Research Article
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Exploring hormone communication and perception of emotion

Abstract

Are the biological mechanisms that facilitate perception of external photon stimuli using the sense of sight also responsible for the perception of internal hormone stimuli using the instinctive sense of emotion? Different regions of the body influence one another by communicating on the molecular scale with small electrical ions as well as larger chemical macromolecules such as hormones. For example, the detection of a predator causes hormones to be produced throughout the body, leading to a rapid physical response. To model such a system, we divide biological phenomena into two stages: sensing and communication, where each stage uses electrical ions and various molecules as signals. Designing a biomimetic computer system that can perform such a task is currently a challenge due to the large size of biological macromolecules and the small size of digital electronic components that are suited for electrons. We derive a general molecular communication theory to describe the interaction of molecules on different time and space scales with a thermodynamic model of hormone equilibration based on the Minimization of Helmholtz Free Energy (MFE). Our work paves the way for future cutting-edge AI systems to utilize heterogenous units of information and as a result, more accurately resembles the style of computation performed by biological systems.

Keywords: emotion, artificial intelligence, hormones, computing, thermodynamics

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Abbreviations: BHN, biological hormone networks; AI, artificial intelligence; IQ, intelligent quotient; e-IQ, emotional-IQ; BNN, biological neural networks; MFE, minimization of helmholtz minimum free energy; MOAI, molecular AI; ANN, artificial neural network; BHN, biological hormone networks; MRI, magnetic resonance imaging; FA, fractional anisotropy; DEC, directionally encoded color; HVS, human visual system; LGN, lateral geniculate nucleus; IpRGC, intrinsically photo receptive retinal ganglion cells; EEG, electro encephalogram; BOLD, blood oxygen level dependence; TOLD, tissue oxygen level dependence; QM, quantum mechanics; ART, adaptive resonance theory

Introduction

Molecular communication and signaling is the primary catalyst for nearly all phenomena occurring in the body, occurring at different temporal and spatial scales. Microscopically, molecules affect cellular events such as apoptosis, or cell death, using signal molecules such as nitric oxide, and other events like cell growth via the human growth hormone somatomammotropin. Macroscopically, molecules are behind higher-level cognitive abilities such as feeling a particular emotion and perhaps even the feeling of creativity. Five decades ago, Alan Turing's efforts to capture human intelligence were established and became known as Artificial Intelligence (AI). New efforts to redefine the possibility space of AI as we know it have been coined Cutting-Edge AI, of which our contribution here emphasizes the exploration of the biological chemical molecular signal effects to include hormones and their resulting behaviors.

A current shortfall of AI systems is that they do not interact with their human users in an emotionally meaningful way; the AI cannot get to know both your Intelligent Quotient (IQ) and emotional-IQ (e-IQ). Learning a human's e-IQ would be particularly helpful for the growing elderly population who often require emotionally attentive interactions with others but lack the means to attain this on-demand. Current AI robotic humanoids and AI algorithms assume a single method of wired communication of electrons that can only convey binary information. Biological Neural Networks (BNN) has been emulated in circuitry and have also been modeled mathematically by the computing community. Numerous machine learning techniques are inspired by the fundamental properties by which BNNs naturally behave but are all inherently limited by electron-centric hardware and storage. Different parts of the human body communicate with one another using electrical signals that quickly travel along neurons, as well as chemical signals that travel slower through other pathways such as the circulatory, lymph, enteric, and other systems. We go beyond this limitation with a Cutting-Edge AI approach to more realistically emulate biological capabilities, such as emotion, within future robotic AI systems.

The main objective of this work is to explore a computational framework for unifying electrical ion communication and molecular hormone communication within the brain and other connected systems. This framework will help to establish a biologically faithful computational model for use in Cutting-Edge AI applications such as the perception and expression of emotion. First, we discuss related work in the neuroscience and computer science communities, then provide a biological review of electrical and chemical signaling in the human sensory system and downstream effects in brain structures related to emotion. We discuss an approach for establishing a computational tool for simulating molecular communication networks in the human body which can allow us to study emotion synthesis and how that is impacted by hormone imbalance introduced by various mental disorders. Next, we review the various hormones, emotion and relevant mental health considerations that may be addressed in the future through our approach. We propose general molecular dynamics principles that describe the interaction of molecules on different time and space scales by deriving a thermodynamics model of hormone equilibration based on the Minimization of Helmholtz Minimum Free Energy (MFE). Finally, we discuss the intended approach for establishing our framework as a computational tool for simulating molecular communication networks in the human body that allows us to study emotion generation and variability arising from the biological differences of various mental disorders.

Related work

The first Computer Science AI deep learning algorithm was biologically inspired by the visual cortex (occipital lobe) and its ability to perform multi-layer processing: layer #1 for piecewise edge detection "on-center, off-surround", layer #2 passing from layer #1 for extrapolating connectivity between close-enough edges, layer #3 for determining the change of change, known as curvature detection, which can determine if a shape is convex or concave, etc. Light sensed by the eyes passes through a series of brain structures such as retinal ganglion cells and the lateral geniculate nucleus, then ultimately converges at the visual cortex, located in the back of the head. The output of the visual cortex provides a state of isolated object recognition and is augmented by the associative hippocampal memory and emotionally encoded amygdala memory. The multiple neural pathways and anatomical structures that facilitate visual perception demonstrate the true complexity of biological Deep Learning. Computers can emulate AI Deep Learning using linear algebra coupled with Boolean logic, but neglect the critical role played by different molecules that facilitate electrical signaling; thus, we hope that Molecular AI (MOAI) can be emulated as well. For example, artificial neural network (ANN) models try to mimic the properties of BNNs, however, Biological Hormone Networks (BHN) have not been mathematically modeled in a systematic way or studied in the context of computation.

It is especially important to consider that the human brain is an imperfect system which is prone to hormonal imbalance, which can lead to mental disorders as well as cause physically debilitating disorders or thought processes that inspire societally damaging behavior. Why do people intentionally take their own lives or the lives of others? Suicidal terrorists have been a long-standing societal issue with many possible underlying causes. The psychology of these individuals requires case studies with a deeper understanding of the biological underpinnings of radicalization. It is possible that individuals who are susceptible to radicalization through brainwashing techniques possess physical differences in their e-IQ center, amygdala, as well as the rational intelligence center, hippocampus. Hormonal imbalances are a likely culprit for individuals that are susceptible to adopting and acting on different ideologies over time. Fluctuations in the emotional demeanor of an individual can be detectable through a timeline of verbal or written communication. An analytical system to determine individuals at risk of an ambiguous personal ideology or memory would be of great use to law enforcement and medical community for performing triage and intervention before it is too late.[1]

The neuroscience community has made important advances in brain imaging techniques in recent years. Improved precision of Magnetic Resonance Imaging (MRI) that illuminates white matter pathways, DT-MRI, allows medical professionals to non-invasively identify anatomy which requires attention from a surgical or therapeutic standpoint.[2] Utilizing advanced registration techniques, high-resolution templates can be created for cohort groups of subjects, such as healthy or individuals affected by a mental condition which causes differences in anatomical sizes for certain regions of the brain.[3] Similarity metrics can be used to compare anatomical structures between a set of cohort templates and a DT-MRI scan of unseen subjects. The template creation strategy and analytical tools is a framework which will enable the pre-clinical DT-MRI studies for understanding and treating brain disorders.[4]

The image processing pipeline of DT-MRI utilizes a T1 weighted MRI image as a registration target for a set of diffusion weighted MRI images obtained by varying the magnetic field direction. The notion behind this novel imaging technique comes from the observation that water molecules will diffuse along the direction of the magnetic field when inside of a fiber traveling in the same direction, producing a high signal. Water molecules will not diffuse outside of a fiber, so a fiber which is perpendicular to the incoming magnetic field will yield a signal of zero. A diffusion tensor is then computed for each voxel that can describe local water diffusion. Sophisticated image pre-processing steps are often required for DT-MRI such as denoising and accounting for other device specific distortions. Each diffusion weighted image is registered to the T1 image, and additional images can be derived from the co-located data such as Fractional Anisotropy (FA), and Directionally Encoded Color (DEC) maps, as shown in Figure 1. The template displayed below was obtained through the Human Connectome Project open dataset and was formed using scans of 842 subjects, 372 of which were male and 470 were female and were between 20-40 years old.[5] The FA image shows the major white matter pathways in the brain and can be used along with other derived images such as the DEC map to create other useful data visualizations such as fiber tractography reconstruction. Tractography is an approach to generate 3D models of anatomy out of the major fiber pathways discovered through DT-MRI and can be visualized in a graphics rendering engine. Using a DT-MRI template and derived images from Figure 1, full brain fiber tractography can be generated. Furthermore, fibers emerging from and terminating into specific brain regions, such as the amygdala, can be selected for detailed analysis shown in Figure 2.

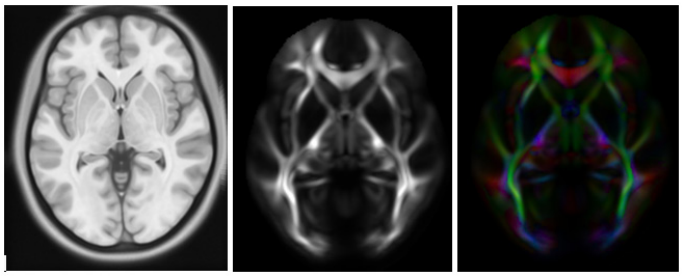

Figure 1 Axial representation of the DT MRI processing pipeline. (a) A T1 weighted image is used as a reference image, (b) FA is computed using multiple diffusion weighted images, and (c) a DEC map is created, where colors indicate fiber orientation.

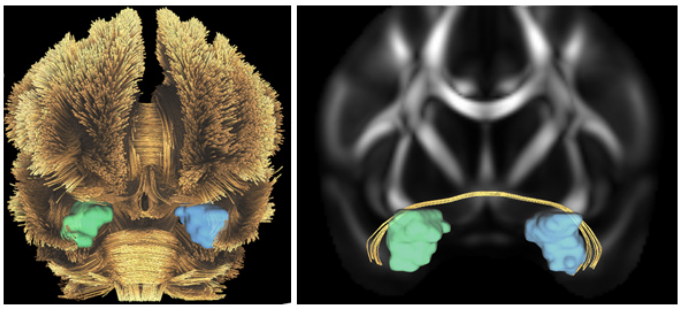

Figure 2 Frontal coronal view of fiber tractography generated using DSI Studio from the Human Connectome project DT MRI data. (a) Full brain fiber tractography with right (green) and left (blue) amygdala shown inside, and (b) Amygdala specific fiber connectivity isolated with FA in the background.

The fiber tractography technique is not yet perfected due to MR scanner limitations as well as a lack of 'gold standard' in-vivo fiber tractography ground truth data.[6] Although tractography is only an approximation to actual anatomical brain connectivity, when coupled with computational chemistry software, we believe 3D renderings

from healthy templates and from templates built from cohort groups of subjects sharing a mental disorder can be utilized in a computational framework for understanding electrical and chemical communication in the brain. The Computational Chemistry and Computer Science fields have developed several open-source tools, such as Avogadro, PyMol, and Ghemical to name a few, for simulating and displaying inter and intra molecular forces on an atomic scale in a 3D rendering engine. Molecule editors like Avogadro offer visualization tools are designed for cross-platform use in computational chemistry, molecular modeling, bioinformatics, materials science, and additional areas. It offers flexible high-quality rendering and a powerful plugin architecture.[7] A typical hormone, glutamate is shown in Figure 3 and an exemplar 'fiber tract' is shown as a carbon nanotube containing multiple glutamate molecules, simulated with Avogadro.

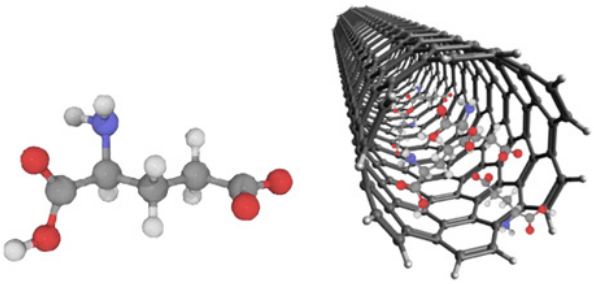

Figure 3 Molecular dynamics rendering software can realistically simulate molecular interactions from (a) A single glutamate molecule, to (b) a collection of glutamate traveling along a 'fiber' (carbon nanotube).

Augmenting a tractography volume with an accurate chemical simulation tool will create a novel testbed for understanding hormone communication in the brain and serve as a synthetic 'anatomical breadboard' for prototyping hardware that can utilize electrical and chemical signals in computation to develop cutting-edge AI applications.

Biological review

The interplay of electrical and chemical signaling mechanisms can be seen all throughout the body in virtually every biological structure. Electrical signaling is a mechanism by which molecules are passed as information through a BNN using conduction along neurons. These electrical signals are known as action potentials. Action potentials utilize ions such as larger sodium and smaller potassium cations. The action potential signaling mechanism is initiated by sodium ions flowing into a cell, and potassium ions flowing out of the cell, maintaining equilibrium in the cell. Only a small concentration of ions needs to enter the cell membrane for the voltage to vary significantly. The firing rate of a neuron is the frequency that a neuron sends an action potential. In digital circuitry, an action potential is simply realized as an increase in voltage along the circuit wire that is represented as a 1 (V>50Hz) or 0 (V<50Hz). This voltage passes through logic gates which can alter the output current. Even a unicellular organism such as slime mold uses electrical signaling and possesses some memory.[8]

It is quite interesting to explore the complex BHN of multicellular human beings which gives rise to emotions. The various emotions we experience are mostly a result of hormone production throughout the body, and perception of those hormones by specific receptors in specific regions the brain, such as in the amygdala. The amygdala can also enhance learning and memory storage media in the adjacent hippocampus through emotionally driven chemical signaling, such as fear-induced visual stimuli as shown in Figure 4.[9,10]

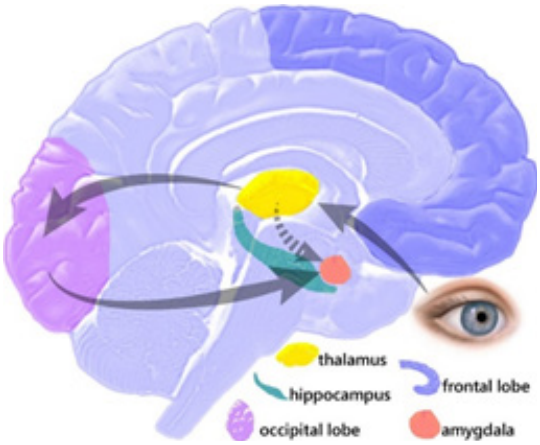

Figure 4 Fast pathway of information from the eye to the Amygdala in the case of a fear response.[10]

Chemical signaling occurs in the body mainly using molecules such as hormones and neurotransmitters. There are many types of hormones and neurotransmitters, but they are all larger, more complex molecules than the small molecules used in electrical signaling mechanisms. Instead of passing through the membrane of a cell, they bind to receptors on the outside of a cell and cause a reaction within the cell. Cells have a mechanism to allow smaller ions in and out, known as an ion channel. Ion channels can be classified based on their gating - the type of stimuli responsible for opening and closing the channel. An electrical gradient across the cell membrane is responsible for opening voltage-gated ion channels as well as closing them. However, binding of a ligand (molecule) to a channel is responsible for the activation and deactivation of ligand-gated ion channels.[11]

A well-studied phenomenon where both types of signaling mechanisms are involved to perform a biological function exists in the human visual system (HVS). At the biological sensor level, the HVS exemplifies a coupled electronic and chemical signaling phenomena beginning in the eyes for tasks such as night vision capabilities, by separating energy from information. Disorders such as focusing for near-sightedness, or photon sensitivity in cataracts are treated separately. In the back of each eye, the retina is composed of hundreds of millions of photon sensors known as photoreceptor cells, which allow us to see the world around us. The retina is composed of a population three main types of cells that form a mosaic surface able to sense light of different wavelengths. *Cone* (color vision) and rod (shade/intensity) cells are the beginning of an information pathway to the brain through circular neighborhood groups of rod and/or cone cells that collectively synapse with bipolar cells. Bundles of bipolar cells then synapse with ganglion cells, which integrate the collective signal and communicate this information in a wired fashion to the brain using an action potential. The information exits they eye via the optic nerve and feeds into the Lateral Geniculate Nucleus (LGN), the visual cortex (occipital lobe), and other processing centers for understanding the environment. A separate information pathway exists in the retina which is mediated by intrinsically photo Receptive Retinal Ganglion Cells (IpRGC). Unlike the rods and cones, IRPGC cells perform chemical signaling by regulating certain hormones, i.e., melatonin, dopamine, related to our circadian rhythms as well as perform other autonomic functions. The complex ecosystem of retinal cells which use electrical and chemical communication is shown below in Figure 5.[12]

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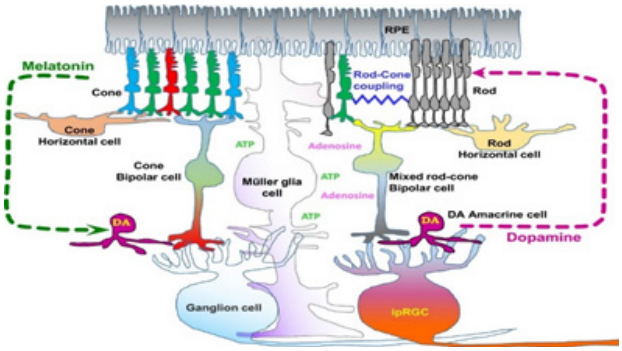


Figure 5 Diagram of retinal cells and the hormones involved with early vision.[12]

Academician Chuck Hagins of National Institutes of Health, National Eye Institute resolved the paradox of single photon detection at human body temperature with the notional 'dark current'. He observed that when a photon is absorbed by a retinol molecule in the dark-adapted rod cell, even such a small change can cause the visual transduction process to occur, whereas this is not possible in the daytime.[13] The biological phenomenon of dark current uses 'negate the converse logic' - namely a lack of dark current implies the detection of a photon. The energy of the dark current results from a constant leakage of potassium from the rod photoreceptor, and an influx of sodium ions via cGMP-gated channels and calcium ions via voltage gated channels into each rod. Calcium ions force the neurotransmitter glutamate to be constantly released from the base of the rod cell at its synapse, creating a downstream inhibition of ganglion cells. In the presence of light, cGMP production stops, sodium channels and calcium channels close, which reduces the release of glutamate. Without glutamate inhibiting the integrator Ganglion cell, an action potential can fire along the optic nerve via saltatory conduction. The altered chemical composition of the dark-adapted photoreceptors modifies the internal energy of the sensor system to enhance the information, depicted below in Figure 6.[14]

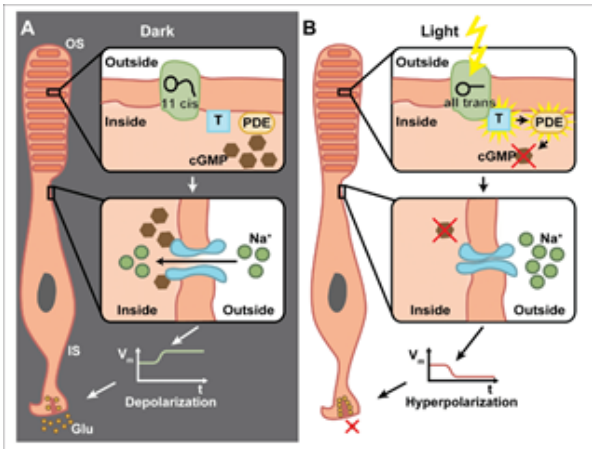


Figure 6 Rod cell under the influence of dark current (left) and in normal daylight conditions (right). Dark current mechanism constantly releases glutamate, while light conditions inhibit release.[14]

Biological sensory systems and processing centers of typically involve pairs of sensors; capturing signals from the external world with two eyes, hearing with two ears, smelling with two nostrils and olfactory bulbs, tasting with numerous taste buds, and touch with thousands of tactile receptors distributed over the skin. Paired sensors exist in intermediate relay organs as well, such as the amygdala, which perceives the internal world of hormones and neurotransmitter communication using molecular receptors. The 'power of sensor pairs' are enhanced by brain regions downstream from perception such as the hypothalamus to regulate body temperature and pituitary gland in order to promote hormone release throughout the body. A consensus seeking effect seems to exist in the brain that begins with input signals from a pair of sensors that must agree to be a signal, and a disagreement may be noise that requires further paired sampling. If a signal is determined to be noise by the brain's sensory fusion areas, it is radiated out of the skull as thermal energy, heat, and can be measured by an Electro Encephalogram (EEG) device. Our brain keeps information flowing through the sensory processing pathway but rejects noise in order to keep a constant temperature. Past research has suggested that activity in the amygdala is dependent on visual awareness. However, recent physiological research has provided evidence to a new hypothesis that the amygdala enhances the visual awareness through bidirectional projections with the visual cortex.[15] There are several functions performed by the amygdalae, such as encoding stimuli with emotional association for memory, facilitating the decision-making processes and emotional responses, and thus serves as a very interesting structure to understand in the context of cutting-edge AI.

Hormones, emotion, and mental disorders

Physical movement, sensing and thinking in our brain requires communication throughout the body using the central nervous system. The largest neuron in the body extends from the motor cortex to the toe, through the spinal cord. There is an extremely high velocity of electrical signal for this part of our body is due to the large width of the neuron and the anatomical location of toe tactile sensors in the motor cortex. Despite its long distance from the motor cortex, we can sense tactile information on our toe with the same latency as a location much closer to the motor cortex, such as the neck. This survival system is possible due to the electrical signal communication capability of the nervous system, oxygen delivery through blood traveling in the circulatory system, and the lymph system which cleans up cell waste (large unused molecules) from all cells in the body with fluid. The lymph fluid is transported to lymph nodes which are 'filtering stations' in the body. Our brain has tens of billions of neurons but also has 100 billion glial cells and Schwann cells which surround the nervous system and perform house-keeping functions. Epithelial cells also play a role in chemical hormone messages throughout our body.

Hormones fill the role of messengers which initiate numerous behaviors in the body. Hormones are responsible for reproduction, growth and development, respiration, metabolism, sensory perception, and many other capabilities. Endocrine hormones are known to modulate emotions, mood and behavior. The hypothalamus in the brain is responsible for maintaining homeostasis and instructs the pituitary gland through messengers to either promote or inhibit production of hormones such as oxytocin for growth, melatonin and dopamine for sleep, serotonin for alertness. The pineal gland produces melatonin to regulate our circadian rhythm (body clock). Our kidneys produce a long-term hormone, cortisol and a short-term hormone, adrenaline. Hormones can either move through a cell membrane or bind to receptors on the cell membrane to cause a change within the cell. In addition to hormone producing centers in the body, there are structures such as the amygdala which process large concentrations of hormones with a dense collection of hormone receptors.

The amygdala is a key structure which mediates emotional processing and appears to be responsive to electrical stimulation in

order to elicit changes in emotional physiology without changing the subjective experience. This is important for studying the effects of amygdala-mediated modulatory effects on cognition.[16] Each side of the amygdala performs specific functions that influence how we perceive and process emotion. Both sides have specific internal and independent memory architecture but are symbiotic when storing, encoding, and interpreting emotion. Studies have shown that stimulating the right amygdala causes negative emotions to surface, including anger, fear and sadness. However, when the left amygdala is electrically stimulated, either pleasant, happy, or negative emotions emerged.

The left side amygdala has been shown to be involved with the brain's reward system, while the right side is heavily involved with memory management and creation, the association of 'when' and 'where' with emotional features.[17] The right side also facilitates fear expression, and processing of fear-inducing situations. While it is known that the auditory system communicates with the amygdala in an excitatory capacity, it has recently been discovered that the amygdala also receives inhibitory chemical communication from the auditory system in the same location. It appears that a timing and ratio of excitation and inhibition can dynamically affect the output of the amygdala and can be interpreted as a general mechanism for auditory stimuli to affect emotional behavior.[18] Such excitation and inhibition phenomena via auditory pathways in the amygdala may have analogous capability with other sensor systems, such as dark current in the eye, mentioned above.

Numerous neurological disorders can affect the amygdala**,** such as depression, anxiety, and Alzheimer's disease.[19] These disorders can manifest themselves in places where the physiology is not adequately equipped to handle the supply and demand of the chemical signaling from other places in the body. A diminished ability to sense and process constant chemical communication via hormones causes imbalances all over the body. Hormone imbalances can disparately affect brain activity. Table 1 in the appendix at the end of this document shows the relationship between several hormone production locations in the body and some disorders and symptoms that can arise from an imbalance of this hormones.[20]

Table 1 some hormone production sites and disorders that can result due to hormonal imbalance[20]

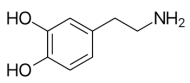
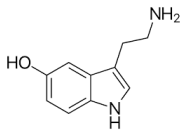
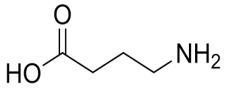
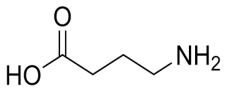
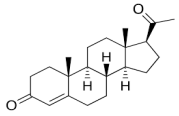
Anatomy	Hormones	Disorders	Symptoms
Thyroid	Dopamine 	Hypothyroidism	Fatigue Difficulty Concentrating/Attention Memory Problems Depression Psychosis
	Serotonin 	Hyperthyroidism	Sleeplessness Anxiety Irritability Racing thoughts
	GABA 		Difficulty Concentrating/Attention Memory problems Depression Mania Psychosis
Ovaries	Estrogen 	High Estrogen	Mood swings/Depression Fatigue Headaches/migraines Memory Loss Thyroid dysfunction Sleep Problems
		Low Estrogen	Mood swings/Depression Fatigue Heart palpitations Osteoporosis Memory loss Sleep problems
	Progesterone 	Low Progesterone	Anxiety/Depression Sleep Problems Postpartum depression Bone loss

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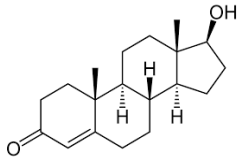
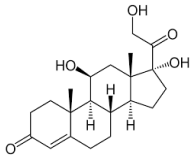
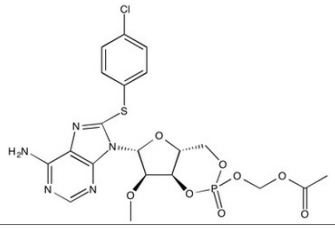
Table continued...

Anatomy	Hormones	Disorders	Symptoms
Testes	Testosterone	Low Testosterone	Mood swings/Depression
			Anxiety
			Difficulty Concentrating/Attention
			Low motivation
			Fatigue
			Sleep Problems
			Low bone density
Adrenal glands	Cortisol/DHEA	Adrenal Fatigue	Low stress tolerance
			Fatigue
			High blood pressure
			Memory loss
			Dizziness
			Premature aging
			Low resistance to infection
			Poor wound healing
Pancreas	Insulin	Blood Sugar Issues	Anxiety
			Depression
			Schizophrenia
			Irritability
			Anger
			Difficulty Concentrating/Attention
			Addiction to sugar

Using high resolution DT-MRI, white matter tracts can be visualized within the amygdala, allowing input and output neurons to be traced to neighboring brain regions. The density of hormone receptors in a single amygdala can be estimated by tract count that is revealed using high-resolution in-vivo imaging.[21] Additionally, it has been discovered that brain tumors can be detected using oxygen sensitive MRI by combining blood oxygen level dependence (BOLD) and tissue oxygen level dependence (TOLD) to differentiate healthy tissue from the tumor.[22] Combining measurements of amygdala tract density as well as tumor likelihood would provide important insight when exploring the physiological characteristics associated with several mental disorders.

The complex interplay between electrical communication and chemical balance of hormones in our body is remarkable, but also difficult to model analytically. Very subtle differences in the properties of biological structures can lead to an imbalance of hormones in the body, resulting in widely different perceptions of the outside world and a different quality of life for individuals. Homeostatic equilibrium within the body requires a delicate balance of hormone production and reception to facilitate effortless chemical and electrical communication. In order to capture a desired internal equilibrium state, we shall derive a set of principles that describe a general model of molecular dynamics for both balanced and imbalanced neurological systems and we then attempt to elucidate how these imbalanced systems are tuned towards normal functioning.

Mathematical model

We wish to state that all molecular signaling follows "Hagins' principles"[16] used to describe the dark current phenomena: Principle #1 Separate material-energy from information, i.e., Energy and Information are two separate entities; Principle #2 The Logic can negate the converse, i.e., if and only if P were true, then Q is true; then, if not Q implies not P. Are Hagins' principles true for all chemical molecular signals? Perhaps this is consistent under circumstances where a quick reaction time to fear-inducing stimuli affords the same dark-current mechanism to increase the probability of detection while lowering the threshold for electrical and chemical communication in other sensor systems. How could early humans adapt to detect a single photon from a predator's eye in a dark cave and survive?

We first conjecture that "nature has limited set tricks that our body can emulate". All molecular signals, including macro-molecules, i.e., hormones obey this same information-energy separation principle, exemplified by the HVS i.e., sodium (Na+), calcium (Ca+), potassium (K+) ions, and glutamate in the human visual system can demonstrate both principles (1) and (2) for other larger molecules at the constraint of our warm body background temperature (i.e., 300ºK=1/40 eV). This seems to go against the Quantum Mechanics (QM) uncertainty principle. We frame the problem in the context of Thermodynamic equilibrium for the linear approximation of ionic molecular signal and subsequently the Fluctuation-Dissipation Theorem of hormone and ionic molecular communications.

We wish to estimate the human body chemical hormones with a large mass, size, and charge that are floating in thermal equilibrium among a rapid fluctuating medium, i.e., lymph, blood, water, etc., containing molecules that are much smaller in size compared to hormones. First, we assume the standard Brownian motion model, where the larger sized chemical hormones will be considered analogous to a macroscopic pollen particle floating with a slow anisotropic velocitv in a water medium that has a much smaller molecular mass m_w and a fast isotropic fluctuation velocity $\bar{v}_w$.

Then, we can apply the medium equal-partition law which is derived according to the Canonical Ensemble.

We assume a two time scale perturbation model of which the relaxation time are inversely proportional to the sizes of hormone senders and their receptors. Larger receptors would have an easier ability to capture the hormone messengers. Our model resembles the Adaptive Resonance Theory (ART) unsupervised learning model.[23] and facilitates the homeostasis principle among two block networks: (1) the lower block nodes represent a sensory processing 'committee', i.e., a sensory decision involving vision and hearing as well as intuition about a predator concealed in the environment and (2) top block nodes serve as the 'messengers' i.e., the adrenal gland located above the kidney will secrete the adrenaline hormone which propagates through blood vessels with oxygen other nutrients to limb muscles to be ready for a "*fight or flight*" response. Together, the decision must operate at the homeostasis Helmholtz Principle at an effortless MFE. Collectively, the bottom block voting represented by the net sensory vector spanned by a 'committee' of all sensory input vectors and top block voting presented the total action vector among 'managers' decision vectors shown below in Figure 7.

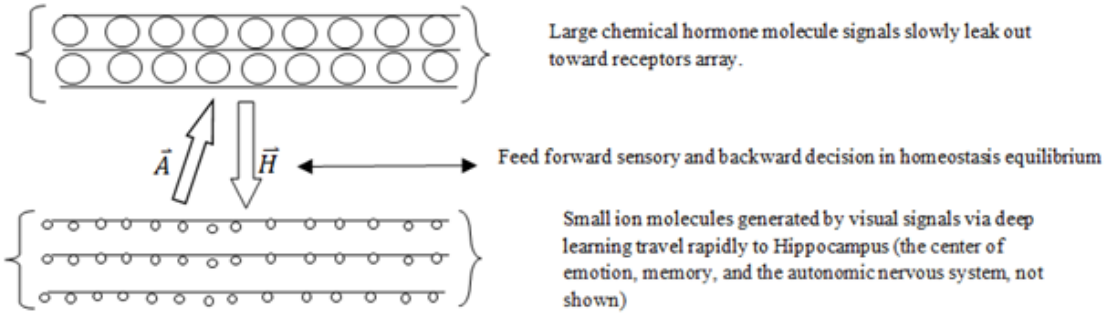


Figure 7 Modified ART structure showing the collective bottom block voting represented by the net sensory vector spanned by 'committee' of all sensory input vectors and the top block voting representing the total action vector among 'managers' decision.

For small input/output (I/O) interactions, such as hormone I/O from other organs, i.e., Amygdales, we describe an equilibration process to tune hormone ionic flow which can mitigate imbalance at MFE. This can be achieved by approximating the chemical (hormone) signal perturbation balance in a pseudo-closed system as an order of magnitude approximation operating at absolute equilibrium, MFE E_H. We begin with Ludwig Boltzmann's definition of entropy S (proportional to the unusable energy at absolute Kelvin temperature T), where W is phase space and k_B is the Boltzmann constant. Given the definitions denoted by $\equiv$:

$$S \equiv k_B Log\, W_{phase};\ \beta \equiv \frac{1}{k_B T}; E_H \equiv H_{tot.} - ST$$

$$W_{phase} \equiv \exp\left(\frac{\mathrm{S}}{k_B}\right) \equiv \exp(\beta ST) = \exp(\beta H_{tot.})\exp(-\beta(H_{tot.} - ST)$$

$$= \exp(\beta H_{tot.})\exp(-\beta E_H) = const.\exp(-\beta E_H)$$

We summarize our intuition by observing that the permutation phase space W of molecular collision probability increases as the MFE decreases, known to Boltzmann as the irreversible thermodynamic phenomena. This is consistent despite the famous Poincare criticism which insinuated that time-reversible Newtonian dynamics do not support irreversibility. Defining the initial boundary conditions allows for the irreversibility constraint to be satisfied.

$$W_{phase}(\uparrow) = const.\exp(-\beta(E_H \downarrow))$$

$$= \text{const. } \exp(-\frac{E_H(|\bar{H} * \bar{A}|^2)}{k_B T}$$

$$= \text{const. } \exp(-\frac{E_H(|\bar{H} * \bar{A}|^2)}{k_B T}$$ Note that the vector $\bar{H}$, is not the same as the scalar H, and represents the Endocrinal Hormone flow whose vector components are directed towards a collection of receptors. Likewise, the action vector $\bar{\mathrm{A}}$ came from all sensory decision components.

$$E_H\left(|\bar{H} * \bar{A}|^2\right) = |H|^2 + |A|^2 + 2|H||A|\cos(\theta)$$

$$\nabla E_H = -2|H||A|\sin(\theta)\nabla\theta = 0;\ \theta = 0$$

$$E_H\left(|\bar{H} * \bar{A}|^2\right) = |H|^2 + |A|^2 + 2|H||A| = (|H| + |A|)^2$$

The action potential $\exp\left(|A|^2\right)$ can be minimized through the traditional deep learning approach.[24] Let $v = |\vec{v}| = \sqrt{v_x^2 + v_y^2 + v_z^2}$ be the fast fluctuation of small ionic particles, and then the Maxwell-Boltzmann equilibrium distribution $f(v)$ is derived in spherical coordinates of the magnitude of velocity V, known as the equal-partition law among the fast fluctuation of the water medium:

$$f(v) = 4\pi(\frac{m}{2\pi k_B T})^{\frac{3}{2}} v^2 \exp\left(-\frac{mv^2}{2k_B T}\right)$$

$$\langle KE\rangle = \left\langle \frac{1}{2}mv^2 \right\rangle = \int_0^\infty \frac{1}{2}mv^2 f(v)dv = 3k_B T \int_o^\infty d\xi\xi exp\left(-\xi^2\right) = \frac{3}{2}k_B T$$

Now we consider the slower time scale decay of chemical hormone molecules having a larger size. Eventually, we can relate both the slow and the fast time scale phenomena with the equal-partition equilibrium law, like large pollen particles being bounced around by small water molecules in thermal equilibrium.

We assume that the fluctuation time scale is inversely related to the size of the molecules, thus for large size hormones, transport will occur slowly through a fast-fluctuating medium pathway toward hormone receptors with a slow current $\vec{I}(\tau)$ in the time scale, where an ionic molecule of mass m_o of charge current $\vec{I}(\tau)$ is communicated by the

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Brownian diffusion Langevin equation with transport constant D_o in 3 isotropic dimensions.

$$\vec{I}(\tau) \equiv Q^s n[A^s(\tau)]\vec{v}(\tau) \quad (1)$$

Here, the ion density *n* of the electric charges Q^s flow through the slow modulating propagation pathway with the time dependent receptor bundle cross-section $\left[A^s(\tau)\right]$ and velocity $\vec{v}(\tau)$. The size of the Einstein-Brownian motion reveals the molecular medium, independent of the Brownian particle and molecular composition.

This observation allows us to model different hormones in an arbitrary media which are found in two different channels of a receptor rich region of the body, for example, the left and right amygdale. In physics, Paul Langevin described that the time evolution of a meaningful two-channel degree of freedom are typically macroscopic variables that collectively change slowly with respect to the quickly changing microscopic system variables, i.e. molecular ions. Fast variables are the cause for the stochastic behavior of the Langevin equation.[25] Due to hormone receptors, we do not need to consider the spatial Laplacian diffusion component in this work since the hormone molecule will be collected by a receptor within a bundle of receptors of area size $\left[A^s(\tau)\right]$ along the propagation pathway,

$$m_o \frac{d\vec{I}}{d\tau} = -D_o \vec{I}(\tau) + \tilde{F}(\tau \mid t) \quad (2)$$

$$< \tilde{F}_i(\tau \mid t)\tilde{F}_j(\tau \mid t'') >_G = \beta(\tau)\delta_{i,j\tau}\delta(t-t') \quad (3)$$

$\beta(\tau)$ is to be self-consistently determined from the thermal equilibrium average of random perturbations due to collisions $\tilde{F}_i$ from the medium molecules.

$$.k_B T = \frac{1}{40} eV; T = 300^o K, or\, 27^o C \quad (4)$$

In the central limiting theorem, these fluctuations have a Gaussian probability distribution G, and a damping coefficient D_o in the correlation function of the random molecular forces. This fact is known as Einstein fluctuation-dissipation relation.[21] Molecule receptors overwrite the Laplacian spatial curvature for a molecule on its propagation pathway through either divergence caused by occupancy or by focusing a molecule to bind. This is like the historic Brownian motion, where an arbitrarily sized macroscopic pollen particle, after falling into a pond, seems to be kicked around by water medium molecules in a nonstop zigzag (thermal) motion. Albert Einstein said, "Brownian motion has demonstrated the existence of water molecules visually, without the microscope." In the same vein, we believe that macroscopic hormone molecules can be characterized by their interaction with medium molecules during their communication charge current, defined as the vector current *I*:

$$\vec{I}(\tau) = Q^s \vec{v}(\tau)[A^s(\tau)] \quad (5)$$

Arbitrary hormone molecules have their own specific charge and flow path cross section that is weakly time dependent, denoted as species $Q^s \ [A^s(\tau)]$, where the superscript s for the sth species of molecule. Note that the location parameter of the hormone is no longer needed for our case because of propagation along the physiological pipelines. According to the equal-partition law, the homeostasis property of human beings will have the medium molecules exhibiting constant thermal motions at an absolute Kelvin temperature *T*.

We define the slow time scale Newton force equation of a large molecule receptor's ion current:

$$\vec{F}(\tau) = m_o \vec{a}(\tau) \equiv m_o \frac{d\vec{v}}{d\tau} \quad (6)$$

Let there be a total force $\vec{F}(\tau) \equiv \vec{F}(\tau) + \tilde{\vec{F}}(\tau \mid t)$ in two different time scales, slow τ and fast *t*. Then, the thermal fluctuations in the fast scale have a zero mean and an arbitrary slow dissipation correlation parameter $\beta(\tau)$ to be self-consistently determined by the fast time sale equal-partition law. We will the drop vector sign along the propagation path:

$$< \tilde{F}(\tau \mid t) >= 0 \ ; < \tilde{F}(\tau \mid t)\tilde{F}(\tau \mid t') >= \beta(\tau)\delta_\tau(t-t') \quad (7)$$

where the unknown slow time scale dissipation $\beta(\tau)$ must be independent from the fast time scale Dirac delta distribution function $\delta_\tau(t-t')$, parameterized at $t = \tau = t'$ and can therefore be factored.

Proof: Given the 1st order exact differential equation, we multiply the integration factor $exp\left(-\frac{D_o}{m_o}\tau\right)$ through the whole equation:

$$exp\left(-\frac{D_o}{m_o}\tau\right)\frac{d\vec{I}}{d\tau} - \frac{D_o}{m_o}exp\left(-\frac{D_o}{m_o}\tau\right)I(\tau) = exp\left(-\frac{D_o}{m_o}\tau\right)\frac{1}{m_o}\tilde{F}(\tau \mid t) \quad (8)$$

From the differential chain rule of products, we combine the left and right two terms into one inside of square brackets:

$$\frac{d}{d\tau}\left[\vec{I}(\tau)exp\left(-\frac{D_o}{m_o}\tau\right)\right] = exp\left(-\frac{D_o}{m_o}\tau\right)\frac{1}{m_o}\tilde{F}(\tau \mid t)$$

Through integration on both sides, we can solve with arbitrary time constants *by the ensemble average of all possibilities.*

$$\text{LHS} = \int d\left[\vec{I}(\tau)exp\left(-\frac{D_o}{m_o}\tau\right)\right] = \vec{I}(\tau)exp\left(-\frac{D_o}{m_o}\tau\right)$$

$$RHS = \int exp\left(-\frac{D_o}{m_o}\tau\right)\frac{1}{m_o}\tilde{F}(\tau \mid t)d\tau$$

To integrate the right-hand side, we multiply $\tilde{F}(\tau \mid t')$ and take the ensemble average of fast variables denoted with *angular brackets* first, from ensemble average Eq (7) follows

$$RHS = \frac{1}{m_o}\int exp\left(-\frac{D_o}{m_o}\tau\right)\left\langle \tilde{F}(\tau \mid t)\tilde{F}(\tau \mid t')\right\rangle d\tau$$

$$= \frac{1}{m_o}\int_{-\infty}^{\infty} exp\left(-\frac{D_o}{m_o}\tau\right)\beta(\tau)d\tau\delta_\tau(t-t') \cong \frac{\beta(\tau)}{m_o}exp\left(-\frac{D_o}{m_o}\tau\right)$$

If we equate RHS to the LHS, we have derived the slow dissipation value $\beta(\tau)$

$$\beta(\tau) = m_o \vec{I}(\tau) \quad (9)$$

Now, we present the *fast* molecule fluctuation-dissipation theorem:

$$< \tilde{F}(\tau \mid t)\tilde{F}(\tau \mid t') >= m_o \vec{I}(\tau)\delta_\tau(t-t') \quad \text{Q.E.D. (10)}$$

Now, equating the equal-partition law of kinetic energy at temperature T (Kelvin) the large hormone molecule at the *homeostasis* effect becomes

$$\frac{1}{2}m_o < \left|\vec{v}(\tau)\right|^2 \rangle = \frac{3}{2}k_B T \quad (11)$$

Since $\vec{I}(\tau) = Q^s \vec{v}(\tau)[A^s(\tau)]$, the average bundle cross section

$[\mathrm{A}^{s}(\tau)]$ must contract in an inversely proportion fashion in order to reduce the kinetic energy of a large hormone molecule flow.

$$\frac{1}{2}m_o\frac{|\vec{I}(\tau)|^2}{Q^s[\mathrm{A}^s(\tau)]}=\frac{1}{2}m_o\frac{(Q^s\vec{v}(\tau)[A^s(\tau)])^2}{Q^s[\mathrm{A}^s(\tau)]}=\frac{1}{2}m_oQ^s[\mathrm{A}^s(\tau)]\mathrm{v}(\tau)^2=\frac{3}{2}k_BT$$

$$\mathrm{K.E.}(\tau)=\frac{1}{2}m_o\mathrm{v}(\tau)^2\approx\frac{1}{\mathrm{A}^s(\tau)} \quad (12)$$

Where the left-hand side receptor bundle cross section area $\left[\mathrm{A}^{s}(\tau)\right]$ must be also dependent on the slow time scale τ in order to balance the chemical current and maintain a stable equilibrium

$$k_BT_{hot\ room}=\frac{1}{40}eV\ ,T_{hot\ room}=27^oC\ ;T_{(homosapiens)}=37^{(o)}C \quad (13)$$

The slow variable dissipation $\beta(\tau)=m_o\mathrm{I}(\tau)=\sqrt{3\mathrm{m_o k_B T Q^s[A(\tau)^s]}}$ turns out to be cross-sectional $[\mathrm{A}(\tau)^s]$ varying, as indicated by the line connecting the left-side amygdala to the right-side amygdala in Figure 2 shows a notional relationship for how isothermal equilibrium is maintained in the feed forward and backward interaction between large and small molecules, which is a step towards enhancing AI algorithm formulation and new computing hardware.

Discussion and future work

With knowledge of the homeostasis hormone concentration for an anatomical region such as the amygdala, *modulation of* the size of the region can lead to hormonal imbalance. High hormone influx into a region with a receptor shortage (the region is smaller than it should be) can affect downstream structures connected with white matter pathways and is the cause of certain mental disorders such as hypersensitivity or physical *insulin-secretion timing* problems like diabetes. High receptor density with low hormone influx leads to a receptor surplus (the region is larger than it should be) and leads to mental disorders such as depression or physical problems like bone loss. Cataloging the receptor type and density for important neuroanatomical regions of healthy individuals would allow tuning of our mathematical model.

Combining anatomically faithful DT-MRI and tractography data with our generalized molecular communication framework would provide a chemical computation engine the location, quantity and two time scale flow dynamics of heterogenous hormones and ions to produce a simulated electrochemical circuit. The change in concentration of certain hormones in specific anatomical regions may lead to a change in entropy and MFE, and could simulate the sensation of feeling certain emotions, i.e., high serotonin levels are associated with happiness, high cortisol levels are associated with stress. Introducing this chemical signaling information as an additional input to conversation generating AI frameworks such as GPT, Grover, etc. could serve to augment the context of generated text data with emotion. Typically, a question-answer style conversational AI answer questions that a human may ask in a factual manner based on a knowledge base built from training data. It is possible to measure more data points surrounding a user's query with 5G technology such as facial micro-expressions, tone of voice, body language, etc. Perhaps the next generation of cutting-edge conversational AI can introduce a fusion of electrical communication (ANN) and chemical communication (BHN) that can form a biasing mechanism to augment machine generated content in a more humanistic manner. It is possible that the role could be reversed, and a conversational AI could ask questions of a human. If such an AI could 'internalize' and perceive the emotion by simulating hormones to match the collected answer, perhaps we would be able to approximate sympathy and empathy.

Conclusion

In this paper we have described a physics-physiology inspired framework to pave the way for future AI and computer hardware design. Our approach includes both electrical and chemical considerations which together give rise to biological phenomena such as perception of internal emotion and sensing of external light. We derived a general molecular communication framework to facilitate future studies that would enable AI systems to more accurately emulate biology. Modeling BHN's requires laboratory emulation of gradually bigger molecules for their communication effects and integration with standard digital circuitry.

We seek collaboration with both National Institutes of Health and the National Science Foundation to bring such a laboratory setup to fruition. Additionally, we wish to learn how hormone signaling networks can be adapted to model an AI system and evaluate novel algorithms with such new technology. Utilizing this technology to perform computations with a fully programmable chemical computer could help bridge the gap and enable computational strategies not achievable using strictly electron-based circuity.[26] There are additional avenues to apply this framework that would be a disruptive technology in computing, such as simulating the growth hormone to enable dynamic molecular computer memory. Physical or simulated AI systems that are produced to be both structurally similar to certain biological systems and possess the appropriate molecular communication capability may provide an alternative to animal models where live animals are physically altered or sacrificed in order to carry out research in a lab setting. Recent advances in aging research have also shown promise for regenerating retinal tissue in-vivo and could be applied to additional areas affected by neurological disorders such as the amygdala. [27]

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Conflicts of interest

The authors declare no conflicts of interest.

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