECM:metal] complex is the molecular correlate of a cognitive unit of information (cuinfo), similar to a computer "bit." These are induced/sensed by the neuron via surface iontophoretic and electroelastic (piezoelectric) sensors. The generic cuinfo are used by neurons to biochemically encode and store cog-info in a rapid, energy efficient, but computationally expansive manner. Here, we describe chemical reactions involved in various processes that underline the tripartite mechanism. In addition, we present novel iconographic representations of various types of cuinfo resulting from "tagging" and cross-linking reactions, essential for the indexing cuinfo for organized retrieval and storage of memory.

KEYWORDS: Memory, tripartite model, cognitive unit of information (cuinfo), neuron, extracellular matrix, trace metal

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Definitions. The following terms are defined here for later discussions, as follows:

- **Tripartite System:** Memory emerges from the dynamic interaction of three physiologic compartments:
  1. Neurons
  2. Neural extracellular matrix (nECM), encasing the neuron
  3. Trace metals, dispersed within the nECM (dopants)

- **cog-info:** Abbreviation of "cognitive information" referring to basic unit of information obtained from the senses, employed by the neuron to compute (mentate).

- **cuinfo:** Cognitive unit of information, embodied as a [nECM:metal] complex (singular and plural); the molecular correlate of cog-info, equivalent to computer bit, which is used by the neuron as an information packet.
The computational components of the brain, the neuron and neural circuits, operate by electric and chemical signaling in an aqueous, but not empty, extracellular environment, comprising nECM with dispersed trace metal "dopants".

**Neuron.** The neuron is intimately connected to the external nECM by numerous electrically active surface features, notably, integrins, gap junctions, nodes of Ranvier, and chemical and electrical synapses. These are sensitive to the nanoscale dielectric, piezoelectric, and elastic properties of the nECM. Some proteins (tenascin) can attach directly to the neural membrane, providing another channel for neural interdigitation with the nECM. Thus, the neuron can be described as a cell that is intimately connected to its environment by virtue of the many electroeffects, sensors, and receptors on its surface membrane.

**Comments on the Histology of Neurons.** The structure of the neuron was initially elucidated from the histological works of Golgi and Cajal and many subsequent neurobiologists. They used a silver nitrate staining method, wherein atomic silver is deposited as nanoparticles, outlining cell structures.

\[
\begin{align*}
\text{Ag}^+ & \rightarrow \text{redox} \rightarrow \text{Ag}^0 \rightarrow \text{O}_2 \rightarrow \text{Ag}_2\text{O}^+ \\
\text{hydrophobic double bonds} & \rightarrow \text{insoluble silver} \rightarrow \text{insoluble black} \\
\text{soluble, clear} & \rightarrow \text{(Tollen's test)} \rightarrow \text{(Golgi, Cajal)}
\end{align*}
\]

Analytic chemists know that soluble silver salts (i.e., AgNO₃) in aqueous solutions are clear and uncolored. Experimental observations indicate that the cation Ag⁺ attaches particularly to lipids (especially double bonds (C=\(\text{C}\)). Exposure to a reducing agent generates elemental silver (Ag⁰), detected as a shiny surface precipitate (e.g., the Tollen’s test for reducing sugars). Shiny silver is easily oxidized, becoming visibly black (Ag₂O). Thus, Golgi and Cajal used the Ag⁺ nitrate stain to selectively visualize the lipidic neural surface membranes as well as intraneural compartments (nucleus, vesicles) of the newly identified neurons with synaptic connectors (Figure 1A). The silver stain technique has been also used to identify lipids for forensic⁴⁹ (Figure 1B), chromatographic applications⁴⁷ (Figure 1C) and neurotoxicity testing.

As the nECM is mainly a three-dimensional (3D) mesh composed of polysaccharide with very few reducing sugars, it does not react with the Ag⁺. Subsequent histologists with other types of stains (Nissle, immunochemical) continued this tradition of exclusively imaging the neuron as the main player in brain function, ignoring the contribution of the nECM. The converse of the tale of the "Emperor’s New Clothes" comes to mind. Everyone, save one boy, perceived the Emperor as clothed, though he was naked. Here, the neuron is viewed as naked, in synaptic contact with other, similarly naked, neurons, though the neurons are “clothed” with nECM.

**nECM Characterization.** The nECM can be described as a block copolymer, comprising a number of glycosaminoglycans (GAGs), polysaccharides of varying dimensions, as well as various proteins (for more details, see the appropriate references in ref 7).⁵¹-⁵⁶ All these contribute many electron rich (Lewis base) moieties that cooperatively chelate individual metal cations. These anionic coordination groupings are termed “binding pocket”, “chelating node”, or “address”. The binding characteristics of each metal cation for the electron rich (i.e., amine, carboxyl, phosphate, sulfate, hydroxyl, ether) moieties of the nECM is reflected by quantitative chemical parameters such as

\[
K_D = \text{dissociation constant}
\]

\[
K_{sp} = \text{solubility constant}
\]

\[
\text{CEC} = \text{critical electrolyte constant}
\]

These parameters reflect the inherent affinity of metals (found in the brain) with the electron rich, moieties presented by the nECM. The entrapment of a metal cation “locked” at a specific configuration/shape, effectively is defined herein as cuinfo (see below), sensed by the neuron.
Metals. The elemental metals are each uniquely distributed among the brain’s anatomic compartments. While most of the metals are present within the neurons, a significant amount, about 10%, is present in the nECM. Table 1 summarizes the gross levels of a number of elements in the brain, arranged as sets of monovalent, divalent, and polyvalent elements.

<table>
<thead>
<tr>
<th>Table 1. Groups of Brain Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>metal</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>K⁺</td>
</tr>
<tr>
<td>Na⁺</td>
</tr>
<tr>
<td>Rb⁺</td>
</tr>
<tr>
<td>Li⁺</td>
</tr>
<tr>
<td>Cs⁺</td>
</tr>
<tr>
<td>Mg²⁺</td>
</tr>
<tr>
<td>Ca²⁺</td>
</tr>
<tr>
<td>Zn²⁺</td>
</tr>
<tr>
<td>Al¹⁺/₂⁻/₃⁻</td>
</tr>
<tr>
<td>Co¹⁺/₂⁻/₃⁻</td>
</tr>
<tr>
<td>Cu¹⁺/₂⁻/₃⁻</td>
</tr>
<tr>
<td>Cr²⁺/₃⁻</td>
</tr>
<tr>
<td>Fe²⁺/₃⁻</td>
</tr>
<tr>
<td>Mn²⁺/₃⁻</td>
</tr>
</tbody>
</table>

Their distribution is not homogeneous, differing among anatomic compartments. Today’s invasive techniques, such as neutron activation analysis, atomic spectroscopy, mass spectrometry, and fluorescent labeling, only permit such analysis on ex vivo slices of the brain.

The process by which neurons specifically accumulate and store each of the elements is not generally known. Vesicles containing Ca²⁺ are known to be released upon neural activation (firing). Little else has been described regarding the selectivity of neurons for one or another traces elemental cation or their accumulation of redox activators (ascorbate, glutathione). However, it is apparent that the trace metals and some oxidants within the blood permeate the nECM to reach the neurons via passage through the nECM surrounding the cell. Some metals may freely diffuse through the nECM; others may be actively transported by metallothioneins or other metal transporters.

RESULTS AND DISCUSSION

Metal Binding Configurations. The elemental metal cations (Figure 2A) dispersed within the nECM can achieve a number of bonding geometries consonant with their electron shell disposition. For example, a divalent metal complex wherein the central atom is combined with 6 different electron rich moieties could exist in 15 geometrically isomeric forms (Figure 2B). Most metal cations diffuse through the nECM as hydrated cations, combined with at least 4 water molecules each.

Figure 2. (A) Table of elements, emphasizing the physiologically relevant trace metals. (B) Configurational possibilities of a single metal cation binding to multiple anionic moieties (chelating node).
anionic sites, one could formulate the metal complexation reactions as (Figure 3):

\[ \text{nECM} + M^{n+} (H_2O)_4 \rightleftharpoons [\text{nECM}: M^{n+}] + 2 \, H_2O \]

where \( \text{nECM} \) is the negatively charged matrix, \( M^{n+} \) is the cation of interest, \( n \) is the charge of the cation, and (H_2O)_4 is the hydration shells.

The illustration is meant to point out that the free energy (\( \Delta G \)), enthalpy (\( \Delta H \)), as well as the activation energy (\( E_{\text{act}} \)) for adsorption/desorption of metal cations to polyanionic substrates to form "cuiinfos" are all low, characterized by rapid rates with little heat generation.

The energetic of metal complexation reactions (on the order of 5–10 kcal/mol) permit rapid, but not always reversible, dynamics. At physiologic levels (concentration of \( 10^{-6} \)–\( 10^{-9} \) M), the trace elements in the nECM bind with low energy requirements (5–10 kcal/mol, the brain expending 400 cal/day), generating little heat, but affording huge combinatorial coding options. By contrast, the Blue Gene IBM supercomputer operates at 100 petaflops/s and uses more than 6.6 MW/h.

**Redox Reactions.** Multivalent elements, such as copper, iron, and manganese, can achieve more than 2 oxidation states, each with a number of complexation geometries, as summarized in Table 2.

<table>
<thead>
<tr>
<th>Oxid State</th>
<th>Coord Config</th>
<th>Coord No.</th>
<th>Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu^{+1}</td>
<td>d^10</td>
<td>4</td>
<td>tetrahedral</td>
</tr>
<tr>
<td>Cu^{+2}</td>
<td>d^9</td>
<td>5</td>
<td>square-planar</td>
</tr>
<tr>
<td>Zn^{+2}</td>
<td>d^10</td>
<td>5</td>
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</tr>
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<td>Fe^{+2}</td>
<td>d^6</td>
<td>6</td>
<td>octahedral</td>
</tr>
<tr>
<td>Fe^{+3}</td>
<td>d^6</td>
<td>6</td>
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</tr>
</tbody>
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Small redox activators, notably oxygen, ascorbate (0.7 mM in nECM), and glutathione (1 mM), with diffusion coefficients of 2–4, 1.6, and 5.6 \( \times 10^{-7} \) cm^2/s, respectively, are also present in the nECM. Thus, the significant concentrations of redox ingredients for site-specific Fenton reactions with reactive metals are present in the neuron and the nECM. A Fenton reaction occurs with cationic copper cycles between oxidation states of Cu(1) and Cu(II). Similarly, iron cycles between Fe(II) and Fe(III) (see Figure 6).

**Tagging Metal Complex via Redox Reactions.** As a consequence of local redox reactions between oxidants (such as ascorbate and glutathione) and multivalent metal complexes, carbonyl groups could be formed on the many glycans comprising the nECM. The many sugars and proteins that make up the nECM are rich in oxidation prone groups (such as primary and secondary hydroxyl OH) that could be oxidized into carbonyl (C=O) groups. Thus, the OH radicals, locally generated by the Fenton reaction, can derivatize the nECM lattice, by introducing aldehyde or keto carbonyl groups at specific locations, or causing carbohydrate ring-opening, leading to the formation of flexible "hinges" (Figure 7).

The energetic of metal complexation to the nECM to form "cuiinfo" is outlined in the energy diagram below (Figure 5):

\[ \text{Rate} = A \, e^{(-E_{\text{act}} / k_B T)} \]

The kinetic of which are described by the Boltzmann rate equation. The energy of activation (\( E_{\text{act}} \)) is low, the rate is rapid (\( k_B \) = Boltzmann constant), and the reaction is not very exothermic (\( v = \) valency state, usually from 0 to +3).

---

**Table 2. Coordinating Configurations**

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</tr>
</tbody>
</table>

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**Figure 3.** Reaction of hydrated metal cation with nECM.

**Figure 4.** Scheme of the reaction of monovalent and divalent metal cation with nECM.

**Figure 5.** Free energy diagram for complexation of M^{n+} to nECM, the kinetics of which are described by the Boltzmann rate equation. The energy of activation (\( E_{\text{act}} \)) is low, the rate is rapid (\( k_B \) = Boltzmann constant), and the reaction is not very exothermic (\( v = \) valency state, usually from 0 to +3).
referred to as cuinfo⁹⁸. This process would provide the cog-info complex with an identifier, a “tag” for sorting and easier recall, such as required to remember strong stimuli (pain, fear, hunger, pleasure, attention). Also, the tagged cuinfo⁹⁸ could help index (classify) the stored cog-info, accelerating recall.

There are multiple positions available in the saccharide subunits of the nECM (chondroitins, heparans, hyaluronates) for such carbonyl formation. Each saccharide (sugar) ring usually presents more than three oxidizable hydroxyl (OH) groups.

Ascorbate and glutathione are redox drivers of such reactions. For example, ascorbate is a very reactive molecule. In blood,⁵⁹−⁶³ it is sequestered within platelets, with high internal platelet ascorbate levels (mM range), compared to low blood plasma levels (μM range). An ascorbate level in neurons has been determined to be in the 1−10 mM range.⁵⁵−⁵⁷ Thus, the neuron has the resources (polyvalent metals and oxidants) to affect redox Fenton reactions within the nECM, whenever it is appropriately activated.

**Stabilizing Metal Complexes within the nECM.**

### a. Enzymatic Cross-linking.

An additional mechanism that forms and affects long-term memory is cross-linking reactions affected by enzymes in the nECM, such as transglutaminases,¹² which induce the formation of a covalent amide linkage between amine and primary amide moieties (such as Lys and Gln side chains), as follows (Figure 8):

The resultant amide bond is not susceptible to peptidases. For example, a fibrin clot is rendered more stable by the cross-linking induced by factor XIII (a transglutaminase). Cross-linking renders the [nECM:metal] complex (a cuinfo) more stable, suitable for long-term storage, but available for recall.

### Nonenzymatic Cross-Linking via Free Radical (Fenton) Reactions.

As a consequence of local redox reactions between oxidants (such as ascorbate and glutathione) and multivalent metal complexes, carbonyl groups (keto or aldehyde) could be formed on the many carbohydrates comprising the nECM (see above). The carbonyl groups can spontaneously condense with amine (−NH₂) groups forming imines (Schiff bases) as follows (Figure 9):

The Schiff base reaction is reversible. It can be maintained by the hydrophobic conditions, such as found in hydrophobic pocket of proteins, which greatly increases its stability. Conversely, exposure to hydrating conditions with slight pH variations could reverse the direction of the reaction, breaking the imine linkage.

Thus, the redox reaction leading to aldo/keto group formation, could effectively derivatize the [nECM:metal] complex, and also lead to cross-linking reactions, stabilizing the ensemble, ensuring storage of encoded cog-info.

Other condensation reactions between carbonyl groups, giving rise to cross-links, are shown in Figure 10. Aldol condensation¹² can occur in physiological media either by enzymatic catalysis (aldolases) or occur spontaneously by general base catalysis. The aldol condensation causes the formation of a covalent C−C bond. Such reactions have been...
shown to occur in the eye and the extracellular matrix of other tissues.

Other types of cross-links can be formed, such as those induced by lysyl oxidase-dependent and those originating from stochastic processes, such as the Maillard reaction, oxidation (for instance, dityrosine), and lipid peroxidation (such as malonyl dialdehyde-lysine cross-links).67−71

The essential point here is that a number of cross-linking reactions and locales are available for stabilizing the nECM:metal complexes, effectively ensuring long-term storage of cuinfo encoding cog-info, critical to memory. Alternatively, these processes can occur in an uncontrolled manner in pathological states in which memory is destroyed (e.g., dementia and Alzheimer’s disease).

Generations of cuinfo. The scheme whereby various generations of cuinfo are transformed by various reactions described above is outlined in Figure 11.

Iconographic representation of various classes of cuinfo is shown in Figure 12.

Pathways involving transglutaminase enzymes, or redox reactions (involving Schiﬀ base condensation, etc), further stabilize the complex by introducing one or more cross-linkers, rendering the metal complex more enduring.

Tagging cuinfo. Aside from the above-discussed Fenton reaction, other modes of tagging cuinfo could involve reactions such as acetylation, phosphorylation,72 sulfation, and methylation. These types of reactions are known to turn on/off certain metabolic pathways for proteins, DNA, and carbohydrates and are used in signal transductions.

Combinatorial Diversity of Tagging and Cross-Linking. We have described ﬁve types of tags (C=O, OAc, SO3, PO3, OMe) and three types of cross-links (transglutaminates, Schiﬀ base, and aldol condensates) (Figure 13). For every cuinfo complex, the nECM provides many potential moieties for affecting these reactions. Thus, in addition to the multitude of metal cations (n > 10) to form the cuinfo complex, the Avogadro-scale combinatorial options17−19 for tagging and cross-linking each cuinfo are also staggeringly huge (iconographic representation, Figure 13).

Hypothetical Model of cuinfo Formed with Tenascin and Zn. Tenascins73,74 are scattered throughout the nECM as monomers, trimers, or hexamers (star shapes).75−78 Knockout mice deficient in tenascins exhibited defective memory.79−82

The ﬁbrinogen globe terminating the tenascins contains polypeptides that are homologous to the C-termini of the β and γ chains of ﬁbrinogen. This region (D-domain) in ﬁbrinogen...
has been shown to bind Zn\textsuperscript{2+} with an affinity on the order of $K_D \approx 18 \text{ uM}$, affecting coagulation parameters, such as clotting time, clot turbidity, ultrastructure, and viscoelasticity.\textsuperscript{83–92} Also, the C-terminal epitope (Haptide) has been shown to be capable of attaching directly to and penetrate the lipid bilayer membrane of mesenchymal cells,\textsuperscript{93–97} as well as neurons (Marx unpublished).

Thus, we propose a hypothetical scheme whereby the tenascins attach directly to the neuron via their Haptide termini. The binding of Zn\textsuperscript{2+} alters the conformation/position of the epitope, effectively encoding cog-info as a $cuinfo^*$, affected/sensed by the neurons with iontophoretic/piezoelectric actuators embedded within the membrane (Figure 14).

The above Figure 14 presents a hypothesized scheme whereby Zn\textsuperscript{2+} binding to a fibrinogen-like region of tenascin induces a local conformational change in the protein, sensed at the neural surface as a “$cuinfo$ event”. Other cations could also be entrapped by the nECM to form variant $cuinfo^*$. Consonant with each element’s unique bonding traits (chelating bond lengths and angles), each type of cation binding event would impose its unique imprint (signal) on the conformation/position of the haptide epitope, induced or sensed by the neuron.

How can one describe a physiologically credible system wherein cog-info is transformed into memory? The proposed mechanism must conform to the limiting conditions of chemistry and physiology, in terms of low energy and rapid kinetics, but provide large encoding capacity. It should be couched in terms reflecting the biochemical underpinnings of all physiologic processes.

Golgi and Cajal developed the silver staining method, whose underlying chemistry we review here. Neurobiologists generally overlooked the nECM, imaging neurons “a la Cajal”, as if they were naked, suspended in space. Ironically, Cajal’s neural images with blank backgrounds blinded subsequent generations of neurobiologists to the importance of the nECM for neural...
Cross-linking (i.e., stabilizing) the nECM as a key component in neural processing of cog-info (mentation), ultimately sensed as recall.

Neurons are remarkably like blood platelets. Both accumulate metabolites, cofactors, and reactants in cytoplasmic granules or vesicles, which are released upon activation. For example, platelets accumulate ascorbate, zinc, fibrinogen, coagulation factors, and so forth in various granules or special cytoplasmic compartments which are released upon activation, all aiding the formation of a stable blood clot. The neurons also accumulate NTs, ascorbate, and trace metals within vesicles, released by action potentials. But to what purpose? We suggest that the neurons manipulate or sense the surrounding ensembles of [nECM:metal] complexes (cuinfo), using piezoelectric, viscoelastic, and iontophoretic sensors/actuators to encode and decode cognitive information (cog-info), from which the neural circuit integrates and consolidates memory. The nECM around the neuron is a relatively static lattice, but the trace metals distributed therein are mobile (dopants), whose reversible binding or desorption from a particular address are sensed by the neuron.

However, such sensing is not binary ($n = 2$), but multinary ($n > 10$). We respectfully defer more detailed discussion of the computational aspects of the tripartite mechanism to a subsequent manuscript (MBM Pt4).

Each bound element imposes a unique geometry to the adsorption locale (address), which is reflected by conformational twisting/dielectric modification, sensed by the neuron. However, metal binding reactions are inherently reversible, with a lifetime depending on the particular element and the anionic moieties. For example, monovalent cations form relatively short-lived complexes, compared to di- and trivalent elemental metals.

Cross-linking imposes covalent constraints on the [nECM:metal] complexes (cuinfo), rendering them much more stable, as exemplified by the cross-linking of fibrin by factor XIII. Transglutaminases enzymes impose covalent cross-links, rendering the cuinfo$^*$ much more resistant to degradative enzymes, effectively permanent. Some cross-linking reactions (Schiff base, aldol condensation, Maillard reaction) are themselves reversible, with stability dictated by local pH and/or enzymes. Cross-linking (i.e., stabilizing) the cuinfo$^*$ is iconographically represented by the “bow” notation in the Figure 12.

We conceive a process whereby the input of sensorial cog-info is encoded within the nECM by metal “dopants”. The initially formed, but unstable, monovalent metal complex (template cuinfo$^*$), is transposed and transformed into ever more stable sets of polyvalent metal complexes (derivative cuinfo) by various types of chemical transformations. We described Fenton reactions (redox) (Figure 6), condensation reactions between oxidized saccharide units (Figures 8, 9, and 12), as well as cross-linking by enzymatic pathways. Some of these occur in the ECM of various types of tissue, notably bone, skin, and eyes. Detailed evaluation of such reactions in brain tissue awaits further elaboration.

A hypothetical overview of the process of sensing an external event as cog-info involves its transformation into a storable form in the brain but outside the neuron (as cuinfo), available for recall by the neural circuitry. The tripartite mechanism permits one to chemically describe a sequence of processes, to rationalize the encoding and recall of cog-info as memory (Figure 15). It addresses the issue of how cog-info can be stored for long periods for recall (short- and long-term memory), and forgotten (by degradation or lack of critical components).

**CONCLUSIONS**

The chemical structures and processes described above are the basis for a molecular description of memory. It explains the highly efficient almost unlimited computational power of the human brain, using minimal amount of energy (400 cal/day equivalent to energy consumption of a standard laptop computer) with minimal heat generation, in aqueous media. The chemical interactions of the tripartite mechanism underlie “long term potentiation (LTP)”* or synaptic plasticity, manifest as short- and long-term memory. Hopefully, the above discussion will stimulate efforts to characterize molecular correlates of declarative, episodic, procedural, and other types of memory.

**AUTHOR INFORMATION**

**Corresponding Author**
*E-mail: gerardmarx@gmail.com (G.M.); chaimgilon@gmail.com (C.G.).

**Author Contributions**
Both authors have equal contribution.

**Notes**
The authors declare no competing financial interest.

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**Figure 15.** Conceptualized process whereby cog-info is encoded as [nECM:metal] complexes (cuinfo) and decoded by the neuron and neural circuitry, resulting in recall (memory), driving behavior.

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