Journal of Geoethical Nanotechnology
Vol. 9, Iss. 1 (2014) 11 – 73

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ON THE RECURRENT FUNCTIONAL RESTORATION AND INDEFINITE FUNCTIONAL PERPETUATION OF THE CENTRAL NERVOUS SYSTEM

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Franco Cortese locates the notion of 'gradual mind uploading' and the discipline of whole-brain-emulation within the broader methodological context of functionally-restorative medicine and functionally perpetuative medicine, characterizing it as a distinct approach within the field of biomedical gerontology and regenerative medicine. By explicating the general approach underlying 'gradual mind uploading', transplantology, prosthesis, cell replacement therapy, whole-body induced somatic cell turnover, tissue engineering, gene therapies and chromosome replacement therapies, he draws methodological continuity between its variations and articulates a methodological and taxonomic system for distinguishing between them. Ultimately, Franco argues that the indefinite perpetuation of the CNS via is possible through the gradual and recurrent functional restoration of its constituent integral-components.

Keywords: Franco Cortese, functionally restorative medicine, functionally perpetuative medicine, integral component replacement therapy, ICRT, gradual integral component replacement therapy, GICRT, cognitive integral component replacement therapy, CICRT, gradual cognitive integral component replacement therapy, GCIRT, Whole-body Induced Somatic Cell Turnover, WISCT, Recurrent mtDNA Replacement Therapy, RMRT, Recurrent gDNA Replacement Therapy, RGRT, ELPIs Foundation for Indefinite Lifespans, life extension, neuroperpetuation, nanotechnology, nanobiotechnology, nanomedicine, whole brain emulation, WBE, gradual mind uploading, biomedical engineering, neurotechnology, neural engineering, biomechatronics, bionics, biomedical gerontology, cybernetics, biomimetic, synthetic biology, synthetic ion channels, ion channel reconstitution, artificial membrane reconstitution, regenerative medicine.

> *Whatever can be repaired gradually without destroying the original whole is, like the vestal fire, potentially eternal*.
>
> – Francis Bacon, *A History of Life and Death* (1638)1

I. INTEGRAL-COMPONENT REPLACEMENT THERAPY

The rise of modern medicine arguably began with the rise of scientific materialism, which made it increasingly apparent that the cause of sickness was physical (i.e. structural, connectional or procedural) rather than spiritual, moral, or metaphysical. If the brain and body were physical systems amenable to physical manipulation, then we could potentially repair them and restore their declining functionality through a series of physical manipulations that restore the physical structures and processes of the body to their previous (i.e. young; error-free) configurations, correlative with normal functionality.

The preventative medicine vs. reparative medicine dichotomy is a hot topic in medical research and policy literature. Whereas preventative-medicine seeks to maintain the bodily conditions thought to prevent disease and functional decline, reparative medicine seeks to ameliorate the bodily causes of disease and functional decline after such causes have taken effect. The predominant opinion favors preventative over curative strategies, feeling that they constitute an approach having a higher probability of success (i.e. it is easier in terms of both methodology and technology to prevent a given physiological disease or dysfunction than it is to ameliorate it after it has taken place) and a lower necessary or minimum degree of complexity.

Two distinct approaches can be identified within the field of curative or reparative medicine. The trichotomy of preventative care, curative care and palliative care can help explicate this distinction. Whereas curative care is more in line with the approach used in reparative or regenerative medicine (i.e. actually seeking to ameliorate the causes of disease or functional decline), palliative care seeks to ameliorate the physical or procedural symptoms caused by the disease (i.e. the systemic effects *resulting from* the structural, connectional or procedural dysfunction). Curative-care seeks to remove or negate the cause of functional decline (i.e. restore the structural, connections or procedural systems causing the systemic symptoms to their previous state(s), correlated with normal or healthy functionality) while palliative-care seeks to merely negate the end-result systemic symptoms of functional decline. Both curative care and palliative care can be considered as alternate approaches within the broader field of functionally restorative medicine because both seek the maintenance of normal emergent functionality; one simply attacks the cause whereas the other attacks the effects. Regenerative medicine is most generally considered as an instance of curative care, though Aubrey de Grey has cogently argued that they can also be seen to constitute an instance of preventative care, in that the early

[1]Bacon, F. (1857). The Works of Francis Bacon. (Vol. 5, pp. 238.) Ed. James Spedding, Robert Leslie Ellis, and Douglas Denon Heath, 14 vols. *London: Longman and Co., et al*, *74*(6), 92.

application of regenerative and rejuvenative therapies can effectively prevent a variety of age-associated diseases like cardiovascular disease, hypertension, osteoporosis, osteoarthritis, diabetes and dementia.

However an as-yet-unexplicated approach possessing aspects of both curative and palliative care has been in development since at least the first successful organ transplants. More recent developments in tissue engineering, organ engineering and cell-replacement therapy also fall within this general approach, which seeks the same end as curative-care, i.e. functional restoration, but in a way categorically dissimilar to the approach taken in normative curative-care; it also avoids the bottleneck of increased complexity that makes curative-care more costly, harder and ultimately less optimal than preventative care. Likewise, it is similar to palliative care in that it attempts to ameliorate the symptoms or effects of the cause without physically manipulating the physical and/or procedural systems mediating the process ultimately resulting in the structural, connectional or procedural correlates of the disease (in other words the physical and/or procedural cause of such symptoms) in such a way as to restore affected biological structures and processes to their previous state correlated with normative functionality. In contrast to curative-care, this alternative approach avoids directly manipulating or interfering with the development or progression of the disease (or more generally state of structural, connectional or procedural deviation) by instead removing the affected structures and processes and replacing them with functionally homologous copies lacking any such functional deviation (i.e. lacking the functional phenotypes or symptoms of the disease or condition).

We will hereafter refer to this new repair-through-replacement approach as Integral-Component Replacement Therapy (ICRT). Instead of developing a method and technology to negate or obviate the physical or procedural cause of functional decline (as in curative-care), this approach instead replaces the physical systems embodying that physical or procedural cause of functional decline with systems functionally-equivalent to the physical or procedural state of such physical systems prior to the introduction of the harmful (i.e. causing functional decline) physical or procedural property. Thus, in the case of organ-transplantation, instead of repairing a dysfunctional organ we replace it with a new, healthy organ in a physical state functionally-equivalent to the patient's own organ prior to the introduction of the physical or procedural cause of dysfunction. This approach bypasses the seeming need to understand the physical and/or procedural dysfunction's source or cause in order to negate its effects. Compare this to the respective cancer therapies of surgery and radiation therapy or chemotherapy. Surgery removes the affected tissue in the hopes of preventing the systemic spread of cancer cells. This is a curative strategy comparable to the repair-through-replacement approach. By contrast chemotherapy and radiation therapy seek to ameliorate the cause of dysfunction in an organ or tissue without removing or replacing the affected organ or tissue. This would be more in line with the normative strategies taken in curative-care.

This approach avoids the bottleneck of complexity encountered by most forms of curative-care: namely, the process of determining (1) what structures and processes are not operating correctly, (2) what physical or procedural states of the structures and/or processes identified in (1) correlate with normal functionality, and (3) what series of physical or procedural manipulations can make the dysfunctional structures and processes identified in (1) conform to the (correct, normative, healthy) physical and procedural states identified in (2). What is specifically going wrong, as well as the specific technological and methodological infrastructure (i.e. required underlying methodologies and technologies) for ameliorating what is going wrong, is typically unique to the specific disease or instance of functional decline. Thus the strategy we take to cure Bronchitis is not the same strategy we take to cure Meningitis. Unfortunately, this means that we cannot use one strategy to combat most other structural or procedural causes of disease and dysfunction, even if they are in the same general category (e.g. viral vs. bacterial infection). Each new disease requires a new (or at least additional) methodological and technological infrastructure for its amelioration, thus driving up ultimate cost and complexity for this normative approach to curative-care as a whole.

All varieties of ICRT, by contrast, work according to the same methodology (and more often than not work according to similar, though non-equivalent, technologies) regardless of the specific disease (i.e. the structural or procedural cause(s) of functional decline) or the specific area of the body affected (i.e. the structure or process exhibiting or embodying the structural or procedural-deviation causing functional decline). We can apply the same basic repair-by-removal or repair-by-replacement methodology to alternate types of physical and/or procedural causes of functional decline.

One can also see the parallels between ICRT and palliative care; both attempt functional restoration without manipulating the physical or procedural causes of functional decline, thereby avoiding the complexity of reversing and ameliorating such physical or procedural causes. But whereas palliative care faces an uphill battle, combating the symptoms while the cause carries on, ICRT can be just as effective as more complex (i.e. specialized) curative therapies because it still removes the cause, albeit without necessarily understanding how to *reverse* the cause (i.e. remove the effects of the disease without replacing the affected structure or process).

II. INTRA-PARADIGMATIC ICRT & EXTRA-PARADIGMATIC ICRT:

We will use the term “integral-component(s)” to denote the components comprising an emergent system, i.e. those biological components being replaced through an ICRT and the biological or non-biological replacement-components used to replace such biological components. We will use the term “in-situ-components” to denote those components *being replaced* (due to structural, connectional or procedural [i.e. operational] damage, degradation, distortion or dysfunction) via an ICRT. We will use the term “replacement-components” to

denote those components used *to replace* the in-situ components throughout the course of an ICRT. Just what is considered an integral-component or in-situ-component in depends on the scale at which an ICRT is implemented, i.e. the replacement-scale, because the scale (i.e. size) of the biological in-situ components being replaced varies in accordance with the replacement-scale. Thus an organ can be considered an integral-component and in-situ-component in the context of organ transplantation just as appropriately as a cell can be considered as such in the context of cellular replacement therapy.

We will use the term "intra-paradigmatic ICRT" to denote those varieties of ICRT that replace in-situ components with replacement-components belonging to same specific or general structural, connectional and/or procedural paradigm, a.k.a. components embodying the same operational (as opposed to functional) modalities, than the in-situ components (e.g. replacing in-situ biological components with analogous biological, as opposed to non-biological, replacement-components). We will use the term "extra-paradigmatic ICRT" to denote those varieties of ICRT that replace in-situ components with replacement-components belonging to a different structural, connectional and/or procedural paradigm (a.k.a. components embodying an alternate operational-modalities) than the in-situ components (e.g. replacing in-situ biological components with non-biological replacement-components, that is, replacement-components embodying the same functional-modality but embodying an alternate operational-modality). For instance, a biological heart and an artificial heart embody the same functional modalities but alternate operational-modalities.

Modern examples of intra-paradigmatic ICRT include *bone marrow and organ transplantation*, *blood transfusion*, *cell-therapies* (including the transplantation of mature cells, stem cells and progenitor cells) and *tissue engineering*. Another contemporary instance of intra-paradigmatic ICRT is W*hole-body Induced Somatic Cell Turnover* (WISCT)[2, 3], a therapy formulated and being explored by scientists Franco Cortese, Dr. Giovanni Santostasi and Dr. Mario Kyriazis at ELPIs Foundation for Indefinite Lifespans as part of an ongoing research project involving the formal description and study of the therapy. WISCT consists of gradually subjecting all of the somatic cells in the body to an incremented two-part process of (1) induced apoptosis and (2) the subsequent replacement of apoptosed somatic cells with pluripotent cells, preferably patient-specific induced pluripotent stem-cells (iPSCs) to minimize immunologic complications. This process is applied incrementally throughout the organism's healthy lifespan until all of the organism's somatic cells are artificially turned-over in such a manner, with the aim of periodically turning-over all of an organism's somatic cells before they have accumulated 6 categories of accumulated age-associated damage (specifically accumulated gDNA damage, telomore depletion, accumulated mtDNA damage, accumulated intracellular junk, accumulated

[2] *Ibid.*
[3] Kyriazis, M. (2013 November). Defying Aging: The ELPIs Foundation for Indefinite Lifespans. *H+ Magazine.* Retrieved from: http://hplusmagazine.com/2013/11/05/defying-aging-the-elpis-foundation-for-indefinite-lifespans/.

post-mitotic cells and accumulated cell-loss) in quantities sufficient to non-negligibly increase the risk of organismal death or to lead to general functional decline. However, after the WISCT, the organism's iPSC-derived somatic cells would begin to accumulate such categories of damage as well. Thus WISCT would be implemented recurrently in order to periodically negate these categories of accumulated age-associated damage as they accumulate recurrently in each successive whole-body round of WISCT. The therapy classifies as a variety of intra-paradigmatic ICRT because in-situ somatic cells are replaced with iPSCs that subsequently differentiate into somatic cells operationally (i.e. structurally, connectionally and procedurally) homologous to the apoptosed somatic cells the iPSCs are replacing (aside from operational deviation due to accumulated age-associated damage), and thus belong to the same operational paradigm. Only subjecting a portion of the total somatic cells constituting a given emergent organ or tissue to induced apoptosis at any given time allows such organs and tissues to retain functionality throughout the cumulative application of the procedure (i.e. after all of the somatic cells in the organism's body had been artificially turned-over in this manner). This is distinct from stem-cell therapies in that cell-loss (i.e. the loss of cells due to necrosis or apoptosis) only constitutes one of a number of age-associated categories of accumulated damage (or more appropriately structural, connectional or procedural deviation with the healthy structural, connectional or procedural profile of biological neurons). In many cases cells accumulate sufficient damage to incur dysfunction, but fail to trigger the self-destruction mechanisms of apoptosis or necrosis, in many cases continuing to excrete toxic products into the extracellular environment, eventually leading to the functional decline of otherwise-healthy cells. Thus the periodic injection of pluripotent cells would constitute an effective strategy for cell-loss, but it would not constitute an effective strategy for accumulated gDNA damage, mtDNA damage, accumulated post-mitotic cells, telomere-depletion and accumulated intracellular lipofuscin. Conversely WISCT constitutes a therapeutic approach that can effectively prevent and treat (i.e. remove) all six of the above-mentioned categories of accumulated age-associated damage. WISCT is not, however, an effective therapeutic approach for preventing or treating accumulated extracellular junk and extracellular crosslinks, both of which are also correlated with functional decline in old age. The therapy is limited to the recurrent removal of all categories of intracellular damage or operational deviation, which it can facilitate by virtue of the fact that iPSCs can be indefinitely replicated and grown in cell cultures in vitro, and such iPSCs will lack any accumulated age-associated damage. But because the extracellular matrix itself is not being metabolized and thereby removed from the surrounding system, forms of extracellular junk will likewise fail to be removed from the surrounding system.

One concern regarding potential complications is the possibility of inadvertently causing functional decline due to the induction of apoptosis in a portion of the somatic cells comprising a given organ or tissue. The potential for functional-decline can be minimized by minimizing the number of somatic cells terminated at one time. However, this in turn increases the ultimate minimum or necessary rate of cell-turnover that is required to turn over all of an organism's

somatic cells before they accumulate sufficient quantities of age-associated damage to lead to functional decline. The rate of cell turnover can be decreased, and the cumulative duration of the whole-body therapy accordingly increased, in order to minimize potentially-negative effects of inducing apoptosis in small portions of organs and tissues. The organs and tissues msot susceptible to functional decline due to the temporary loss of constituent somatic cells are those organs and tissues possessing microscale heterogeneity, i.e. microscale structure (in which a component or distinct feature of an organ or tissue, i.e. a distinct functional unit, consists of a small number of cells). This is because in biological structures comprised of a small number of somatic cells, the loss of a given cell will be more of a functional loss than it would be for biological structures comprised of a larger number of somatic cells. For instance, long-distance single-cell traversals and connections in the CNS pose perhaps the worst-case scenario in terms of susceptibility to functional loss due to the loss of constituent somatic cells. In this case there is nothing to structurally, connectionally or procedurally (or indeed even functionally) supplant these long-distance single-cell connections and traversals during the interval of time between termination via induced apoptosis and replacement with an injected iPSC. The brain, possessing a high level of microscale heterogeneity, is another example of an organ particularly susceptible to functional decline due to the temporary loss of single somatic cells (i.e. neurons and glia). Thus the slowest rate of cell turnover sufficient to turn over all the somatic cells in the CNS before they accumulate sufficient quantities of age-associated damage to non-negligibly increase the risk of organismic death should be applied to the CNS, as the loss of a given somatic cell will adversely affect the functioning of the organ to a greater extent than any other in the body.[4] Conversely, organs and tissues with microscale homogeneity, i.e. organs and tissues not possessing distinct sub-systems or distinct microscale structures, are less susceptible to functional decline as a result of the loss of a given portion of their constituent somatic cells. Organs possessing microscale homogeneity include skin and blood, both of which have a much higher natural turnover rate (i.e. the replenishment of apoptosed or necrosed cells by dividing somatic cells or for some organs and tissues by adult stem-cells, which do not possess the crucial properties that embryonic stem-cells and iPSCs do, namely self-renewal and pluripotency) than other organs and tissues. Thus it is likely preferable to use different induced somatic cell turnover rates for different organs, e.g. a lower turnover rate for the brain and a comparatively higher turnover rate for the skin. Additionally, the fact that the number of somatic cells constituting a given organ (or distinct functional sub-system, e.g. an aeortic artery) in the body varies enormously makes it likely that applying differential rates of induced somatic cell turnover in accordance with the absolute size of an organ or tissue will be preferable as well. If the heart and the stomach respectively consist of different numbers of somatic cells, then applying the same induced turnover rate to both of them will result in a higher turnover rate in the heart than in the stomach, because it consists of less somatic cells. Thus ideal induced

[4] Incidentally, the potential for WISCT to cause functional decline in a given organ or tissue is inversely proportional to the size of the organism – i.e. organs and tissues in larger organisms will be less susceptible to functional decline as a result of induced apoptosis because their organs and tissues consist of a larger number of somatic cells.

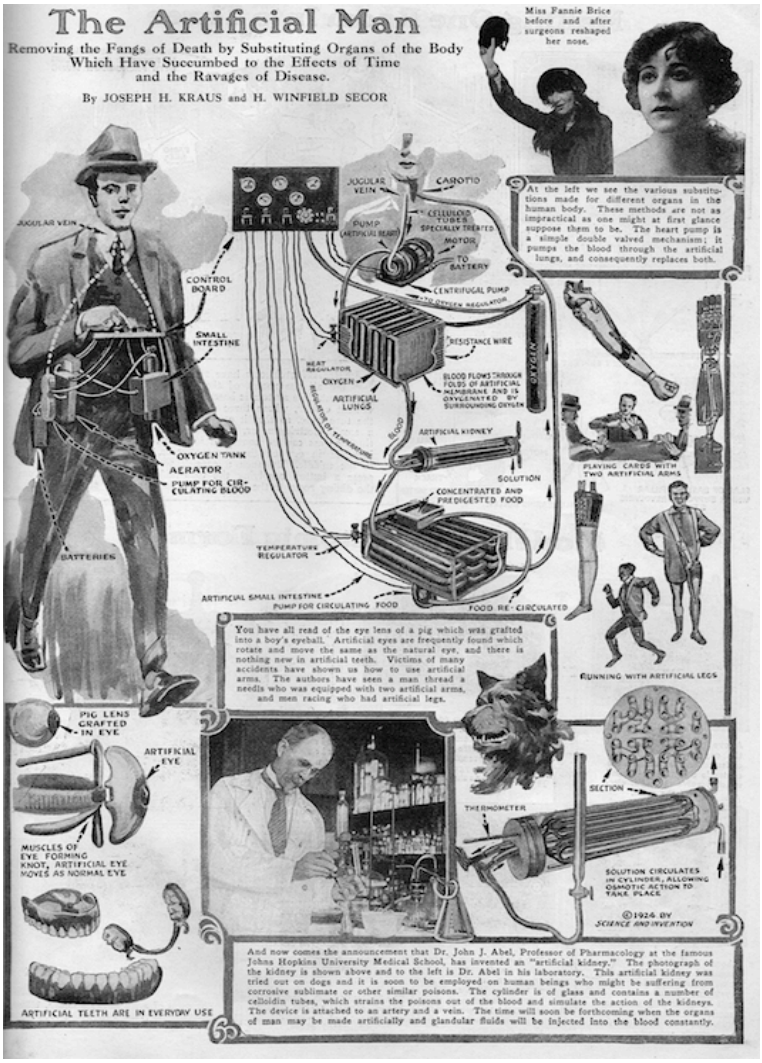
turnover rates should take into account not only whether an organ possesses microscale homogeneity or microscale heterogeneity, but also the number of somatic cells it consists of in relation to itself as a functional whole. Likewise, in terms of induced somatic-cell turnover in the brain, the rate of induced somatic cell turnover should account for the total number of somatic cells comprising the functional unit or whole that the replaced somatic cell is a part of (e.g. applying the same rate of induced somatic cell turnover to one of the smaller functional units in the human CNS, like the thalamus or anterior commissure, as is applied to one of the larger functional units in the human CNS on the same scale as the thalamus or anterior commission, like the corpus callosum, would result in a vastly unequal rate of somatic cell turnover in relation to the functional wholes that those somatic cells were each part of, respectively. Inducing apoptosis in a given number of neurons would constitute a much larger temporary functional-loss (and resulting degree of functional decline and susceptibility to functional decline) for the thalamus than an equal number of apoptosed neurons would for the corpus callosum.

Another potential complication is the possibility of disrupting the normative homeostatic and developmental processes mediated by the coordination of cell division with cell loss. While it is generally more preferable to begin the therapy after development (i.e. after the full sexual maturation of the organism), as this minimizes the probability of inadvertantly disrupting normative developmental processes, the potential to disrupt homeostatic processes would still be present. Much like the previous concern, this potential complication can be minimized by decreasing the rate of induced somatic cell turnover and extending the duration of the cumulative whole-body procedure. WISCT could be begun in humans during a patient's mid-twenties and gradually implemented over a period of twenty, forty, or even sixty years depending on how low a rate of induced turnover is optimal for minimizing concerns of functional decline due to temporary loss of somatic cells and the disruption of normative homeostatic or regulatory mechanisms.

Another example of intra-paradigmatic ICRT is *Recurrent gDNA Replacement Therapy* (RGRT) and *Recurrent mtDNA Replacement Therapy* (RMRT), therapeutic approaches that are also being studied at ELPIs Foundation for Indefinite Lifespans by Franco Cortese, Dr. Giovanni Santostasi and Dr. Marios Kyriazis5. Both therapies seek to recurrently replace mtDNA (mitochondrial DNA) and gDNA (genomic DNA), respectively, with error-free copies synthesized in vitro and transported into the cell cytoplasm and cell nucleus, respectively, using contemporary transfection techniques (a.k.a. gene vectors), such as viral vectors, chemical transfection techniques (e.g. calcium phosphate, highly branched organic compounds, cationic liposomes or cationic polymers), electroporation, sonoporation, optical transfection, protoplast transfusion, impalefection, hydrodynamic delivery and particle-based techniques (e.g. magnetofaction, nanoparticle carrier, particle bombardment, nucleofection, heat shock). The

[5] Cortese, F. A. B. (2013 October). Integral Component Replacement Therapy. In *Research. ELPIs Foundation for Indefinite Lifespans.* Retrieved from: http://elpisfil.org/page4.htm

transfection of mtDNA is referred to as protofection in the literature and has been previously proposed as a curative therapy for both inherited mitochondrial diseases as well as age-associated mtDNA damage. However, the *periodic* transfection of error-free copies of mtDNA synthesized in vitro as an explicit method of *recurrently* (and thereby potentially perpetually) negating accumulated mtDNA damage, and the technological and methodological specifications involved in those additional therapeutic elements (e.g. how often the therapy would have to be recurrently implemented so as to periodically negate mtDNA damage, based upon the statistical rate of mtDNA error-accumulation) have to our knowledge not yet to be formally studied. gDNA, by contrast to mtDNA, is too large to be encapsulated by standard viral gene vectors. However, the large majority of gDNA consists of non-coding sequences, i.e. sequences without transcriptional function. Some of this non-coding DNA has regulatory and epigenetic function, but the large majority of it consists of non-functional DNA without any regulatory or epigenetic function. Thus the in vitro synthesis of error-free copies of gDNA lacking all identifiably non-



Credit: Kraus, J. & Secor, H. (1924 November). Science and Invention Magazine, Vol. 4 Issue 11.

functional sequences could allow the necessary size of gDNA to be decreased by an amount sufficient to allow its encapsulation as a payload by contemporary transfection techniques, or else to allow its encapsulation in a reasonable number of stages. *Telomerase therapies* constitute another variety of intra-paradigmatic ICRT because they seek to restore depleted telomeres with new telomeres structurally, operationally and functionally homologous to the depleted telomeres they are replacing. In each of these cases, the in-situ biological components are replaced with analogous biological components, and thus qualify as instances of intra-paradigmatic ICRT.

Contemporary conceptual (in the sense of lacking the underlying technological infrastructure required for their implementation, despite having a possibly-sufficient methodological infrastructure) examples of intra-paradigmatic ICRT include *nanotechnological cell repair* (e.g. cell repair nanobots as conceptualized by Drexler[6] and Frietas[7]) in which the cell components themselves are repaired by replacing each missing or degraded molecule with the correct analogous molecule, as well as nanotechnological repair of the cellular chromosome (thus keeping the cell components in repair vicariously by maintaining the system that transcribes and synthesizes the proteins constituting cellular components rather than correcting structural, connectional or procedural deviation in the cellular components themselves), i.e. C*hromosome-Replacement-Therapy*[8] (CRT), both of which fall within the field of nanomedicine.

Modern examples of extra-paradigmatic ICRT include *prosthesis*, *artificial organs*, *neuroprosthesis* and *sensory-substitution*; in each of these cases the in-situ biological components are replaced with functionally-analogous non-biological components. The first recorded instance of medical amputation and prosthesis is thought to be in the Rig-Veda, compiled between 3,500 and 1,800 B.C.E.[9] The concept of cyborgs, a term first introduced in 1960 by Clynes and Kline[10] to describe the integration of non-biological systems with the human body (predominantly to facilitate living in extra-terrestrial environments) can also be considered a conceptual precursor of extra-paradigmatic ICRT, especially insofar as such non-biological systems are used to replace existing biological systems, i.e. functional restoration (as opposed to functional extension or addition). While the term was coined in 1960, the idea has been around since at least the 1920s, as evidenced by an image in the 1924 November issue of Science and Invention magazine entitled, "*The Artificial Man: removing the fangs of death by substituting organs of the body which have succumbed to the effects of time and the ravages of disease*."

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[6] Drexler, K. E. (1986). *Engines of Creation*. Garden City, NY: Anchor Press/Doubleday.
[7] Freitas, R. A. (1999). *Nanomedicine*. Landes Bioscience. Austin, TX.
[8] Freitas, R. A. (2007). The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanobots for Chromosome Replacement Therapy. *Journal of Evolution and Technology*. 16(1): 1-97. ISSN 1541-0099.
[9] Vanderwerker (1976). A Brief Review of the History of Amputations and Prostheses. *Inter-Clinic Information Bulletin.* 15(5-6):15-16.
[10] Clynes, M. E., & Kline, N. S. (1960). Cyborgs and Space. *Astronautics*, pp. 14(9), 26-27. Retrieved from http://cyberneticzoo.com/wp-content/uploads/2012/01/cyborgs-Astronautics-sep1960.pdf.

An illustrative example of therapies in regenerative medicine that do not constitute a variety of ICRT include the use of *genetic engineering* (i.e. gene silencing or gene knockdown to remove the presence of a dysfunctional or otherwise-undesired gene, or the insertion of novel genes) to prolong lifespan, for instance by silencing genes whose presence is correlated with shorter lifespans or the insertion or activation of genes correlated with longer lifespans. These kinds of therapies would not constitute varieties of ICRT because they seek to modify the existing structures and processes of the body in such a way as to increase lifespan rather than recurrently replacing the existing structures and processes of the body with error-free copies synthesized in vitro. Another illustrative instance is *Strategies for Engineered Negligible Senescence* (SENS), which seeks to remove various kinds of accumulated age-associated damage without removing and replacing the structures and processes affected by such damage. For instance, whereas ICRT would replace damaged mtDNA with error-free copies synthesized in vitro, SENS seeks the allotropic expression of mtDNA (i.e. expressing mtDNA inside the cell nucleus); whereas ICRT would replace cells containing accumulated intracellular junk with cells lacking accumulated intracellular junk, SENS seeks to introduce genes for novel (i.e. exogenous) enzymes that would allow lysosomes to metabolize such previously-unmetabolizable intracellular junk.

Potential crossovers between paradigms are possible as well. In line with the nanotechnological varieties of intra-paradigmatic ICRT outlined above, we could for example replace the gDNA and protein transcription and synthesis machinery (e.g. based upon the same paradigm as MEMS[11, 12] and NEMS[13, 14, 15, 16]) of cells with a non-biological system designed to protect and repair the gDNA and mDNA (e.g. through its recurrent replacement with error-free copies), which tin effect supplements the protein transcription and synthesis functions of the cell-nucleus entirely. We could configure this system to be more robust than the cell's existing machinery. Because we would have to design such a system, fixing problems (i.e. determining what is wrong as well as implementing the physical manipulations necessary to correct what is wrong) is ipso facto easier because the operational mechanisms of the system would be known in detail, which isn't the case for biological DNA protection and repair and protein transcription and synthesis systems. We could build redundancies into the system, such that if something malfunctions a redundant process can be there to take over its function before local operational deviation scales into emergent functional decline (which is more likely in systems having a high degree of component interconnection and interdependence, as in biological systems).

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[11] *MEMS & Nanotechnology Exchange*. What is MEMS Technology? (2011). Retrieved from https://www.mems-exchange.org/MEMS/what-is.html.
[12] Lyshevski, S. E. (2002). *MEMS and NEMS: Systems, Devices, and Structures*. Boca Raton, Fla.: CRC Press.
[13] Narayan, A. (2004). Computational Methods for NEMS. *nanoHub.org*. https://nanohub.org/resources/407.
[14] Mozafari, M. R. (2007). *Nanomaterials and Nanosystems for Biomedical Applications*. Dordrecht, Netherlands: Springer.
[15] Drexler, K. E. (1992). *Nanosystems: Molecular Machinery, Manufacturing, and Computation*. New York: Wiley.
[16] Bhushan, B. (2004). *Springer Handbook of Nanotechnology*. Berlin: Springer.

III. INDEFINITE FUNCTIONAL PERPETUATION THROUGH GRADUAL AND RECURRENT FUNCTIONAL RESTORATION

While integral component replacement therapy has a long and somewhat diverse history, we feel that it has been heretofore unacknowledged as an overarching approach encompassing the historical and contemporary examples listed in the preceding section. We also feel that the aspects categorically differentiating it from normative curative-care, and which distinguish it as a distinct approach to functional restoration and perpetuation, have yet to be recognized by the wider medical and gerontological community.

The approach has a number of benefits that approaches to curative-care lack. We do not necessarily need to understand the disease or the structure, connectional and/or procedural source of emergent functional decline in order to remove it and restore declining function (or at least not the extent with which we would need to understand it in order to remediate it using a normative curative approach). This is a major advantage of ICRT. If we know how to synthesize or otherwise configure the affected structure (or an extra-paradigmatic functional analogue) then we can simply replace the affected structure without necessarily being able to remove the disease or structural source of functional decline *from* the affected structure without removing the entire structure altogether. Under the terms of the approach, then, we do not need to be concerned about having to develop new approaches to combat new types and/or new sources of age-correlated molecular damage and structural/procedural deviation appearing in future. The basic approach is generally applicable to all sources of structural and/or procedural distortion and functional decline by virtue of the fact that the approach does not seek to reverse the condition or structural/procedural deviation afflicting a given structure or process, but instead seeks to replace the afflicted structure or process an an error-free copy synthesized in vitro.

This also means that *recurrent* iterations of whole system ICRT (in which the replacement-components of the last ICRT iteration become the in-situ components *being replaced* in the next ICRT iteration), hereafter referred to as 'Recurrent Integral Component Replacement Therapy' (RICRT) can achieve indefinite functional perpetuation through recurrent iterations of functional restoration.

Moreover, there are a number of additional advantages available if an extra-paradigmatic ICRT is performed:

1. Because non-biological replacement-components are ipso facto designed, we would understand not only (1) their basic mechanisms underlying their operation, but also (2) how their low-level operational-modalities (i.e. on the scale of the smallest manipulable or configurable integral components of the system) converge to create the system’s high-level functional-modalities (i.e. on the scale of the largest differentiable integral components or sub-systems).

Thus if we wanted to implement an alternate (i.e. non-ICRT) approach to functional restoration (e.g. ameliorating structural, connectional or procedural deviation without replacing the affected integral-component(s) wholesale), the complexity of the task is greatly reduced in the context of manipulating systems having previously undergone an extra-paradigmatic ICRT. Ameliorating disease without removing and/or replacing the affected structures or sub-systems typically involves understanding the operational-modality (i.e. range of operating mechanisms) of both the affected structure/system and the source of structural/sub-systemic deviation or functional decline. We wouldn't need to experimentally deduce or infer the underlying operating mechanisms, as they would already be known by virtue of the fact that non-biological systems would need to be designed in order to be used at all.

2. Integral components can be made to be readily detachable and attachable, with recurrent iterations of ICRT in mind. This lessens the potential for accidental damage to adjacent structures in the removal of a given in-situ-component and the integration of a given replacement-component.

3. Non-biological systems can have additional systems embodying functional-modalities that the in-situ-component(s) it is replacing do not possess. Adding functional-modalities (i.e. functional addition as opposed to functional replication/restoration) is made easier by several factors: (a) we are designing the systems, so we can design them to have extra space for the mechanisms underlying the additional functional-modalities, without distorting the structures and processes underlying the functional-modalities also possessed by the in-situ componentsbeing replaced; (b) changes to low-level operational structure can be correlated with changes to emergent functional-modality because we understand the basic operating mechanisms and how they converge to instantiate emergent functional-modalities (a consequence of having designed the system). Additional functional-modalities making recurrent implementation of a ICRT easier include: (1) a component-index, such that the relative location of every component is known and transporting a given replacement-component to the correct in-situ-component can be simplified and systematized; (2) a transport system for importing replacement-components into the body and exporting removed in-situ components out of the body; (3) additional space for systems and technologies used to detach and/or integrate a given integral-component; (4) a monitoring system (i.e. sensors operatively connected to a CPU) for detecting when a given integral-component is in need of replacement; (5) protected in-situ stores of replacement-components, such that transporting new integral components into the body (and the technological infrastructure used to facilitate transport) is somewhat obviated by keeping the correct replacement-components in close proximity to the in-situ components they will eventually replace.

4. Integral components can be made more durable or less labile than the biological in-situ components they are replacing, thus allowing us to extend the span of time between recurrent iterations of ICRT (because integral components would degrade at a slower rate).

5. The integration or inclusion of redundant integral components that can be activated to take over the in-situ-component's functions and role in the emergent system's underlying operational mechanisms throughout the span of time in which it is being removed and replaced with a functionally-analogous replacement-component (during which it by definition cannot serve its role and perform its function because that requires structural, connectional, procedural or otherwise-operational connection to the other integral components comprising the system or sub-system) is made much easier.

IV. COGNITIVE INTEGRAL-COMPONENT REPLACEMENT THERAPY

It is generally accepted that the brain embodies or otherwise-instantiates our phenomenal consciousness (i.e. the capacity to feel; the sum total of our qualia at any given moment; awareness; sentience as opposed to sapience). The body is the mind's input-output system; its sensors and its actuators; its means of reacting to and interacting with the world. Embodiment may be necessary for consciousness to form, but we can nonetheless expect that regardless of what we replace the integral components comprising the rest of our bodies with, our phenomenal consciousness will be maintained. We could replace our bodies entirely and simply supplant it with suitable sensory information input directly conferred to the brain via neurostimulation, as in the brain-in-a-vat philosophical thought experiment[17], and still expect phenomenal consciousness to be preserved.

Thus we could replace our entire body with a cybernetic system suitably configured to functionally supplant our sensory organs (e.g. via sensory substitution), our actuators and our homeostatic and regulatory mechanisms. Continuing advances in sensory substitution[18] and sensory prosthesis, robotics, and maintaining the bodies homeostatic and regulatory mechanisms ex-situ (e.g. cardiopulmonary bypass[19]) will developmentally converge to provide the ability to keep the biological brain alive without a body-as-such.

But the neurons and glia comprising the brain are subject to the same eventual cellular senescence that the other somatic cells of body are. Thus in order to achieve truly indefinite functional perpetuation through recurrent functional restoration, the replacement of the integral components comprising the brain is also necessitated.

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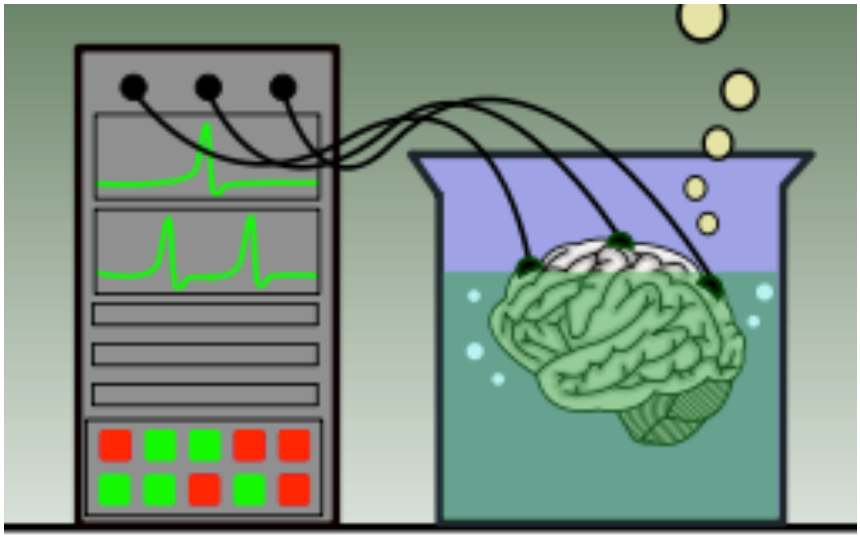
[17] Hickey, L. P. (2011). The Brain in a Vat Argument. *Internet Encyclopedia of Philosophy*.

[18] Kaczmerek, K. A. (1995). *Sensory Augmentation and Substitution*. The Biomedical Engineering Handbook Vol. 1. Ed. J. D. Bronzinio. Boca Raton, FL: CRC Press.

[19] Stoney, W. S. (2009). *Evolution of Cardiopulmonary Bypass*. Circulation, (119) 2844-53. DOI: 10.1161/CIRCULATIONaHA.108.830174.



Credit: Brain in a vat. (n.d.). In Wikipedia: Public domain. Retrieved October 31, 2013, from http://commons.wikimedia.org/wiki/File:Brain_in_a_vat_(template).svg

V. Recurrent Gradual Integral-Component Replacement in the CNS

The gradual replacement of integral components seems to be one of the body's predominant methods of repair and functional maintenance; we see this in the senescence of the somatic cells comprising most tissues and organs (excepting stem-cells, germ cells, gametes, gametocytes and neurons) and their replacement with dividing somatic cells or adult stem cells[20], i.e. cell turnover[21, 22]. If the body attempted to replace organs or tissues wholesale, rather than through the gradual replacement of single cells[23], the problem of replicating that organ or tissue's functionality (which other biological systems are dependent on) during the interval of time in which it is removed and replaced would also need to be accounted for. This concern can be obviated by instead gradually replacing the cells comprising a given emergent organ or tissue, because biological redundancy allows a given organ or tissue to function independent of the proper functioning of *all* of its integral components; thus an organ's functionality will decrease in proportion to the amount of cells (i.e. integral components) that are dysfunctional, rather than losing emergent functionality entirely as soon as one or a certain number of its integral components malfunctions. Instead, functional decline increases in proportion to the degree of "microscale" operational-malfunction in its constituent integral components.

Biological turnover in the brain, in contrast to biological turnover in the body, occurs at the

[20] Pellettieri et al. (2007). Cell Turnover and Adult Tissue Homeostasis: From Humans to Planarians. *Annual Review of Genetics*. 41: 83-105.
[21] Spalding et al. (2008). Dynamics of Fat Cell Turnover in Humans. *Nature*. 453(7196): 783-7.
[22] Berggman et al. (2009). Evidence for Cardiomyocyte Renewal in Humans. *Science*, pp. 324(5923), 98.
[23] Wade, N. (2005, August 2). Your Body is Younger than You Think. *NY Times Online*. Retrieved from http://www.nytimes.com/2005/08/02/science/02cell.html?pagewanted=all&_r=0.

molecular rather than cellular scale. Whereas the replacement-scale in most organs and tissues of the body is cellular, the replacement-scale in the brain is sub-cellular, wherein brain cells (i.e. neurons) are themselves gradually replaced at the molecular scale[24]. We can speculate why this is the case. The unique synaptic connections of neurons (hereafter referred to as a connectional profile; the total connectional profile of all neurons in the CNS, taken together, is generally synonymous with the connectome of that CNS) determines the emergent functionality of the brain-region they comprise; cellular turnover (or gradual replacement at the cellular, as opposed to sub-cellular, level) as it occurs in the rest of the body would involve the senescence of cells (e.g. via programmed-cell-death) and their replacement with undifferentiated or transdifferentiated adult stem cells. This would fail to maintain the connectional profile of the neuron being replaced. If cellular turnover in the CNS were implemented at a slow enough rate for the up-scale connectional profile (i.e. the emergent connectional profile of a group or network of neurons) to make the connectional profile of that new neuron similar to the connectional profile of the neuron it supplements, via interacting with adjacent neurons in much the same way as the senesced neuron did previously, which is likely because it is in the same location as the senesced neuron (i.e. function drives form25), then all the neurons comprising a given brain region, or comprising the entire CNS for that matter, could hypothetically take place in a way that preserves the approximate connectional profile of brain regions and the single neurons comprising them. The chances of maintaining the connectional profile of the CNS and its constituent neural sub-systems increases in proportion to how long we wait between (1) replacing a given neuron and (2) replacing another neuron either (a) sharing direct synaptic or ephaptic connection with it or (b) comprising the same emergent neural network or region; this is because a longer interim time (hereafter referred to as replacement-time) scales to a longer time during which the existing connectional profile can re-connect to each new neuron in the same way that they connected with the senesced neurons such new neurons are replacing. The interval of time between (1) and (2) will be referred to as the replacement interval time (RIT). The notion of graduality (defined as a measure of how gradually a cognitive ICRT is implemented, proportional to the magnitude of the RIT) is fundamentally important in cognitive ICRT because graduality is a large determining factor in terms of how well the connectional profile, and thus operational and functional-modalities, of the CNS is maintained. Because the notion of graduality creates a unique set of concerns not present in non-cognitive varieties if ICRT, we will distinguish between cognitive integral-component replacement therapy (CICRT) and normative ICRT.

But molecular turnover avoids the problem of negating the existing connectional profile of replaced (i.e. senesced) neurons, hypothetically allowing the complete *safe* material turnover in the CNS to proceed at a faster safe rate (where the safety of the turnover rate is defined as the

[24] Star, E.N., Kwiatkowski, D.J., and Murthy, V.N. (2002). Rapid Turnover of Actin in Dendritic Spines and its Regulation by Activity. *Nature Neuroscience*, 5: 239-246. DOI: 10.1038/nn811.
[25] Chen, S. X., & Haas, K. (2011). Function directs form of neuronal architecture. *Bioarchitecture, 1*(1), 2-4.

degree with which the existing connectional profile of the CNS is maintained).

VI. INTRA-PARADIGMATIC GCICRT

We could potentially use the same intra-paradigmatic varieties of ICRT as used in the body, such as but not limited to nanotechnological cell repair (e.g. via molecular replacement or macromolecular replacement, or via chromosome replacement therapy, i.e. CRT) or biotechnological cell repair (e.g. gDNA and mDNA replacement therapy). We could also iteratively reseed the biological brain with new biological neurons via a variety of cell-replacement therapies (e.g. stem cells, pluripotent cells, transdifferentiated cells). It is important to note, however, that we must be particularly careful applying this approach the CNS. The morphology and synaptic connections of a neuron, as well as the relative weight or strength of a neuron's synaptic connections, determines its operational-modalities. Recurrently reseeding the CNS with stem-cells that would then take the place of cells that had already senesced (at a rate determined by the statistical rate of neuronal senescence) would present no problem, as the operational idiosyncrasies encoded in its unique morphological, connectional and synaptic-weighting profiles are already negated at that point, and replacing the void with a fresh neuron would do no harm. But implementing the approach underlying WISCT, i.e. terminating cells via programmed cell death and replacing them with pluripotent cells, might do the CNS more harm than good *if* it is implemented using a replacement-time that isn't of a long enough duration, as it would effectively negate the unique connectional, synaptic-weighting and morphological profiles encoding everything from memory to behavioral predilection. This concern could be minimized by extending the replacement interval time; by increasing the replacement interval time we increase the probability of maintaining existing connectional profiles. Alternatively, if there were a method of (1) recording morphology, synaptic connection (i.e. connectomics) and synaptic weighting, and of (2) artificially inducing synaptogenesis, then it may be possible to use pluripotent cells (or, less preferably, cells differentiated into neurons but still "fresh" in the sense of lacking unique, history-dependent morphological, connectional or synaptic-weighting profiles) and through a process of artificially-induced synaptogenesis replicate (to as close an approximation as technological/methodological precision will allow) the connectional, morphological and synaptic-weighting-profiles of the neurons being terminated and replaced. The use of exogenous neuron cell cultures (i.e. neurons or neuron gown in vitro) to supply "fresh" neurons for such a procedure is also a possibility, as neuron cell cultures have been in use for longer than a decade[26]. But transporting fully-differentiated neurons into the CNS is likely to be significantly harder than seeding the CNS with stem cells or pluripotent cells would be; on the other hand, the process of artificially-induced synaptogenesis may be significantly easier in vitro than in vivo, due to such factors as more space (thus allowing for the use of technology that takes up more space) and control over environmental conditions.

[26] Potter, S. M., & DeMarse, T. B. (2001). A new approach to neural cell culture for long-term studies. *Journal of neuroscience methods, 110*(1), 17-24.

In addition to the intra-paradigmatic integral component replacement therapies outlined above, wherein in-situ integral components are replaced with *biological* equivalents, extra-paradigmatic ICRT (i.e. replacing in-situ components with *non-biological* replacement-components) is another route to the indefinite functional perpetuation of the CNS, and one with a host of advantages over intra-paradigmatic varieties of CICRT.

VII. PROCEDURAL-CONTINUITY AND PHENOMENAL CONSCIOUSNESS

Phenomenal consciousness is our subjective awareness; experientiality; sentience; the sum total of our qualia at any given moment; the capacity to feel. Phenomenal continuity denotes maintaining the same phenomenal consciousness (which is not synonymous with an equivalent or phenomenally isomorphic phenomenal consciousness) throughout the course of a gradual cognitive integral-component replacement therapy (GCICRT). Phenomenal-discontinuity, then, denotes failing to maintain the same phenomenal consciousness throughout the course of a GCICRT. We suspect that undergoing a sufficiently non-gradual cognitive ICRT will cause phenomenal-discontinuity. This is an inference from comparing the notion of gradual uploading to destructive uploading. In destructive uploading we suspect that the Whole-Brain-Emulation (WBE) possesses a distinct phenomenal consciousness not bearing phenomenal continuity with its biological original. We know this because if it were possible for such a WBE to be created without destroying its biological original, then they would both exist simultaneously, as separate (though presumably phenomenally-isomorphic, if we synchronize their sensory inputs with sufficient accuracy) phenomenal consciousnesses. Thus if we had no *gradual* integral-component replacement procedure, and instead replaced the whole brain wholesale, with a functionally-isomorphic WBE for instance, we could conclude that phenomenal continuity was *not* maintained between the biological brain and the WBE.

Likewise, we lose (i.e. through normative cellular senescence) approximately one neocortical neuron per second, which scales to roughly 85,000 per day and 31 million per year[27, 28]. We can infer from this that the loss of a single neocortical neuron is not perceptible to our phenomenal consciousness. Thus we can conceive of replacing the neurons comprising our CNS with functional equivalents one at a time, allowing each functional equivalent to causally interact with surrounding biological neurons before any of the neurons that functional equivalent causally interacts with (e.g. chemical and electrical synaptic connection; ephaptic coupling) are likewise replaced.

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[27]Pakkenberg, B. and Gundersen, H.J.G. (1997). Neocortical Neuron Number in Humans: Effect of Sex and Age. *The Journal of Comparative Neurology*, 384: 312-20. PMID: 9215725.

[28]Pakkenberg, B., Pelvig, D., Marner, L., Bundgaard, M.J., Gundersen, H.J.G., Nyengaard, J.R. and Regeur, L. 2003). Aging and the Human Neocortex. *Experimental Gerontology: Proceedings of the 6th International Symposium on the Neurobiology and Neuroendocrinology of Aging*, 38(1-2): 95-99. http://www.sciencedirect.com/science/article/pii/S0531556502001511.

We suspect that it may be possible to replace the entire CNS in this manner, gradually, while still preserving phenomenal consciousness. This is an inference following from the conjunction of the following premises:

(1) Every constituent molecule composing our neurons is replaced through the process of molecular turnover (i.e. through normal cellular metabolic processes) every 7 years at least, yet despite this fact we feel as though we have retained phenomenal continuity throughout the duration of those seven years;

(2) The loss of one neocortical neuron is imperceptible to our phenomenal consciousness much in the same way that the loss of a one of the molecules, compounds or molecular clusters comprising our neurons (replaced via molecular turnover) is imperceptible to our phenomenal consciousness. It follows, then, that it may be possible for us to gradually replace our constituent neurons in the same way through which the molecules composing our neurons are gradually replaced (i.e. through the gradual replacement of integral-components) while still retaining phenomenal-continuity.

This hypothesis is reified by the concept of neural redundancy in general (i.e. the ability for various areas of the CNS to take over the functioning of other parts of the CNS lost or damaged irreparably) and Karl H. Pribram's Holonomic Brain Theory[29, 30, 31] in particular, which provides a theoretical model for explaining experiments, in which large portions of the CNS was removed without significantly altering organism-behavior, suggesting that selective brain damage doesn't necessarily erase specific memories. Note, however, that the property of neural redundancy is generally accepted by the neuroscience community independent of Pribram's theory.

Procedural-continuity denotes constant causal-interaction amongst integral components (in other words, a duration of time in which there is no instance of complete cessation of causal-interaction between the integral components comprising the system – i.e. no instance during which all the integral components of a system cease interacting with each other simultaneously; thus single integral components can cease interacting for brief intervals of time without incurring procedural-discontinuity as long as there are other integral components of the same emergent system interacting during those intervals of time). In the CNS, procedural-discontinuity (i.e. the cessation of causal interaction amongst the integral components of the CNS at one time)

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[29]Prideaux, J. (2000). Comparison between Karl Pribram's "Holographic Brain Theory" and more conventional models of neuronal computation. *Virginia Commonwealth University*. http://www.acsa2000.net/bcngroup/jponkp/.

[30]Pribram, K. H. (1991). *Brain and Perception: Holonomy and Structure in Figural Processing*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

[31]Pribram, K. H. (1971). *Languages of the Brain: Experimental Paradoxes and Principles in Neuropsychology*. New York: Prentice Hall/Brandon House.

correlates with the dissolution or destruction of phenomenal consciousness. The cessation of all causal interaction amongst neurons in the brain is synonymous with brain death. Even in cases where the heart has stopped and the individual is able to be revived (up to hours after heart-failure if the individual's body-temperature is kept low, because this slows metabolism and thus cellular senescence), complete cessation of causal-interaction amongst neurons in the brain has not occurred. Causal interaction amongst neurons is slowly decreasing as cells senesce, but individuals able to be revived will not have undergone an instance of complete cessation of causal interaction amongst the neuron comprising their CNS.

Thus we can infer that the degree with which we can maintain causal interaction amongst the integral components of the brain as we gradually replace them is correlative with the likelihood of maintaining phenomenal continuity (via maintaining the procedural-continuity of cognitive integral components) throughout the course of a GCICRT. The amount of integral-component-causal-interaction we can maintain is inversely proportional to the scale at which we implement a cognitive ICRT (i.e. the size of the integral components we treat as the in-situ-components; e.g. neural region, neural cluster, neural network, neuron, transmembrane protein, macromolecule, molecule, atom, etc.) – that is, the smaller the component we replace, the more causal-interaction we can maintain during the time in which the in-situ-component is removed and its replacement-component is integrated in its place.[32]

[32] There are two alternative positions one can take in regards to quantifying the degree of procedural continuity possessed by a given system composed of integral components. Both of positions accept that the degree of procedural continuity maintained throughout the gradual replacement of constitutive integral components constituting each of the functional wholes in the CNS correlates with the probability of maintaining phenomenal continuity throughout the cumulative whole-CNS procedure. Which of the two positions one takes will affect the turnover rate applied to a given system. Which position is correct one does not appear to be inferable from the premises of the present formulation. The first position maintains that the best way to quantify procedural continuity is to correlate it with the number of integral components that a given removed-and-replaced integral component makes functional connection with. According to this position, and in the context of a neuronal replacement-scale (i.e. wherein neurons comprise the integral components being replaced), the degree of procedural continuity correlates with the number of neurons that neuron makes synaptic or ephaptic connection with. The second position maintains that procedural continuity should take into account the number of integral components (sharing the same replacement scale) constituting the next up-scale functional whole, rather than the number of integral components a given integral component makes functional connection with. According to the second position, and in the same context as the first (i.e. using a neuronal replacement scale), the degree of procedural continuity would correlate with the number of neurons constituting the neural network (e.g. cortical microcolumn in the context of the cortex) that that neuron is a part of. The first position would maintain that those neurons making the least number of synaptic or ephaptic connection with a number of other neurons that should, when replaced, be given a longer interval of time before another neuron it makes connection with is replaced. The second position would maintain, conversely, that it is those neurons that are part of a very large neural network (i.e. an up-scale functional whole comprised of many integral components on the replacement scale) that should be given a longer duration of time before another neuron comprising the same up-scale functional whole (e.g. neural network) is replaced. This applies both to intra-paradigmatic as well as extra-paradigmatic integral-component turnover. In the case of WISCT, which when applied to the biological CNS constitutes an intra-paradigmatic variety of GCICRT, this same decision must be made - whether neurons making a large number of synaptic or ephaptic connections should be given a longer intermediary timespan before another neuron making connection with it is replaced, or whether conversely neurons partially comprising an up-scale functional whole that is composed of a large number of neurons should be given the longer time interval before another one of its constituent neurons is likewise replaced. It is important to note that

Because we have removed the in-situ-component from the rest of the cognitive system, thereby discontinuating or ceasing its causal interaction with other integral components, any interaction amongst the integral components *of that* in-situ-component (i.e. if the in-situ-component was a whole neuron, its integral components would be sections of phospholipid-bilayer and transmembrane proteins) no longer qualifies as causal interaction of cognitive integral components (because the in-situ-component is no longer a causally-interactive part of the emergent cognitive system). Thus if we implement a neuronal GCICRT, the lowest level (in terms of scale) at which we can maintain integral-component-interaction is on the scale of single neurons. If we implement a subneuronal GCICRT, then the lowest scale at which we can maintain integral-component-interaction is the sub-neuronal scale of individual transmembrane proteins and sections of phospholipid-bilayer.

We can thusly conclude that how close we get our replacement-scale to approximate the existing scale of biological turnover in the CNS (i.e. molecular turnover), in terms of both replacement-time and replacement-scale, correlates with the likelihood of maintaining phenomenal continuity throughout the course of a GCICRT. We can conclude this because (1) the previous thought experiment suggested that procedural-continuity (i.e. the degree with which integral-component interaction is maintained, or more specifically not decreased) correlates with phenomenal-continuity, exemplified most prominently in the case of brain-death, wherein the amount of integral-component interaction gradually drops to zero as cells in the CNS senesce, (2) the existing, biological CNS undergoes complete molecular turnover every seven years (in other words half of the material comprising the CNS has been replaced every 3.5 years) and yet we feel, subjectively, to have maintained phenomenal continuity throughout that time, and (3) we lose approximately one neuron a second and it isn't perceptible to our phenomenal consciousness.

Previous conceptions of GCICRT, as in gradual mind uploading[33, 34] entail replacing one neuron at a time. This can be seen to result from defining graduality procedural-continuity in reference to time rather than to the amount of causal interaction amongst integral components. Conversely, GCICRT as defined and outlined in the present formulation allows for the simultaneous replacement of two neurons so long as they do not (a) share direct synaptic or ephaptic connection with each other and possibly, but not necessarily, as long as they do not (b) comprise the same emergent neural network or region.

If the degree of causal-interaction amongst integral components were constant across different paradigms (e.g. biological vs. non-biological, physical-functional vs. semiofunctional)

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regardless of which of the two positions one takes, both agree that the minimizing the replacement scale will maximize the chances of maintaining procedural continuity and thus phenomenal continuity throughout a whole-CNS GCICRT.

[33] Kurzweil, R. (2005). *The Singularity is Near: When Humans Transcend Biology*. Viking: Ney York, pp. 198-203.

[34] *Ibid.*, pp. 548-549.

then using time as a measure of graduality would suffice. But consider the case of a Whole Brain Emulation (WBE) and its original. The rate of causal interaction amongst emulated integral components is a function of available computational capacity that can be used to process the WBE (i.e. doubling the amount of computational capacity will allow us to emulate such a WBE twice as fast). Here we have an instance in which the rate of integral component interaction is faster in the WBE than in the biological original. If we used time as the measure of graduality then using the same replacement time (as measured in units of time, as opposed to the number of integral-component causal interactions per unit of time) would create a GCICRT only 50% as gradual in the WBE (if it is being emulated at 200% real-time) as GCICRT in the biological original. If, conversely, we used instead the number of integral component causal interactions per unit of time as the measure of graduality, then the same degree of graduality could be maintained throughout GCICRT in the WBE as it would be in the biological original. Objectively measured time is, however, the next-best approximation of the degree of causal interaction in the absence the ability to directly measure causal interaction of cognitive integral components.[35]

Moreover, because we have argued integral-component-interaction to be inversely proportional to the replacement-scale used (i.e. a smaller replacement-scale results in a higher degree of maintained-integral-component-interaction), we can hypothetically achieve the same degree of graduality using different ratios of replacement-time to replacement-scale. If lack of sufficient miniaturization prevents the use of a molecular replacement-scale comparable to the replacement-scale used in normative molecular turnover in the CNS, increasing the replacement-time will allow us to achieve the same degree of graduality that is found in normative (i.e. biological) molecular turnover in the CNS. If we are able to determine (1) the replacement-scale **Sb** and the replacement-time **Tb** used in normative molecular turnover in the CNS, and the smallest replacement-scale **Sa** we are able to achieve in externally-mediated GCICRT (i.e. the smallest neuronal integral-component we are able to functionally-replicate; e.g. insufficient miniaturization could result in only being able to achieve functional-replication and safe, i.e. non-destructive, in-situ-component-removal and replacement-component-integration on the neuronal, as opposed to sub-neuronal, scale) then we can use the following formula to determine

[35] In discussing WISCT, we suggested that a more appropriate method of determining what integral component replacement rate should be applied to a given cognitive system in order to maximize the maintenance of procedural continuity and phenomenal continuity, we suggested that turnover rates take into account the ultimate size of the next up-scale functional whole a given integral component is a part of, such that lower turnover rates are applied to systems consisting of a lesser number of neurons, while a higher turnover rate would be applied to systems consisting of a larger number of neurons. This has to do with the fact that the loss of an arbitrary number of neurons will constitute a larger functional loss to the larger system than it would for the smaller system. It is conceivable that this applies to the gradual replacement of integral cognitive components in extra-paradigmatic GCICRT as well. This would be in accordance with the second of the two contrary positions regarding how to quantify procedural continuity and thus how to determine the most optimal turnover rate (i.e. most likely to maximize preserved procedural continuity, thereby maximizing maintained phenomenal continuity) to specific functional wholes (i.e. brain regions, neural circuits, neural regions, etc. - depending upon what replacement scale is used), because the loss of a given integral component is always characterized in terms of a functional loss of the next up-scale functional whole it is a part of. In this context, when applying a GCICR, different integral component replacement rates would be used according to how large the up-scale functional whole which those integral components comprise.

the replacement-time **Ta** that must be used in order to approximate the same degree of graduality that occurs throughout normative (i.e. biological) molecular turnover in the CNS:

$$Ta = \left(\frac{Sa}{Sb}\right) Tb$$

Where **Sb** is the replacement-scale occurring in normative molecular turnover in the CNS, **Tb** is the replacement-time occurring in normative molecular turnover in the CNS, **Sa** is replacement-scale occurring in externally-mediated GCICRT (i.e. the smallest replacement-scale we are able to achieve), and **Ta** is the replacement-time needing to be applied throughout the externally-mediated GCICRT in order to preserve the same degree of graduality that exists in normative molecular turnover in the CNS.

In quantifying **Ta**, synonymous with the amount of causal-interaction occurring between integral components (of the scale used as the replacement-scale) per unit of time, we could use of either (a) the number of causal interactions occurring between co-affective or "causally adjacent" components within the interval of replacement-time Ta, which is synonymous with the frequency of causal interaction, or alternately (b) the number of state-transitions a given component undergoes within the interval of time Ta. While (a) and (b) should be generally correlative, in that state-transitions are facilitated via causal interaction among components, (b) may be a more methodologically-rigorous metric because it allows for quantitative comparison between categorically-dissimilar types of causal interaction, which otherwise couldn't be summed into a single variable or measure. For example, if one type of molecular interaction has a greater effect on the state-transitions of either component involved (i.e., facilitates more state-transitions or a state transition of greater magnitude) than does another type of molecular interaction, then quantifying a measure of causal interactions may be less accurate than quantifying a measure of the magnitude or number of state-transitions, or alternatively an average taking into account the number of state transitions and their comparative magnitude(s).

It should be noted that this is at best a next-best approach to maximizing procedural-continuity amongst integral components, and the ultimate possible degree of procedural-continuity able to be maintained amongst integral components is inversely proportional to the replacement-scale.[36]

[36] It is important to note that the correlation of phenomenal continuity with procedural continuity suggests that the use of serial computers to implement whole brain emulations may be problematic. In serial computers, rather than performing a number of computations simultaneously, it performs one at a time and switched between a number of ongoing, separate processes fast enough for it to seem to human users like it is doing everything at once. However, for serial computers simulating or emulating integral cognitive components (e.g. neurons) would incur that at any given time it is only simulating one operational state or transition function, and switching between all of the operational states and transition functions occurring in the whole CNS at any given time. Due to the fact that in a whole brain emulation (belonging to the semiofunctional paradigm), the information processing constitutes embodiment, only one integral component would be embodied at any given time. This would presumably incur as

VIII. A Brief History of the Indefinite Functional Perpetuation of the CNS

The notion of replicating the functions of the mind in non-biological systems can be argued to have its roots in the field of Artificial Intelligence, which in turn can be argued to have even deeper historical roots in the notion of computers in general and even mechanical calculators and logic machines (e.g. the mechanical calculators of the 17th century[37]). The notion of replicating a specific personality in non-biological substrates, which became synonymous with the term mind uploading, appeared in fiction with Frederik Pol's 1955 *The Tunnel Under the World* and in Arthur C. Clarke's 1956 *The City and the Stars*[38, 39]. The notion seems to have first appeared in academic literature, in 1971:

> "We shall assume that developments in neurobiology, bioengineering and related disciplines… will ultimately provide suitable techniques of 'read-out' of the stored information from cryobiologically preserved brains into nth generation computers capable of vastly outdoing the dynamic patterning of operation of our cerebral neurons. We would then join a family of humanoid 'post-somatic' bio-electrical hybrids capable of contributing to cultural evolution at rates far exceeding anything now imaginable."[40]

While this notion classifies as the functional replication of a specific personality in a non-biological medium, it lacks the fundamental distinction of graduality and the notion that phenomenal continuity can be maintained between the biological original and its emulated copy by gradually integrating the respective integral components of the two over time.

Frank Tipler also presented a version of the functional replication of a specific mind[41, 42] (as opposed to mind in general), but his formulation also lacked the fundamental aspect of graduality. In fact, it seems that most historical recapitulations of the idea lacked a consideration for the

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much procedural discontinuity as physically disconnecting (or operationally halting) all of the neurons in the brain, essentially equivalent to brain death. Thus in order for whole brain emulations to maintain phenomenal continuity (i.e. with its past and future self), massive parallelism on the same order as seen in the biological brain may be necessary.

[37] Calculators. (n.d.) *In Encyclopedia Britannica Online*. Retrieved from http://www.britannica.com/EBchecked/topic/89155/calculator.

[38] Bainbridge, W. S. (2004), Literary Representations. *Berkshire Encyclopedia of Human-Computer Interaction*, p. 438 ed.

[39] Blackford, R. (2004), *Stranger Than You Think: Arthur C. Clarke's Profiles of the Future, in Prefiguring Cyberculture: An Intellectual History*, p. 253 ed. Tofts, D., Johnson, A., and Cavalarro A.

[40] Martin, G.M. (1971). Brief proposal on immortality: an interim solution. *Perspectives in Biology and Medicine* 14(2): 339. PMID 5546258.

[41] Tipler, F. (1989). The Omega Point Theory as Eschaton: Answers to Pannenberg's Questions for Scientists. *Zygon: Journal of Religion & Science*, 24(2): pp. 217-53. DOI: 10.1111/j.1467-9744.1989.tb01112.x.

[42] Tipler, F. (1994). *The Physics of Immortality: Modern Cosmology, God and the Resurrection of the Dead.* Doubleday: New York.

principal importance of graduality. In 1964 Norbert Weiner wrote:

> "This is an idea with which I have toyed before – that it is conceptually possible for a human to be sent over a telegraph line… At present, and perhaps for the whole existence of the human race, the idea is impartible, but it is not on that account inconceivable."[43]

Another anticipation of the functional replication and restoration of the CNS was put forward by Greg Easterbrook in 1995:

> "Suppose as biological life draws toward its inevitable conclusion a person's patterns of consciousness could be transferred to an electrical support apparatus. The part that matters about you might then exist a very long time, possible an infinite time… Of course people might not want to have their consciousness go on after the body expires… Weird paradoxes might result: for instances if whatever gizmo reads the patterns of your consciousness in order to preserve it made two copies, would you perceive yourself as alive in two places?... Yes, once we have defined pure mental patterns as living consciousness, this means that there may someday be something approximately like electronic life… the development of forms of life that have no biological origin seems close to inevitable."[44]

But Hans Moravec seems to have been the first contemporary thinker (excepting J.D. Bernal) to put forward the notion of *gradual* mind uploading[45]:

> "'That computer sitting next to you in the operating room would in effect be your new brain. As each area of your brain was analyzed and simulated, the accuracy of the simulation would be tested as you pressed a button to shift between the area of the brain just copied and the simulation. When you couldn't tell the difference between the original and the copy, the surgeon would transfer your brain into the new, computerized one and repeat the process on the next areas of your biological brain. Though you have not lost consciousness or even your train of thought, your mind – some would say soul – has been removed from the brain and transferred to a machine' Moravec said. 'In a final step your old body is disconnected. The computer is installed in a shiny new one, in the style, color, and material of your choice."[46]

In *Mind Children*[47] he describes this scenario in more detail, wherein a robot surgeon opens the skull, analyzes the topmost layer of neurons and emulates these in an external computer:

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[43] Rhodes, R. (1999). *Visions of Technology: A Century of Vital Debate About Machines, Systems and the Human World.* Touchstone: New York, p. 239.
[44] *Ibid.*, pp. 358-359.
[45] Broderick, D. (2001). *The Spike: How Our Lives Are Being Transformed by Rapidly Advancing Technologies.* Forge: New York, pp. 232-233.
[46] Fjermedal, G. (1986, October). Artificial Intelligence. *Omni Magazine*, Vol. 9 Iss. 1, p. 38.
[47] Moravec, H. (1988). *Mind Children: The Future of Robot and Human Intelligence.* Cambridge, Mass. Harvard University Press.

> "By precise injections of current and electromagnetic pulses, the electrodes can override the normal signaling activity of neurons. They are programmed to inject the output of the simulation into those places where the simulated tissue signals other sites… The brain tissue is now impotent – it receives inputs and reacts as before but its output is ignored."[48]

Thus the surgeon simulates the brain layer by layer, removing each layer as it is replaced by an equivalent simulation, which is operatively connected to the existing biological brain via (1) ignoring the output of those neurons already simulated and (2) using microelectrodes to supply the output of the now-simulated neural region to the rest of the brain. Moravec contrasts the body-identity position of identity (that identity is constituted by the material *stuff* of the body) to the pattern-identity position (that identity is the pattern and process embodied by the material stuff of the body). This notion is intimately related to Moravec's realization of the importance of graduality, and he uses the gradual metabolic replacement of the body's material constituents as supportive evidence for the pattern-identity position.

However, there are aspects of the present formulation that are absent in Moravec's. The non-computational, physical (e.g. electromechanical) replication of cognitive integral components is one. Also, Moravec does not explicate the fact that the likelihood of maintaining phenomenal continuity (i.e. "staying the same person") is a function of how gradual the procedure is – i.e. that phenomenal continuity is dependent on and correlative with the degree of graduality exercised throughout a GCICRT limits certain actions on the part of a given mind (i.e. those actions causing significant procedural-discontinuity amongst cognitive integral components), though this notion could very well be inherent in his formulation, as he does note the importance of graduality in general, even though he doesn't explicate its relationship to procedural-continuity and the positive correlation between procedural-continuity and phenomenal continuity in particular. Moravec writes: "As a computer program, your mind could travel over information channels, for instance encoded as laser message beamed between planets."[49] This notion fails to foresee that in order to send the mind as a message, all causal interaction amongst integral components must be temporarily ceased (i.e. the mind must be "put on pause" so to speak) and so would be equivalent to the non-gradual computational replication of mind (i.e. "destructive uploading") or the complete cessation of causal interaction amongst cognitive integral components, a.k.a. brain-death. One would indeed wake up on the other side, but without having retained phenomenal continuity with the self that as left behind at the transmitter[50].

The notion was also explored by Ray Kurzweil[51], who envisioned nanobots seeding the CNS

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[48] *Ibid.*, pp. 110-111.
[49] *Ibid.*, pp. 114.
[50] Cortese, F. (2013). Clearing Up Misconceptions About Mind Uploading. *H+ Magazine.* Retrieved from http://hplusmagazine.com/2013/06/17/clearing-up-misconceptions-about-mind-uploading/.
[51] Kurzweil, R. (2005). *The Singularity is Near: When Humans Transcend Biology.* Viking: Ney York. pp. 198-203.

and recording the activity of a given neuron until that nanobot could replicate its functioning by computationally emulating it. And while the importance of graduality is present in Kurzweil's formulation, he, like Moravec, arguably fails to see the true extent of its importance and its repercussions on other aspects of gradual uploading. In the notes to chapter four, he writes:

> "Robert A. Freitas Jr. proposes a future nanotechnology-based brain-uploading system that would effectively be instantaneous. According to Freitas (personal communication [to Kurzweil], January 2005), "An in vivo fiber network as proposed in http://www.nanomedicine.com/NMI/7.3.1.htm can handle 10^18 bits/sec of data traffic, capacious enough for real-time brain-state monitoring. The fiber network has a 30 cm^3 volume and generates 4–6 watts waste heat, both small enough for safe installation in a 1400 cm^3 25-watt human brain. Signals travel at most a few meters at nearly the speed of light, so transit time from signal origination at neuron sites inside the brain to the external computer system mediating the upload are ~0.00001 msec which is considerably less than the minimum ~5 msec neuron discharge cycle time. Neuron-monitoring chemical sensors located on average ~2 microns apart can capture relevant chemical events occurring within a ~5 msec time window, since this is the approximate diffusion time for, say, a small neuropeptide across a 2-micron distance (http://www.nanomedicine.com/NMII/Tables/3.4.jpg). Thus human brain state monitoring can probably be instantaneous, at least on the timescale of human neural response, in the sense of 'nothing of significance was missed.'"

Transferring the functionality of the biological neurons to the simulated or emulated neurons *instantaneously* (i.e. at the same time) would in effect negate the very utility of a *gradual* uploading procedure, and should be equivalent to destructive uploading, in that there is no phenomenal continuity between the biological CNS and the emulated CNS. Freitas may simply be observing here the fact that monitoring two successive brain-states in a row could be effectively instantaneous, or falling within a duration of time that is negligible in comparison to the operational rates of biological neurons. But Kurzweil's first sentence, "Robert A. Freitas Jr. proposes a future nanotechnology-based brain-uploading system that would effectively be instantaneous", seems to imply that the instantaneous functional-supplementation of biological neurons for the computational emulations is what is being suggested (i.e. that once all the nanobots are in place we could "switch" mediums effectively instantaneously). This makes sense considering that Kurzweil anticipates most people integrating so much non-biological hardware (e.g. simulated or emulated neural-networks) to their biological brains that the non-biological portion will constitute the large majority of our total CNS, at which point losing the biological portion of one's total CNS will be comparable to, say, the loss of a single neuron to the unmodified biological CNS – in other words, not a substantial enough loss to cause concerns of phenomenal-discontinuity.

The notion of Mind-Uploading grew into the more formal academic discipline of Whole Brain Emulation[52, 53, 54, 55, 56] (WBE) throughout the 2000s. During this time the use of neurofunctional replication *as a means of functionally restorative and functionally perpetuative medicine,* i.e. as a means of life-extension, was at least somewhat marginalized in favor of more conventional uses and applications of WBE. Instead, talk of the advantages and utility of WBE focused upon (1) elucidating the workings of the brain so as to better understand disease (e.g. neurodegenerative diseases) and better formulate effective treatments (aided by the ability to perform virtual tests prior to physical tests, and by a better understanding of neural operation in general) and (2) implementing an emulation of the human CNS for the sheer scientific grandeur of the project. These aims appear to have wider contemporary appeal than functionally restorative medicine (and a wider scope, certainly), and thus help generate larger amounts of research funding and attention. But without the notion of graduality, and the gradual integration of a WBE with an existing biological CNS for functionally restorative and perpetuative purposes, WBE does not ipso facto classify as an instance of GCICRT or as a life-extension therapy. This does not prevent it from classifying as an ancillary (i.e. related and convergent) technology, nor does it prevent varieties of WBE that are gradually integrated with the biological CNS they are based upon from qualifying as an instance of GCICRT and as a life-extension therapy. And, indeed, while researchers and proponents of WBE (e.g. Randal A. Koene) have espoused its potential as a means of life-extension, and likely feel that its use as a life-extension therapy constitutes its most significant application, its use as a life-extension therapy has received

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[52] Sandberg, A. and Bostrom, N. (2008). Whole Brain Emulation: A Roadmap. Technical Report #2008-3. *Future of Humanity Institute*, Oxford University. Retrieved from www.fhi.ox.ac.uk/reports/2008-3.pdf.
[53] Sandberg, A. Bostrom, N. and Koene, R. (2011). The Society of Neural Prosthetics and Whole Brain Emulation Science. http://www.minduploading.org.
[54] Sandberg, A. (2013). *Feasibility of Whole Brain Emulation*. Theory and Philosophy of Artificial Intelligence, SAPERE. Berlin: Springer-Verlag, 251-64.
[55] Koene, R. A. (2012). Fundamentals of Whole Brain Emulation: State, Transition and Update Representations. *International Journal of Machine Consciousness*, Vol. 4(01), 5-21. DOI: 10.1142/S1793843012500023.
[56] Koene, R. A. (2012). How to Copy a Brain. *New Scientist*, 216 (2888), 26-27. http://dx.doi.org/10.1016/S0262-4079(12)62755-9.

comparatively less attention in academia and industry than their other utilities and applications. However, even without being characterized as a means of life-extension, development and progress in WBE still serves to further progress and development in those varieties of WBE that *do* classify as an instance of GCICRT and as a means of life-extension, because they share much of the same technological and methodological infrastructure. Increasing the ways that we can emulate integral-cognitive-components and increasing the predictive accuracy of such emulations will impact instances of WBE that aim to gradually replace the CNS with such emulated functional-analogs just as much as they will impact normative WBE that doesn't seek to gradually replace the biological CNS they are based upon. Thus while embodiments of WBE can indeed classify as varieties of GCICRT, and certainly work to promote and advance the long-term state-of-the-art in CICRT, WBE as an academic discipline does not *necessarily* classify as such ipso facto, and only varieties of WBE that involve the gradual integration of a WBE with its biological original qualify as a variety of GCICRT.

Lastly, we turn to the earliest identifiable historical description of GCICRT, in J.D Bernal's 1929 *The World, the Flesh and the Devil: An Enquiry into the Future of the Three Enemies of the Rational Soul:*

> "For one material out of which nature has been forced to make life, man will have a thousand; living and organized material will be as much at the call of the mechanized or compound man as metals are to-day, and gradually this living material will come to substitute more and more for such inferior functions of the brain as memory, reflex actions, etc., in the compound man himself… **Every part would be accessible for replacing or repairing and this would in itself ensure a practical eternity of existence, for even the replacement of a previously organic brain-cell by a synthetic apparatus would not destroy the continuity of consciousness.** The new life would be more plastic, more directly controllable and at the same time more variable and more permanent than that produced by the triumphant opportunism of nature."[57] (Emphasis added).

Bernal's work preceded the notion of computationally or mathematically emulating the brain, but he clearly envisions replicating the functionality of neurons in non-biological systems in general (e.g. "the replacement of a previously organic brain-cell by a synthetic apparatus"[58]), and even foresees the fundamental importance of graduality in preserving the "continuity of consciousness" which is synonymous with what we have referred to as "phenomenal continuity". Bernal also foresees some implications developed in the present formulation of GCICRT, including the utility of replacing "previously-organic brain-cell[s]" with functionally analogous units that are "more plastic, more directly controllable and at the same time more variable and more permanent" than the biological structures they replace.

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[57] Bernal, J.D. (1969). *The World, the Flesh and the Devil: An Enquiry into the Future of the Three Enemies of the Rational Soul.* (2d ed.). Bloomington: Indiana University Press.
[58] *Ibid.*

IX. EXTRA-PARADIGMATIC GCICRT

There are several varieties of extra-paradigmatic GCICRT. *Physical-Functional* or *physico-functional* CICRT denotes varieties of ICRT that replace the integral components of the CNS with non-biological, physically embodied systems (i.e. electromechanical and/or electrochemical systems – MEMS, NEMS, etc. – that transport ions and manipulate neurotransmitters). *Semiotic-Functional*[59] or *semiofunctional* CICRT denotes varieties of ICRT that replace the integral components of the CNS with computational or mathematical models (e.g. simulation, emulation, etc.). For instance, a simulated neuron could be equipped with sensors for sensing local electric potential and neurotransmitters, thereby allowing it to translate incoming biophysical signals identified by sensors into equivalent computational input that can be "recognized" by the model, and with actuators to likewise translate computational output into biophysical signals that can be "recognized" by synaptically connecting biological neurons via the manipulation of local biophysical parameters (e.g. releasing stores of neurotransmitters in accordance with the synaptic output of the simulated neuron).

Semiophysical-functional CICRT denotes a sub-class of physical-functional CICRT that replaces in-situ components with biophysically accurate computational emulations, whereas strict semiofunctional CICRT denotes varieties of ICRT that replace in-situ components with a computational, mathematical or otherwise-semiotic model of the abstracted signal-processing occurring in the neuron[60] rather than the biophysical "hardware" of the brain. If a biophysical emulation emulates the dynamics of ion-transport and neurotransmitter-diffusion, one could argue that such an emulation is simulating the hardware that is in turn simulating the "software" (i.e. abstracted or informational signal-processing) of the brain, whereas strict semiofunctional CICRT can be seen to skip the intermediate hardware step and simulate the software of the brain, directly, on alternate hardware than the biophysical hardware of the biological brain, as opposed

[59]The choice of the more inclusive term "Semiotic" over the perhaps more intuitively-apprehensible term "Computational" is to deter the misinterpretation that this class of neurofunctional replication, restoration and perpetuation therapy is limited to current or conventional computational paradigms, in terms of either hardware or software. Nor is this necessary limited to Universal Turing Machines. The categorical property differentiating this class from the other main class of neurofunctional restoration and perpetuation therapy is that whereas the other class uses first-order representation to embody neuronal or NSU system-states (i.e. representing system-states and transition functions directly), the Semiofunctional class represents second-order representation to embody neuronal or NSU system-states (i.e. representing neuronal or NSU system states *using different combinations of the first-order system-states and transition-functions*, for instance using the two system states and one transition-function of transistors to represent the multitude of system states and transition-functions occurring in the biological CNS or a CNS comprised partially or fully of NSUs). Just as signal processing is a more inclusive category than its subset, computation, so too is semiotics (i.e. the use of signs) a more inclusive category than its subset, signal processing.

[60] For the purposes of the present paper, the term "semio-functional" will denote both the semio-physical-functional and "strictly semio-functional" [i.e. semio-functional] paradigms of GCICRT, as opposed to pertaining solely to the "strictly semio-functional" paradigm. Likewise, the term "physical-functional" or "physicofunctional" will denote both the physicofunctional and "strictly physicofunctional" [i.e. physicofunctional] paradigms of GCICRT.

to simulating the hardware *as software* on alternate hardware[61].

Likewise, physico-semiotic functional (or physicosemiofunctional) CICRT denotes a sub-class of physical-functional CICRT that replaces in-situ components (e.g. neurons) with physically-embodied systems that perform the abstract signal-processing of the brain without necessarily implementing the same class of physical hardware embodying the same class of operational (as opposed to functional) modalities. For instance, there are various types of model used in the computational simulation of neurons. The most basic neuron model following the simple weighted-sum model used in artificial neurons is the Hodgkin-Huxley model (which represents various biophysical properties or structures as their basic electric-parameter analogues; the phospholipid bilayer is represented as a capacitance, voltage dependent ion channels as a linear conductance, leak channels as a non-linear conductance, electrochemical gradients (representing the dynamics of ion-transport and membrane polarization) as batteries and ion-pumps/exchangers as current sources.); the cable model (which treats neuron terminals as a bifurcating cylinder broken down into individual isopotential segments in turn modeled as capacitors and resistors connected in parallel; and compartmental models, in which "each ion channel type corresponds to a pair of parallel connected potentials and variable resistances per compartment. Compartmental simulations numerically simulate the equivalent network."[62] There are other types of model (e.g. integrate and fire, leaky integrate and fire, exponential integrate and fire model, the FitzHugh–Nagumo model, the Morris–Lecar model, the Hindmarsh-Rose model the soliton model, etc.) but the model-types listed will suffice for the scope of the present discussion.

We could thus envision constructing an electrical system (i.e. not necessarily computational, containing no transistors or logic elements, instead composed of simple electrical components as in the cable and compartmental models) that physically replicate an equivalent electrical network using standard electrical components (e.g. batteries, capacitors, resistors, electrical conductors, etc.) that the neuron components and parameters are reduced to (i.e. represented by) in the cable theory, compartmental and multi-compartmental neuron models. This would be one possible

[61] Semio-functional varieties of GCICRT have the advantage of being readily modifiable (i.e. the creation of new structures, connections, and processes, i.e. system-states) and modulable (i.e. variable-control of existing structures, connections and processes, i.e. system-states); simulating or emulating physical hardware (i.e. giving rise to the "direct" information or signal processing operations occurring in the neuron) *on alternate physical hardware* allows us to change the parameters and specifications of such virtual (i.e. second-order) hardware as easily as we would encode new information on a file. By contrast using physical hardware to *directly* instantiate the information or signal processing occurring in the neuron necessitates that any changes to the parameters and specifications of the physical hardware actually be made in physical space. It is important to note that this is only the case for physicosemiofunctional varieties of semiofunctional GCICRT, because they are using first-order hardware to simulate (I.e. instantiate as software) second-order hardware rather than second-order software. Semio-functional ICRT (i.e. those varieties that do not have virtual or second-order hardware, instead performing the "direct" information or signal processing using first-order, physical hardware).

[62] Sandberg, A. and Bostrom, N. (2008). Whole Brain Emulation: A Roadmap. Technical Report #2008-3. *Future of Humanity Institute*, Oxford University. Retrieved from www.fhi.ox.ac.uk/reports/2008-3.pdf.

embodiment of a physicosemiofunctional ICRT, in which the neuron's abstract signal-processing (as opposed to the specific physical hardware of ion-channels, ionic solutions and neurotransmitters) is replicated using alternate physical hardware, configuring and connecting *physical* capacitors, resistors and variable-batteries as opposed to simulating them as such using standard computational hardware (e.g. logic gates, transistors).

X. PHYSICO-FUNCTIONAL& PHYSICOSEMIO-FUNCTIONAL GCICRT

In this section we will turn our attention to the "strictly-physico-functional" and "physicosemiofunctional" paradigms of GCICRT (that is, those paradigms of GCICRT that replicate to some extent the physical hardware of cognitive integral components, e.g. facilitate the manipulation of ions – or electric potentials in general – rather than replicating the brain's "software", e.g. a numerical approximation of the signal processing facilitated by the brains physical hardware, implemented on alternate physical hardware) and better differentiate the two main paradigms of GCICRT, physico-functional and semiofunctional. We will hereafter refer to the replacement-components (used to functionally-replicate in-situ components being replaced) as Neuron-Supplementation-Units (NSU); again, this is meant to be a broad category encompassing whole-neuron-NSUs, sub-neuronal-NSUs and super-neuronal-NSUs.

We have identified two main classes of GCICRT and NSU-design: (1a) *Semio-functional* (i.e. "2nd-order", "representational" or "semiotic" embodiment) and (2a) *Physico-functional (*i.e. "1st-order", "non-representational" or "physical" embodiment). The former corresponds to computational approaches to neurofunctional supplementation, restoration and perpetuation that simulate, emulate or otherwise mathematically, computationally or semiotically model the integral components of the brain (i.e. that use 1st-order components, system-states and/or state-transitions to represent 2nd-order components, system-states, and/or state-transitions), whereas the latter corresponds to physically embodied or "1st-order-embodied" approaches to neurofunctional supplementation, restoration and perpetuation. The semiofunctional class of GCICRT has been by far the most predominantly-explored class of neurofunctional supplementation, restoration and perpetuation therapy, embodied first as the notion of Mind Uploading throughout the 1990's and then more formally in the discipline of Whole-Brain-Emulation.

The distinction between the two can be considered analogous to the difference between (1b) *First Order* or *Non-Representational Embodiment* and (2b) *Second Order* or *Representational Embodiment*. Second order embodiment entails using the first order (i.e. physical) components to represent or signify (i.e. semiotically instantiate) the integral components and sub-systems of the brain. In the case of a Whole-Brain-Emulation using integrated circuits (i.e. the currently predominant hardware paradigm for personal computers) as hardware, the transistors are switching between two system-states (one representing 1, the other representing 0) in order to

instantiate the components of the brain and their many system states (at whatever emulation-scale) as second-order, virtual, semiotically-instantiated components, i.e. using different combinations of the first-order components's two system-states to represent them.

Conversely first-order embodiment entails using the system-states of first-order components to determine the emergent system state(s) and transition-function(s) of the system[63] rather than using the system-states of first-order components to semiotically-instantiate (represent, signify, computationally-embody) second order system-states and transition-functions that then determine the emergent system-states of the entire system (i.e. brain), as in second-order embodiment.

XI. PHYSICAL-FUNCTIONAL GCICRT:

The physical-functional class of GCICRT, however, can at this point be further sub-divided into two sub-classes. The first can be called "cyber-physical-functional", which involves controlling artificial ion channels and receptor-channels via normative computation (i.e. an internal CPU or controller-circuit) operatively connected to sensors and to the electromechanical actuators (i.e. kinematic components) of the artificial ion channels and the artificial receptors.

The cyberphysical functional sub-class replicates the functionality of neurons by sensing the presence of an electrochemical gradient, a.k.a. the difference in electrochemical potential (synonymous with relative ionic concentration) between the respective sides of a neuronal membrane, and activating the actuators of the artificial channels to either open or remain closed in response to specific sensed electric potentials (or a sufficiently-large *difference* in electric potentials on each side of the neuronal membrane) based upon programmed rules. This sub-class is an example of a cyber-physical system, which designates any "system with a high level of connection or interaction between its physical and computational components"[64]. The field of cyber-physical systems grew out of the larger field of embedded systems, which designates any system "using embedded computational technology"[65] and encompasses many if not most electronic devices and appliances. The other main sub-class of the physical-functional class of neurofunctional supplementation, restoration and perpetuation will hereafter be referred to as the passive-physical-functional sub-class.

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[63] Determining the transition functions of the system is somewhat analogous to determining the next subsequent set of component system-states, because the transition function is what facilitates the transition from one system-state to the next.

[64] Wolf, W. (2009). Cyber-physical Systems. *Embedded Computing*, pp. 88-89. http://www.jiafuwan.net/download/cyber_physical_systems.pdf.

[65] Embedded Processor. (2013). *Encyclopaedia Britannica Online*. http://www.britannica.com/EBchecked/topic/185535/embedded-processor.

Passive Physical-Functional GCICRT

The difference between electric and electronic systems may serve to clarify the distinction between the cyber-physical-functional and the passive-physical-functional class of neurofunctional supplementation, restoration and perpetuation. Electronic systems are differentiated from electric systems by being active (i.e., performing computation or more generally signal-processing), whereas electric systems are passive and aren't meant to transform (i.e. process) incoming signals (though any computational system's individual components must at some level be comprised of electric, passive components). Whereas the cyber-physical-functional sub-class has computational (i.e. signal-processing; representational; semiotic) technology controlling its processes, the passive-physical-functional approach has components emergently constituting a computational device.

The difference between computation and cybernetic control, or between computer science and control theory, can be thought of as analogous to the difference between the cyber-physical and the passive-physical sub-classes of the physical-functional approach.

The Encyclopedia Britannica describes "cybernetics" as "the science of communication and control theory that is concerned especially with the comparative study of automatic control systems (as the nervous system and brain and mechanical-electrical communication systems)", and in turn describes "control theory" as "field of applied mathematics that is relevant to the control of certain physical processes and systems." Thus the field of cybernetics has an almost fundamental focus on the control of physical processes and systems via *feedback* between sensors and actuators.

Such passive systems differ from computation in that they only rely upon feedback between integral components for their normative operation, wherein a system comprised of mechanical, electrical, and/or electromechanical components is configured to produce specific system-states or processes in response to the sensed presence of specific system-states belonging to either its environment or itself.

An exemplary embodiment of the passive-physical approach as applied to the functional supplementation of ion channels would consist of providing artificial ion channels with a means of opening in the presence of a given electric potential difference (i.e., voltage) and providing artificial receptor-channels with a means of opening (for a predefined amount of time correlative with the normal rate of postsynaptic membrane depolarization) in response to the unique attributes of the neurotransmitter it corresponds to (such as sensors based on chemical bonding, as in ligand-based receptors, or alternatively sensors that sense electric charge), *without* a CPU correlating the presence of an attribute measured by sensors with the corresponding electromechanical behavior (i.e. actuation of actuators) of the membrane needing to be replicated

in response thereto. In passive-physical systems there is no sensor-CPU-actuator arrangement. The biological brain works more in the manner of passive-physical systems than in the manner of cyber-physical systems.

We could, for instance, construct an artificial ion channel from piezoelectric materials (e.g. separate segments radially-connected by piezoelectric materials so as to collectively form the wall of a channel), structurally configured (in terms of the relative dimensions of segments and piezoelectric-connectors, the number of segments, the spacing of segments and the electric properties of the segments) such that the presence of a certain electrochemical potential induces internal mechanical strain in the piezoelectric-connectors causing the spacing between the segments of the artificial ion channel to close or open, respectively, thereby closing and opening the channel-pore. Such a system would undergo internal mechanical strain in response to one electrochemical potential while remaining unresponsive (or insufficiently responsive) to another electrochemical potential. Depending on the size, shape, number and spacing of piezoelectric-connectors and segments, as well as their specific electric properties as determined by the material they are constructed form, the manner in which they were doped and the specific dopants used, such piezoelectric materials could be made to be responsive to a specific electric charge (e.g. designed to contract or expand for a positive charge but not for a negative charge, or vice-versa) and/or responsive to the specific magnitude of the charge (i.e. opens in proportion to the magnitude of the charge until a threshold value is reached in which it cannot increase the diameter of the open channel-pore further in response to a larger magnitude of electric potential difference).

Biological neurons operate in a similarly passive way, in which integral components are organized to exhibit specific responses to specific stimuli in basic stimulus-response fashion by virtue of their own properties, as in passive-physical-functional NSUs, rather than by external control of individual components via the operative connection of a CPU to sensor(s) and actuator(s), as in the cyber-physical-functional approach.

Cyber-Physical-Functional GCICRT

However, the cyber-physical-functional approach is preferable if it proves to be sufficient due to the ability to reprogram semiofunctional and cyber-physical-functional systems (e.g. computers), which isn't possible in passive systems without necessitating either (1) a physical reorganization of the components – which itself necessitates an increase in the required technological infrastructure, thereby increasing cost and minimum or necessary complexity, or (2) manipulating environmental parameters to indirectly affect integral-component operation (e.g. manipulating ionic concentrations via release and/or uptake of ions to create the same effect as a physical/structural change).

If we desired, for instance, a given ion channel to increase its channel-diameter (i.e. increase

ionic permeability) in response to a higher or lower magnitude of difference in electric potential across the membrane than it normally does, or in response to the opposite electric charge than it normally does, all that is required within the cyber-functional NSU-paradigm is reprogramming the CPU to correlate (e.g., via an associative array or "lookup table") a given actuation (i.e. actuator system-state) with a new sensor-system state. This is as easy as rewriting data a data storage device because the NSU would already have a set of actuator system states correlated with a set of sensory system states. But to implement an analogous process within the passive physical functional NSU paradigm, to use the example of artificial ion channels configured out of radially connected segments of piezoelectric crystal (wherein applied electric charge induces internal mechanical strain in the piezoelectric segments, causing the unit to either open or close as a whole in response to specific electric charges or specific magnitudes of electric charge) that was used above, would involve physically changing the number of segments, the spacing of segments or the microscale piezoelectric properties of the segments (such as through replacing the segments with alternative piezoelectric segments doped differently). In other words enacting operational changes in the cyberphysical functional system paradigm involves simply reprogramming the CPUs that correlate sensor-system states with patterns of actuation (i.e. actuator system states); conversely enacting operational changes in the passive physical functional paradigm involves physically changing the structural, connectional or procedural properties of the physical components. This process could be simplified to some extent by designing and manufacturing such physical components to change from one structural, connectional or procedural state to another (i.e. designed and manufactured to have certain structural, connectional or procedural properties or aspects directly modulable); otherwise it would appear to involve sending a system in to remove the component and replace it with an analogous component. This would in turn be easier than biological integral component replacement, simply because the design specifications of non-biological systems can be known and because non-biological systems can be designed so as to have their components be readily detachable and attachable, with their eventual replacement in exchange for new functionally analogous components in mind, but it would not be easier than the cyber-functional or semiofunctonal integral component replacement.

This limit on reprogramming also imposes a limit on our ability to modify and modulate the operation of NSUs (which will be necessary to retain the function of neural plasticity – presumably a prerequisite for phenomenal consciousness, phenomenal continuity and memory). The cyberphysical functional approach is preferable due to a larger degree of variability in its operation: it would be easier to operatively connect the actuators that control the operation of the electromechanical integral membrane components (e.g., ionic channels, ion pumps) to sensors *via* a CPU (i.e. programming the CPU to elicit a specific sequence of ionic channel opening and closing in response to specific sensor-states) than it would be to design artificial ionic channels to respond directly to the presence of an electric potential with sufficient precision and accuracy.

In the cyberphysical functional approach the replacement membrane material is designed so as to be (a) hydrophobic, (b) electrically insulative, and (c) thin enough to act as a capacitor via the electric potential differential (which is synonymous with voltage or the difference in electric charge created by the difference in intra-cellular and extra-cellular ionic concentration, as well as the ratio of the concentration of different types of ions, i.e. K+ and Na+) on the respective sides of the neuronal membrane.

The artificial ion channels could consist of electromechanical channels that open for a fixed amount of time in the presence of an ion gradient (a difference in electric potential between the two sides of the membrane), which could be accomplished electromechanically via a means of sensing membrane depolarization (such as the use of (1) reference electrodes or (2) multiple sensors that sense the ionic concentration directly on each respective side of the membrane) operatively connected to a CPU programmed to open the electromechanical ion channels for a length of time corresponding to the rate of normative biological repolarization (i.e., the refractory period of an action potential; the time it takes to restore the polarization of the neuronal membrane to the resting membrane potential following an action-potential), thus allowing the influx of potassium ions at a rate equal to the rate of K+ influx in biological ion channels.

Likewise, sections of the postsynaptic membrane are replaced with replacement membrane sections containing embedded sensors that sense the presence of those neurotransmitters that ligate (i.e bind with) the biological receptor being functionally supplemented. Each artificial receptor is designed to detect the neurotransmitter that ligates the biological receptor it is functionally supplementing**.** The postsynaptic sensors are connected to a CPU programmed to elicit specific changes (i.e. increase or decrease in ionic permeability via opening and closing the artificial ion channels) in accordance with the change in postsynaptic membrane potential that normally results from postsynaptic receptor binding in the vicinity of the receptor being functionally supplemented. The increase or decrease in ionic permeability in response to specific sensed neurotransmitters can be facilitated by (1) increasing or decreasing the diameter of ion channels – such as through an increase or decrease in electric stimulation of piezoelectric crystals – or (2) an increase or decrease in the number of open channels, i.e. differential activation of integral membrane components.

While the detection of particular types and relative quantities of neurotransmitters is typically ligand-gated, we have a variety of potential approaches using non-biological systems and media. For ligand-based receptors, sensing the presence and steepness of electrochemical gradients will not suffice (especially as it concerns postsynaptic ligand-gated receptors). However, the use ligand-receptor fitting to replicate the functionality of ligand-based receptors is not strictly necessitated. If there is a difference in the charge (i.e., valence) between the neurotransmitter needing to be detected and other neurotransmitters, and if the degree of that difference is

detectable given the precision of the sensors available for use use[66], then a means of sensing a specific charge may prove sufficient even for the functional supplementation of ligand-gated receptors.

There is a possible alternative to the functional supplementation of ligand-based receptor fitting in the event that sensing electric charge proves insufficient. Different chemicals (e.g., neurotransmitters and also potentially electrolyte solutions) have different volume-to-weight ratios. If we equip the replacement membrane sections with an empty compartment capable of measuring the weight of its contents, this would thus allow for the identification of specific neurotransmitters (or other relevant molecules and compounds) according to their unique weight-to-volume ratio (because the volume of the container is already known). By operatively connecting the unit's CPU to this sensor, we could program specific operations (i.e., receptor opens allowing entry for fixed amount of time, or remains closed and unresponsive to changes in ambient – i.e., proximate – changes to electric potential for a certain amount of time) to occur in response to the detection of specific neurotransmitters by electrochemical sensors.

Though it is unlikely to be necessitated, this method could also work for the identification of specific ions and thus could potentially constitute the operating mechanism underlying the artificial ion-channels' operation as well—though this would likely require higher precision volume-to-weight comparison than is required for neurotransmitters, and may ultimately prove unnecessary becayse the sensing of ambient (i.e. proximate, local) electric potential is both much easier and constitutes a much more established subfield of sensor technology.

Once an entire CNS is gradually replaced with NSUs, each NSU would still presumably be translating its input and output into biophysical input and output, despite the fact that all biological neurons have already been replaced. In such a case, each sensor actuator assembly would be removed and replaced with the normative input and output of the NSU, determined by which paradigm it falls under and what subclass within that paradigm it constitutes. This would take place in the same gradual manner with which the initial GCICRT took place.

Passive-Physical-Functional GCICRT Revisited via the Fields of Synthetic Ion-Channels, Ion Channel Reconstitution & Artificial Membrane Reconstitution

The passive physico-functional paradigm need not be limited to electromechanical systems (e.g. MEMS and NEMS). We could, for instance, recurrently replace the integral membrane components with structurally and molecularly homologous integral membrane components. We could recurrently replace transmembrane proteins at the macromolecular or even monomeric

[66] The sensors that are 'available for use' are determined by the degree-of-miniaturization of the sensors. Certain sensing methodologies might not by amenable to a sufficient degree of miniaturization to be used in situ, simply by virtue of the specific nature of their sensing methodology (e.g. Atomic Force Microscopy and its underlying technological infrastructure lack sufficient miniaturization to be used in vivo).

level (e.g. the separate proteins constituting the components of an integral membrane protein, such as ion channel or postsynaptic receptor), as was described in outlining nanotechnological, nanobiotechnological and nanomedical varieties of ICRT found in the work of Freitas and Drexler – i.e. typical cell repair nanobots. Due to the fact that the operational modalities embodied by biological neurons are classifiable within the passive physico-functional paradigm, this would be an instance of passive physico-functional, neurofunctional replication. We could also synthesize complete ion channels (i.e. membrane embeddable channel forming pores) via normative methods of chemical synthesis, in vivo or in vitro, and then remove the existing transmembrane proteins and substitute in their place the new, structurally, molecularly (or biopolymerically) and functionally homologous ion channels (or alternate transmembrane proteins). This would also be classified within the passive physico-functional paradigm.

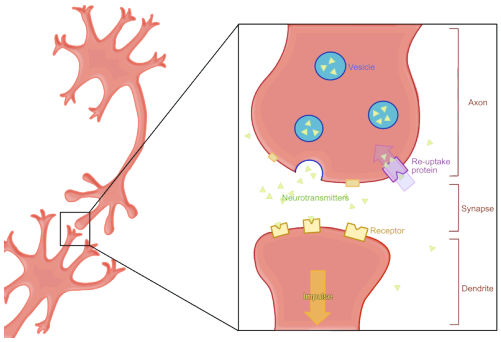
We could also synthesize in similar fashion synthetic, non-biological channel forming transmembrane pores that possess varying degrees of compositional, structural and functional homology to naturally occurring ion channels and receptors. The utility in synthesizing synthetic channel forming pores is similar to the utilities of extra-paradigmatic ICRT. We could synthesize integral membrane components with structural and/or procedural properties that make their recurrent synthesis and replacement with homologous replacement-components easier, more predictable, and ultimately more successful. We could synthesize integral membrane components possessing lesser lability and greater or longer-term durability, or that are more thoroughly understood and that can be predictively modeled with higher accuracy, or that can be synthesized easier, or that can be made so as to be readily detachable by adding ligand-activated sites that change conformational structure in such a way as to detach from the surrounding phospholipid-bilayer in which it is embedded.

We can differentiate these approaches (the recurrent replacement of the phospholipid bilayer and integral membrane components, i.e. transmembrane proteins, with (1) homologous channel forming pores and (2) channel forming pores with varying degrees of homology with the in-situ components being replaced) from the electromechanical variety of the passive physico-functional paradigm by referring to the former as chemico-kinetic sub-sub-paradigm and the latter as electromechano-kinetic sub-sub-paradigm.

Note that, much as in the previous paradigms and sub-paradigms, it is conceivable that we will be able to replace the non-signal processing (i.e. regulatory and homeostatic) mechanisms of the neuron with artificial control systems that maintain the integral components in the place of the previous biological homeostatic and regulatory mechanisms of the cell (e.g. structures like nucleus, gDNA, mDNA, cell organelles, and processes like the ATP cycle). Such mechanisms, structures and processes exist (in neurons at least) in order to maintain the energetic and structural (i.e. structurally supportive) requirements of the integral membrane components that are actually facilitating the signal processing (or more generally membrane depolarization)

activities of neurons. Due to the fact that we would be providing our own means of meeting and maintaining the energetic, structural, connectional and procedural requirements for facilitating normative membrane and integral membrane component operation (a.k.a. signal processing functionality), we could conceivably eliminate such biological cellular metabolic, regulatory and homeostatic mechanisms, structures and processes *as long as* they do not constitute part of the signal processing functions of the cell (which is distinct from indirectly maintaining such signal processing structures and processes or providing the necessary environmental conditions for their normative operation). If we *did* discover that any homeostatic or regulatory structures and/or processes also directly facilitate neuronal signal processing then we would need to take these into account via functional replication in the same way we did for the endogenous in-situ integral components.

There is an existing scientific discipline relevant to our inquiries and concerns here. However; the field's significance to functionally restorative and perpetuative medicine in general, and ICRT in particular, has yet to be recognized by the wider medical and gerontological communities, or indeed by the theoreticians and practitioners of the field itself.



Credit: Reuptake. In Wikimedia Commons: Public domain. Retrieved October 31, 2013, from http://commons.wikimedia.org/wiki/File:Reuptake_both.png

The field of Synthetic Ion-Channels[67, 68, 69, 70, 71, 72, 73], Ion channel Reconstitution[74, 75, 76, 77, 78,

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[79, 80] and Membrane Reconstitution[81, 82] consist of the in vitro synthesis (i.e. reconstitution), analysis and characterization of planar bilipid membranes and channel forming pores (e.g. ion-channels) both homologous to existing (i.e. naturally occurring) ion channels as well as ones not structurally or functionally homologous to existing ion channels. The discipline emerged out of the fields of Supramolecular Chemistry and Bio-organic Chemistry in the early 1980s and throughout the past three decades[83] has experienced an array of experimental successes in the synthesis and characterization of biologically-homologous and synthetic ion channels. A huge diversity of ion channels structurally, compositionally and functionally homologous as well as heterologous to naturally occurring ion channels have been synthesized, analyzed and characterized in vitro.

Synthetic ion channels can be characterized by their chemical structure on the one hand, or

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Reviews. 35, pp. 1269-1286. DOI: 10.1039/B512423A. For a comprehensive review of 2006-2009 developments, see: Matile, S., Jentzsch, A. V., Montenegro, J., & Fin, A. (2011). Recent Synthetic Transport Systems. *Chemical Society Reviews*, 40(5), pp. 2453-2474.

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by their transport characteristics on the other. In terms of chemical structure, macrocycle-based channels[84], crown ethers-based channels[85, 86], calixarene-based channels[87], cyclodextrin-based channels[88], rigid rods-based channels[89], minimalist channels[90], G-quartet-based channels[91, 92] metal organic-based channels[93, 94], hybrid channels[95] (i.e. modifications to non-synthetic ion-channels) and carbon nanotubes[96] have been found to act as ion channels in lipid membranes. In terms of transport characteristics, ion channels can be characterized according to their ion selectivity[97,] voltage-response[98] (linear potential dependence and non-linear [e.g. rectifying and exponential] potential dependence), ligand-response[99, 100, 101] (e.g. channels having conductances

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that can be modulated by the addition of other chemical groups, such as via the formation of supramolecular aggregates, via intermolecular blockage and via intramolecular blockage) and in some cases light response[102] (in light-gated synthetic ion-channels) and thermal response[103] (in thermal-gated synthetic ion channels). Thus the field is not only well established but has yielded a diverse array of synthetic ion channel types with a robust range of design motifs and modulable transport characteristics. They are typically much smaller than naturally occurring ion channels as well (e.g. in some cases up to 20x smaller), which makes their in vivo manipulation, transport and integration with the endogenous phospholipid bilayer much easier.

However, the field has yet to envision the use of synthetic ion channels and phospholipid bilayer membranes to recurrently replace the degraded, missing or otherwise operationally-deviant integral components of biological cells in general and neurons in particular, i.e. as a route to functionally restorative and perpetuative medicine. The use of synthetic ion channels in the field's literature appears to be limited to the elucidation of the biophysical functioning of membranes and transmembrane proteins (i.e. a better understanding of membrane and ion channel operation), especially in studying the relationship between structure and function, and their use as novel biosensors and drug-delivery mechanisms.

We argue that the techniques and technologies developed in the field of Synthetic Ion channels and Ion channel Reconstitution (which includes the synthesis and reconstitution of lipid bilayer membranes as well) can be used to greatly simplify the logistical challenges of synthesizing replacement-components for integral membrane components in neurons, and in integrating such channel-forming pores with the existing phospholipid bilayer of biological neurons.

Indeed, this variety of GCICRT could conceivably supplant the normative approach used in nanomedicine and cell repair machines. Rather than replacing missing or degraded in-situ components at the molecular scale, it is conceivable to instead synthesize whole portions of phospholipid bilayer and whole integral membrane proteins (e.g. ion channels) in vitro (simply because it is easier [i.e. we can use synthesis techniques that lack sufficient miniaturization to be used in vivo] and because we can then utilize the existing technological and methodological infrastructure developed in the fields of synthetic ion channels and ion channel/membrane reconstitution for the structural-functional design [i.e. correlating function with structure, which enables us to synthesize ion channels according to functional objectives, or in other words with specific transport characteristics in mind], synthesis and characterization of ion channels and

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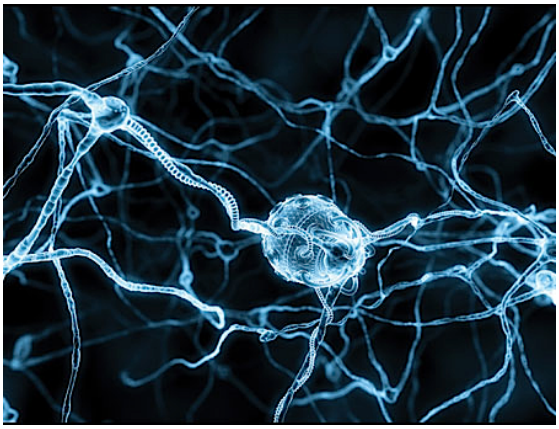
sections of phospholipid bilayer) and use the same nanomedical infrastructure conceptually developed by Robert A. Freitas to transport the pre-synthesized integral membrane components and integral membrane sections to the correct location in the CNS. This decreases fundamental technological requirements considerably, opening up the possibility of implementing GCICRT using a microelectromechanical technological infrastructure rather than a nanoelectromechanical one, and thereby allowing it to be realized, experimentally verified and successfully implemented sooner than it would be otherwise (i.e. before the necessary nanoelectromechanical technological infrastructures are available for use).

It may also be possible to synthesize whole neurons in vitro in this fashion (i.e. without protein transcription and synthesis) for their use as the replacement-components in CGICRT using a neuronal replacement-scale. While we would not be able to synthesize the cell organelles and the gDNA and mDNA (or at least not using the methodological and technological infrastructure developed in the field of synthetic ion channels and ion channel/membrane reconstitution), we may not have to, so long as they do not play a direct role in the cell's signal-processing activities. The reason such intracellular systems are in place is to meet the structural and energetic requirements necessary for the synthesis and maintenance of the phospholipid bilayer and transmembrane proteins. If we were capable of synthesizing such components without recourse to gDNA-mediated protein transcription and synthesis, we could essentially replace such endogenous cellular infrastructure with our own, artificial means of synthesis. We would be able to obviate the necessity for the intracellular infrastructure by providing our own homeostatic and regulatory systems to meet the energy and structural requirements of synthesizing and maintaining the neuronal membrane. We would still however, need to provide a suitable intracellular structural support system (similar to the cytoskeleton) as well as a means of synthesizing and releasing pre-synaptic vesicles containing neurotransmitters; these concerns are not addressed by the technological and methodological infrastructure developed in the field of synthetic ion channels and ion channel/membrane reconstitution.

XII. SEMIO-FUNCTIONAL GCICRT

The Semio-Functional class of GCICRT has two basic methods of integration: in vivo and ex-vivo. This is the case regardless of the scale at which it is implemented – e.g. whether the integral components consist of whole functional regions or "subsystems" of the brain (as in contemporary approaches to neuroprosthesis), neural networks, single neurons or subsections of single neurons. We will describe each type according to a neuron-scale GCICRT, in which whole neurons comprise the in-situ components being replaced. In in vivo integration, a biological neuron is modeled (e.g. emulated computationally). The biological neuron is structurally and procedurally disconnected from adjacent neurons and removed, and the computational substrate running the emulation is encased in a suitable housing (to keep it protected by local ionic solutions) and placed in the same location as the neuron it is replacing. It is provided with

sensors for detecting biophysical input from other neurons and translating this into an informational form usable by the emulated neuron (i.e. translating biophysical input into virtual/computational input) and actuators for translating its computational output into the biophysical actuation (e.g. stimulation) of adjacent neurons (i.e. translating computational output into biophysical output).



Nanobot Neuron
Credit: Photo: Philippe Van Nedervelde/E-SPACES/CG4TV
http://spectrum.ieee.org/semiconductors/nanotechnology/rupturing-the-nanotech-rapture

In ex-vivo integration, the computational substrate emulating the neuron is kept outside the body and communicates with in vivo biophysical sensors and actuators wirelessly (e.g. via transmission of EM waves). In this type of integration, the biological neuron can either be removed as it was in in vivo integration, or it can be causally quarantined from adjacent neurons (i.e. kept from interacting with other neurons while the emulated neuron functionally supplements it). There is the possibility of functional distortion due to a lag-time created by the time it takes for signals to travel to and from the in vivo sensors and actuators to the ex-vivo computational substrate. Keeping the ex-vivo computational substrate in perpetual close proximity to the body can minimize these problems. As long as the distance separating them is not too great, the slow rate of operation possessed by biological neurons makes it likely that such small lag times should not be phenomenally perceptible, nor large enough to cause operational deviation or distortion.

The sensors could range from the use of reference electrodes to detect membrane depolarization (i.e. sensors based on standard electrical equipment) to ion selective electrodes and chemical sensors detecting the presence and perhaps quantity of neurotransmitters and relative ionic concentrations.

Much as in the Physical Functional paradigm of GCICRT, once a whole CNS is gradually replaced with NSUs, each NSU would still be translating its input and output into biophysical

input and output, despite the fact that all biological neurons have already been replaced. In such a case, each sensor-actuator assembly would be removed and replaced with the normative input and output of the NSU, determined by which paradigm it falls under and what subclass within the paradigm it constitutes. This should take place in the same gradual manner with which the initial GCICRT took place.

Any of the various subclasses of GCICRT (e.g. physico-functional, semio-physico-functional, semiofunctional, physicosemiofunctional) can hypothetically be used concurrently during the same iteration of recurrent-GCICRT (e.g. replacing one in-situ component with a physico-functional NRU and replacing another integral component of the same emergent system with a semio-functional NSU). But in order to operatively connect two causally adjacent NSUs of alternate paradigms, an integrational unit of the same basic design as those used to integrate semio-physical NSUs with causally adjacent biological in-situ components (via the coordination of biophysical actuators and sensors) is necessitated because they embody alternate first order (i.e. physical) operational modalities (despite embodying the same emergent functional modalities), which would otherwise prevent causal interaction 'on the same terms'.

Most embodiments of the semiofunctional paradigm involve the use of computation. However; while computational varieties are preferred for a variety of reasons (the ability to simply rewrite information as a means of modifying and modulating operationality and functionality, instead of articulating a series of physical manipulations leading to a given desired change, as is necessitated within the physico-functional paradigm) an even more basic embodiment of the semio-functional paradigm is possible.

The most basic embodiment of the Semiofunctional paradigm is the use of associative arrays (a.k.a. lookup tables) for neurofunctional replication. In this sub-approach, regardless of the replacement-scale, the in-situ components are stimulated (e.g. via microelectrodes or nanoelectrodes, or through manipulation of local biophysical parameters such as the release and/or uptake of ions and/or neurotransmitters) iteratively across a range of possible “inputs” (i.e. the possible ways in which the in-situ component can be “stimulated” or causally affected) and the response or “output” of each possible stimulation or stimulation pattern is recorded. Relevant variables could include the number of stimulations, the pattern of stimulation, the magnitude of the stimulation and the duration of the stimulation. The outputs (or in-situ component responses) are then correlated with the inputs that caused them. The replacement-components would thus comprise simple associative arrays that produce a preprogrammed output in response to a given input, according to the correlation of in-situ component stimulation (input) and response (output) previously recorded. The aspect distinguishing this subclass from computational classes of the semiofunctional paradigm is that there is no actual computation or information processing taking place. Rather than computing the correct response via a biophysical or abstracted simulation or emulation for instance, a simple index of inputs and outputs is used. Whereas computation could

determine the output resulting from a previously un-encountered input, an associative array could not. The recognition of input for such an associative array would be facilitated by electrical, chemical or biophysical sensors and the output would be facilitated by electrical, chemical or biophysical actuators, much as in the computational classes of the semiofunctional paradigm.

An intuitively apprehensible embodiment of this subclass is the replacement of a single neuron with a single associative array. We can represent different combinations of incoming synaptic transmissions as different inputs: the sequences of synaptic activation possible at any given time are determined, the neuron is subsequently stimulated according to each of these possible sequences of synaptic activation, and the output of each (e.g. neuron reaches threshold potential and fires; neuron fails to reach threshold potential and fails to fire) is then recorded and correlated with the input that caused it.

Alternately we could treat each synapse (or a collection of synapses for that matter) as a single associative array, and connect these synaptic associative arrays modularly, such that the input would be the possible types of input that a given postsynaptic receptor could receive (e.g. different combinations and relative quantities of neurotransmitter, or ambient [i.e. local] ionic concentrations).

This scheme as it stands, however, would fail to account for neuronal plasticity, and the ways in with the operational (i.e. structural, connectional or procedural) profile of the neuron changes according its history of activity (e.g. LTP, synaptogenesis). We could however, code the ways in which the operational profile of neurons change in response to received input (or in other words in response to its history of operation) as a set of rules, embodied likewise as an associative array. One type of input, or mode of operation, produces one type of operational change (e.g. LTP, synaptogenesis), whereas another type of input produces an alternate type of operational change. Operatively connecting the associative array representing neuronal operation with the associative array representing the rules determining how operation changes according to operational history, such that the correlated input-output is altered according to the rules of the second associative array in a way homologous with the operational changes made in response to operational history as it occurs in the biological neuron, constitutes a conceivable way to account for (i.e. functionally replicate) neuronal plasticity within the associative-array sub-paradigm of the Semiofunctional paradigm.

Like all varieties of CGICRT, the replacement-scale is variable. We could potentially represent collections of ion channels or single ion channels as single associative arrays in the same manner.

XIII. SUBNEURONAL PHYSICO-FUNCTIONAL GCICRT

GCICRT using a subneuronal replacement-scale presents a tremendous amount of difficulties compared to GCIRT using a neuronal scale (i.e. wherein in-situ components comprise single neurons). And indeed, it is likely that GCICRT on a neuronal scale will not be disruptive to our phenomenal continuity for a variety of reasons outlined above. Nonetheless, subneuronal GCICRT, while more technically difficult, is still possible, and for this reason we will outline the various foreseeable technical methodologies that could be used to successfully implement a subneuronal CGICRT. Also, concerns of probability aside, the only replacement-scale we *know* GCICRT to be implementable without causing phenomenal continuity is the molecular replacement-scale used in normative biological turnover in the CNS; thus the comparatively more complex process of implementing a GCICRT on the subneuronal scale might still be attractive to people particularly fearful of disrupting their phenomenal continuity.

Integrating replacement membrane sections with adjacent sections of the existing phospholipid bilayer membrane becomes a lot less problematic if the scale at which the membrane-sections are manipulated or handled (determined by the size of the replacement membrane sections) is homogenous, as in the case of biological tissues, rather than molecularly heterogeneous, as in the case of single transporter proteins – that is, if we are affixing the edges of a given replacement membrane section to a biological tissue, rather than to complexes of individual phospholipid molecules.

Reasons for hypothesizing a higher probability for homogeneity at the replacement-scale include (a) the ability of experimenters and medical researchers to puncture the neuronal membrane with a micropipette (to measure membrane voltage) without rupturing the membrane beyond functionality (i.e. inducing lysis or cell rupture), and (b) the fact that sodium and potassium ions do not leak through the gaps between the individual bilipid molecules, which would presumably occur if it were heterogeneous at this scale. If we find homogeneity at the scale of sectional replacement, we can use more normative means of affixing the edges of the replacement membrane section with the existing phospholipid bilayer membrane, such as micromechanical fasteners, adhesive, or fusing via heating or energizing. However, there is a hypothetical approach that could facilitate sectional replacement on the scale of molecules and molecular complexes, where integrating the nonbiological replacement sections occurs according to the rules of atomic and molecular bonds and interactions rather than according to the rules of macroscale physics.

If we cannot synthesize the replacement membrane sections using molecules or compounds that stably bond with phospholipid molecules, an alternate approach is possible. First, an intermediate chemical that stably bonds to both the phospholipid bilayer molecules constituting

the phospholipid bilayer and the molecules or compounds constituting the replacement membrane section is determined. If such an intermediate molecule or compound cannot be found, a second intermediate chemical that stably bonds with two alternate and secondary intermediate molecules (which themselves bond to either the biological membrane or the replacement membrane section, respectively) could hypothetically be used. The chances of finding a sequence of chemicals that stably bond (i.e., form stable bonds with the preceding and succeeding chemicals in the sequence) increases in proportion to the number of intermediate chemicals used.

Note that the likelihood of synthesizing the replacement membrane sections from molecules or compounds that stably bond *directly* with the phospholipid molecules constituting the biological neuronal membrane is decreased by the fact that the replacement membrane has to possess certain attributes in order to be functionally isomorphic with the neuronal membrane. It must be (1) amphiphilic (possessing both hydrophilic and lipophilic groups); (2) electrically insulative; and (3) thin enough to act as a capacitor via the electric potential differential (which is synonymous with voltage) between the two sides of the membrane. Because (1) and (2) are determined by molecular composition, this limits our available choices for molecules and compounds that could constitute the replacement membrane sections.

The same process would be used to affix the integral membrane components (i.e. the non-biological analogs of transporter proteins, a.k.a. transmembrane proteins; e.g. ion transporters, voltage-dependent ion channels, ligand dependent ion channels, post-synaptic receptors) to the replacement membrane. We have an added dimension of variability or "play" in this case however, because whereas the previous case the molecular makeup of one of the components being integrated was already fixed or predetermined (the biological phospholipid bilayer), the molecular composition of both components needing to be integrated is not predetermined in the case of integral component embedment.

What is the advantage of using an alternate material for the neuronal membrane? The only reason we would seek to use an alternate molecular composition for the replacement membrane sections is if it proved sufficient at replicating the functional modalities of the biological phospholipid bilayer while also possessing less lability – such as a molecule or compound with stronger chemical bonds, or a compound with more degrees of freedom between chemical/functional groups and/or between molecular bonds in general). The advantage of higher rigidity and/or flexibility is decreased susceptibility to molecular degradation (e.g. sections of the phospholipid bilayer being severed from the adjacent phospholipid molecules constituting the phospholipid bilayer), which means that the time between each replacement iteration (i.e. each separate GCICRT procedure) *for any given component* is lower. Thus we can wait longer to implement a second GICRT – because it will have taken longer for the integral components comprising neurons, like the integral components constituting the replacement membrane sections and their integral membrane components, to have degraded to the point of functional

degradation, distortion or deviation in the emergent neuron it is a part of. Note however, that in no way is rigidity universally correlative with more structural integrity. Indeed, sufficient degrees of freedom between a material's constituent molecules allows for the flexibility that deters tearing, shearing, and other common structural deformations resulting from load transfer. It is likely that an interplay between the two (rigidity and flexibility), in terms of both homogenous combination (the rigidity/flexibility tradeoff in a given material) and heterogeneous combination (rigid parts with flexible connection), will achieve the highest decrease in component degradation (i.e. piecemeal breakdown), deformation, dysfunction and general loss within a given interval of time.

One additional utility in using a material other than phospholipids for the neuronal membrane is the possibility of eventually replacing the ionic solutions permeating the CNS with electric fields that preserve the same electric potential difference (i.e. voltage) across the neuronal membrane, such as through the use of solid-state electronics capable of generating electric fields. It is important to note that the ionic solutions permeating the brain generate or manifest such electric fields already; replacing such ionic solutions would simply skip the intermediate step of using ionic solutions to instantiate electric fields, instead generating the electric potential difference constituting the signals of the CNS 'directly' via solid-state electronics. This would allow us to facilitate an increase in the rate of neuronal operation (and thus the rate of thought and perception) comparable to the gain in the rate of neural operation possible in computational varieties of semiofunctional GCICRT (i.e. gradual integration with a WBE). Phospholipid bilayer membranes require an aqueous environment not only for their normative operation, but also for their basic structural integrity. Thus using an alternate membrane material that can facilitate ion transport in aqueous environments while also being to maintain structural integrity in non-aqueous environments has the added utility of being able to facilitate a smooth transition from the manipulation of ionic solutions to the manipulation of electric fields generated by solid state electronics (or any other solid-state/non-aqueous integral-component-paradigm). If we wished to implement such a transition gradually using a subneuronal replacement-scale we would likely have to isolate a given section of membrane, enclose it, remove the ionic solutions permeating it and replace them with equivalent electric fields (using a similar sensor actuator arrangement as used in all varieties of extra-paradigmatic CGICRT), iteratively until the entire neuron is enclosed and gradually supplemented.

It is likely that we will find synthesizing the replacement membrane sections from phospholipid molecules so as to form a phospholipid bilayer that is structurally and functionally isomorphic to the endogenous biological phospholipid bilayer more preferable than replacing it with a material of alternate molecular composition, at least insofar as we do not seek to replace the ionic solutions permeating the CNS with analogous electric fields. The complexity of the task of determining a series of molecules allowing replacement membrane sections to stably bond with sections of the existing phospholipid bilayer, as outlined above, may outweigh the potential

advantage in increasing the duration of time between each successive iteration of GICRT. It may also be possible to modify the existing phospholipid-bilayer so as to increase its structural integrity, in a way more optimal than designing a new material, such as through the integration of molecular cross bracing and affixing molecular compounds configured to act as structural support and to facilitate maximally-distributed or strategically-distributed load transfer to the existing biological phospholipid bilayer.

An exemplary instance of physical functional NSU integration is outlined as follows. An integration unit positions itself above the membrane section. The integration unit locates its starting position by using the data acquired in the process of neuronal "scanning"[104], during which the constituents of a given membrane-section are determined and assigned a number corresponding to a type of replacement membrane section in the integration unit's section inventory (essentially a store of stacked replacement membrane sections with integral membrane components either pre-embedded or else readily attachable from a separate store). A means of disconnecting a section of phospholipid bilayer membrane from the biological neuron is depressed; one potential embodiment is a hollow compartment with edges that sever the phospholipid bilayer membrane via force (e.g., edges terminate in blades), energy (e.g., edges terminate in heat elements), or chemical corrosion (e.g., edges coated with or secrete a corrosive substance). The detached section of phospholipid bilayer membrane is then drawn out and compacted, to be drawn into a separate compartment for storing waste organic materials. The replacement membrane section is then transported in a downward direction through the same compartment. Being perpendicular to the face of the container, moving the section down through the compartment should force back into the cell any intra-cellular fluid that may have leaked into the constructional container's internal area when the phospholipid bilayer membrane section was removed back into the cell. Once the replacement membrane section is in place, the preferred integration method (the possible variations of which are outlined above) is applied. This process would be repeated iteratively until the entire neuronal membrane is thusly replaced.

Subneuronal (i.e., sectional) replacement also necessitates that any dynamic patterns of polarization, a.k.a changes in membrane potential or membrane polarization (e.g., an action potential), are continued during the interval of time between the removal of a section of phospholipid bilayer and its substitution with a replacement membrane section. This could achieved by sensors (e.g. chemical, electrical[105]) that detect membrane depolarization, operatively connected to actuators that electrically stimulate the membrane via microelectrodes or nanoelectrodes (falling within the same paradigm used in the contemporary fields of

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[104] Martins, N. R., Erlhagen, W. and Freitas Jr., R. A. (2012). Non-Destructive Whole-Brain Monitoring Using Nanorobots: Neural Electrical Data Rate Requirements. *International Journal of Machine Consciousness.* 4(1): 109-140. http://www.nanomedicine.com/Papers/NanoroboticBrainMonitoring2012.pdf.

[105] Pine, J. (1980). Recording Action Potentials from Cultured Neurons with Extracellular Microcircuit Electrodes. *Journal or Neuroscience Methods*, 2(1), pp. 19-31. DOI:10.1016/0165-0270(80)90042-4.

neuromodulation and neurostimulation[106, 107, 108]), or that manipulate ionic concentration on the opposing side of the temporary membrane gap via the release and/or uptake of ions from biochemical inventories so as to induce membrane depolarization on the opposite side of the temporary membrane gap at the appropriate time (i.e. the time correlating with when the wave of membrane depolarization would have reached the opposing side of what is now the temporary membrane gap, prior to the removal of the in-situ section of phospholipid-bilayer). A simple mathematical calculation should be able to determine the length of time it normally would have taken the wave of membrane depolarization to reach the opposite side of the now-removed section of phospholipid bilayer by taking into account the replacement size and the velocity of membrane depolarization typical to that type of neuron or the composition of the removed section of phospholipid bilayer – data that would be recorded during the brain 'scanning' procedure. While it will likely prove unnecessary, it is possible to simulate or even emulate the section of biological membrane being removed (i.e. configure a biophysically accurate computational model of the phospholipid bilayer and its transmembrane proteins), translating the biophysical input of the sensors into computational input for the simulated or emulated membrane and operating the electronic, electromechanical and/or biophysical actuators in response to the operational states (i.e. computational output) of the simulated or emulated membrane (e.g. electrically stimulating, or alternately releasing ions, to induce membrane depolarization according to when the computational model predicts the wave of membrane depolarization to reach the other side of the simulated or emulated membrane). This sensor actuator assembly is analagous to the Semio-Functional Paradigm of GCICRT, and is likely to use largely the same technological and methodological infrastructure.

XIV. SUBNEURONAL SEMIO-FUNCTIONAL GCICRT

Whether in vivo or ex-vivo semiofunctional GCICRT is implemented, a subneuronal GCICRT follows the same basic procedure as a neuronal or super neuronal GCICRT. A section of phospholipid bilayer is either removed or causally quarantined (i.e. stopped from causally interacting with adjacent sections of phospholipid bilayer, such as continuing waves of membrane depolarization), and a series of biophysical sensors and actuators are placed along the edge of the quarantined section, sensing membrane depolarization and inputting the corresponding informational parameters into the membrane section emulation, and likewise translating the computational output into a series of biophysical actuations (e.g. direct electrical stimulation of the membrane, or manipulation of local ionic concentration toward that same objective) are placed along the edges of the section of membrane being functionally supplanted by the emulation. Once two sections of emulated membrane occur in a row (i.e. without a

[106] Siegfried, J. (1982). *Neural Prosthesis and Neurostimulation*. Basel: Karger.
[107] Minnesota Health Technology Advisory Committee. (1998). Implantable Neurostimulation Devices. St. Paul, MN. http://www.health.state.mn.us/htac/neuro.htm.
[108] Eljamel, S. (2013). *Neurostimulation: Principles and Practice*. Chichester, West Sussex: Wiley-Blackwell.

biological section of membrane separating them), the biophysical sensors and actuators separating those two sections can be removed and each separate emulation can be integrated into a shared emulation encompassing the space occupied by both sections of phospholipid bilayer. In this piecewise fashion, each section of phospholipid bilayer can be replaced with a corresponding emulated analogue until the entire neuron (i.e. all secions of phospholipid bilayer) are encompassed by the emulation.

XV. EXTRA-PARADIGMATIC SUB-SUBNEURONAL GCICRT IS LIKELY INFEASIBLE

GCICRT is unlikely to be feasible below the subneuronal scale (i.e. treating constituent portions of single integral membrane components – e.g. portions of single transmembrane proteins, as opposed to whole transmembrane proteins – as the in-situ components of an ICRT). This is because such transmembrane proteins need all their chemical groups in place in order to function whatsoever (i.e. retain their transport characteristics). Consider the act of replacing a portion of the transmembrane protein constituting an ion channel; what could we replace it with (other than an error free copy of the same chemical group, compound, molecule or macromolecule) that would supplant its function, allowing the emergent ion channel to function as a whole?

XVI. MORPHOLOGICAL CHANGES FOR NEURAL PLASTICITY

The finished physical functional units would need the ability to change their emergent morphology, not only for active modification or modulation of single neuron operation, but even

Scheme of a DNA-origami based ion channel.
Credit: Technische Universität München
http://phys.org/news/2012-11-artificial-ion-channels-dna-origami.html

for basic functional replication of normative neuron behavior by virtue of the fact that morphological and operational variability appear to be necessary for neural plasticity and by consequence learning and memory[109].

One approach to NSU morphological variability involves the use of retractable, telescopic dendrites and axons (with corresponding internal retractable and telescopic dendritic spines and axonal spines, respectively) activated electromechanically by the unit-CPU.

Morphological changes[110] (i.e. the topology of the neuronal-membrane) could be facilitated by providing the edges of each membrane section with an electromechanically hinged connection (i.e., a means of changing the angle of inclination and declination between immediately adjacent sections). By changing the angle of inclination and declination between each replacement membrane section, the emergent morphology of the membrane can be controllably varied. This approach could also conceivably be used as an alternative to retractable terminals (i.e. axons, dendrites and axonal/dendritic spines) by attaching additional membrane sections with a very steep angle of inclination (or a lesser inclination with a greater quantity of segments) to create emergent sections of replacement membrane that extend out from the biological membrane in approximate morphological isomorphism with biological axons, dendrites and axonal/dendritic spines.

Other aspects of morphology would need to be variable as well, including the relative type, quantity and location of integral membrane components (i.e. the nonbiological analogues of transmembrane transporter proteins, e.g. ion channels; ion pumps; postsynaptic receptors; presynaptic voltage dependent calcium channels[111]). This could consist of an internal NSU compartment designed to (1) detach a given membrane-section, (2) transport it into the internal compartment of the NSU soma or terminal, (3) transport it along a track that stores alternative

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[109] Programmable changes to neuronal morphology and integral-membrane-component-configuration appears to be somewhat more limited. It would entail either (1) an integration of new sections of phospholipid-bilayer and/or transmembrane-proteins in the same manner as intra-paradigmatic GCICRT, or (2) a sensor-actuator arrangement programmed to facilitate the manipulation of local biophysical parameters (e.g. release of ligands or the manipulation of local electric potential to selectively open and close ligand-gated and voltage-gated ion-channels). Moreover, extra-paradigmatic physicofunctional NRUs do not have the potential problem of cell-lysis during the severing of the membrane in order to facilitate the integration of an exogenous membrane-section, which simplifies the process of the controlled changes to neuron (or NRU) morphology and integral-membrane-component-configuration.

[110] Note that in terms of neural plasticity, integral-membrane-component reconfiguration is more important than topological-variability in the neuronal membrane itself.

[111] Voltage-dependent calcium channels induce an influx of calcium ions into the pre-synaptic membrane, which bind with transmembrane synaptotagmin proteins embedded within the synaptic vesicles in which neurotransmitters are stored, leading to the creation of a fusion pore via the fusing of membrane of the synaptic vesicle with the presynaptic membrane, and thereby allowing the neurotransmitters inside the synaptic vesicle to diffuse out the fusion pore and into the synaptic cleft.

membrane sections stacked face-to-face (to compensate for limited space), and (4) subsequently replaces it with a membrane section containing an alternate transmembrane component (e.g., ion pump, ion channel, [voltage-gated or ligand-gated], etc.) embedded therein.

Alternately, we could detach, switch and reattach individual integral membrane components (e.g. artificial ion channels) in the method of integral membrane component reconfiguration outlined above, rather than detaching and reattaching replacement-sections with pre-embedded integral membrane components. Indeed, detaching and reattaching replacement sections could cause unintentional lysis (bursting or rupturing of the cell), thereby dramatically upsetting local biophysical parameters like ionic concentration unless a temporary protective cover were secured over the temporary membrane gap before the membrane section is transported into the internal compartment of the neuronal soma or terminal. Thus replacing individual integral membrane components rather than sections of membrane may make more sense logistically, in terms of technological and methodological economy as well as in terms of cost and energy requirements. This would not, however, allow for the expansion of total membrane surface area (but neither would it preclude morphological or topological variation of the existing membrane surface area) unless we provided each membrane-section with a means of multidirectional expansion, such as but not limited to constructing them to be telescopic and affixed to a likewise telescopic structural base or scaffolding (i.e. the analogue of a telescopic cytoskeleton comprised of retractable and protractable segments). Even in this variation, however, there is a definitive limit on the extent with which the neuronal membrane surface area can be controllably expanded, whereas replacing individual sections of replacement membrane is necessarily unlimited. A combinatory approach is possible as well, in which all membrane sections are made to be detachable (and thus expandable via the attachment of more membrane sections). However, detachable (as opposed to embedded) integral membrane components are the preferred method of integral component reconfiguration within the present sub-paradigm of ICRT.

This approach could be supplemented by one that necessitates a smaller technological and methodological infrastructure, thus being more optimal in terms of technological and methodological economy, energy expenditure, necessary complexity and ultimate cost. If the artificial integral membrane components' degree of miniaturization is high enough (i.e. significantly smaller than their biological analogues) then differential activation of components or membrane sections will achieve the same effect as changing the organization or type of integral membrane components, effectively eliminating the need to actually interchange membrane sections at all.

Moreover, this also constitutes a route to economic feasibility by making the NSUs amenable to standardization and mass manufacturing. Note that this is only possible if we limit the scale of neuronal GCICRT (thus treating whole-neurons as the integral components of a cognitive GCICRT, wherein neurons are replaced one at a time), rather than extending the scale of

GCICRT to subneuronal membrane sections and integral membrane components (i.e. transmembrane proteins).

The first approach to morphological variability and reconfigurable integral component architecture incurs (1) that the integral components are made to be readily detachable and re-attachable to facilitate the replacement of a given integral component with another, as well as to add integral membrane components (i.e. additional sections of replacement membrane) to expand the surface area and/or volume of the NSU), and (2) a hinged connection (or an alternate type of bearing allowing relative motion between replacement membrane sections), i.e. means of changing the relative angle of inclination and declination between integral membrane sections, thereby allowing for the modification of emergent membrane morphology via modification of the levels of inclination and declination between the integral membrane sections. However, this would not necessarily incur a morphological change of equal magnitude to, for instance, changing the emergent morphology and integral component architecture of the NSU from one *neuron type* or *class* to another. Thus it is likely that we will be able to mass-produce alternate NSU models for each alternate type of neuron in the CNS, rather than one single NSU model with a degree of morphological variability and integral component-architecture reconfigurability great enough to account for the morphological variation found in all neuron types.

If we didn't have the possibility of morphological variability and reconfigurable integral component architecture then the process of fabricating NSUs would not be amenable to standardization (and thereby to mass manufacture) at all, thus increasing the ultimate cost and decreasing the economic feasibility of a Physical-Functional GCICRT by virtue of the fact that we would need a unique NSU matching the morphology and integral component architecture of the neuron it is replacing. If the NSUs do not possess sufficient morphological variability and integral component reconfigurability then we cannot use one mass produced NSU model for every neuron of a given type.

The two approaches to neuronal plasticity outlined above (namely (1) direct morphological change and integral component reconfiguration, and (2) differential activation of integral membrane components) bring the possibility of mass production into play. If we can achieve a degree of morphological variability and integral component reconfigurability sufficient to account for the morphological variartion found in neurons of the same cell type, then we would be able to mass-produce a morphologically variable NSU model for each *neuron cell type* in the CNS rather than configuring a unique NSU in-situ for every *neuron* in the CNS, period.

This would not be possible if we were to implement a GCICRT on a subneuronal scale (e.g. the replacement of integral components on the scale of single ion channels). This is because mass production involves the prefabrication of the NSUs, and subneuronal GCICRT involves the in-situ integration and gradual, piece-by-piece configuration of the NSU (hereafter referred to as

piecemeal integration). We would still be able to mass-produce subneuronal integral components (e.g. voltage-dependent ion channels, ligand-dependent ion channels, ion transporters, postsynaptic receptors, etc.), but not whole NSUs. It might, however, be possible to achieve coarse subneuronal GCICRT, wherein the integral components comprise replacement membrane sections with tens, hundreds or thousands of embedded integral membrane components (e.g. artificial ion channels, ion pumps, postsynaptic receptors, etc.), by mass-producing a *modular* NSU built to readily disconnect and detach its various integral components and subsystems, to allow for piecemeal integration compatible with standardization and mass-production. NSU modularity would also help facilitate the transport of replacement integral components into and throughout the CNS by decreasing the total size of a given transport unit's payload.

Morphological modification within the semio-functional paradigm is categorically easier. Because it is in an informational form, and we have full control over what the informational structure of our emulation is (i.e. changing an informational structure, process, property, parameter, etc. is as easy as rewriting words in a word file – because the means of both writing and rewriting information into the emulation is already inherent in the ability to emulate them in the first place). Due to this fact, making changes is significantly easier than it is within the Physical-functional Paradigm, and especially the passive-physicalist paradigm, wherein we would actually have to implement a series of physical modifications designed to create a new emergent integral component architecture.

CONCLUSION

Thus the indefinite functional perpetuation of the CNS via the recurrent functional restoration of its integral components constitutes a viable and distinct approach within the larger fields of regenerative medicine, functionally restorative medicine and functionally perpetuative medicine, characterized by the underlying approach of replacing damaged structures and processes with error-free copies synthesized in vitro and subsequently integrated with the existing biological system. This approach has a number of advantages over other therapeutic strategies in functionally restorative medicine that seek to treat disease or accumulated age-associated damage by manipulating the progression of the disease or accumulated damage directly, such as the ability to apply the same underlying approach to potentially any disease, damage or accumulated structural or procedural deviation. ICRT in general and its gradual and recurrent application to the CNS in particular can utilize much of the same methodological and technological infrastructure developed for use in the fields of MEMS, NEMS, nanotechnology, nanomedicine, biotechnology, nanobiotechnology. cybernetics, systems theory, biomimetic systems, bionics, biomechatronics, synthetic biology, synthetic ion-channels, ion-channel reconstitution and artificial membrane reconstitution. Functional perpetuation through recurrent iterations of functional restoration – i.e. the general approach designated here as Integral Component Replacement Therapy and argued to encompass a variety of functionally-restorative

medical therapies including transplantology, prosthesis, tissue engineering, bioprinting, cell replacement therapies, gene replacement therapies, neural emulation and biomemetic systems – constitutes a distinct approach within the larger field of functionally restorative and perpetuative medicine.

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