# Early Diagnosis of Alzheimer's Disease by NIRF Spectroscopy and Nuclear Medicine

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## 1. Rationale

Cancer is the second major cause of death after Heart Disease, and Alzheimer's Disease (**AD**) is the third major cause of death with major, human and financial/economics trillion dollar consequences for the society. Nuclear Medicine is concerned with applications in Medicine of Nuclear Science and Engineering techniques and knowledge. Three major Nuclear Medicine techniques that are established for diagnostic and research purposes are:

- **Positron Emission Tomography (PET) and CAT/CT**
- **Nuclear Magnetic Resonance Imaging (NMRI/ MRI).**

However, these three techniques have also major limitations in terms of either cost or image resolution, as well as patient irradiation in the case of CAT/CT and PET. On the other hand, *Near Infrared Chemical Imaging Microspectroscopy* and certain *Fluorescence spectroscopic techniques* are capable of *single cancer cell and/or single molecule detection and/or imaging*. Such powerful capabilities, combined with low cost of diagnostics, make these novel techniques very attractive means for early detection of diseases such as cancer and Alzheimer's, that are promising to reduce the fatality rate of patients through adequate diagnosis and treatment of such diseases at early stages.

## 2. Social Impact of AD on Caregivers

There are **15 million** Alzheimer's and dementia caregivers providing 17 billion hours of unpaid care valued at **$202 billion; Current projections for 2030 are at least $1 Trillion !**

***(Source*:** Alzheimer's Association *2011 Alzheimer's Disease Facts and Figures)*

*The social impact of AD healthcare is thus arguably even greater than that of heart disease and cancers.*

## 3. What is Alzheimer's Disease (AD)?

This is a human brain disease that affects a significant fraction of the population over 62-65 years of age by causing problems with short-term memory, thinking, spatial orientation and behavior, worsening over a time span of up to 20 years and in 60 to 80% of cases leading to *dementia,* "*a general term for* memory loss *and* other intellectual abilities *serious enough to interfere with daily life*" ***(Source:*** Alzheimer's org., 2011***); in fact , serious enough to prevent a normal life without continuous help from caregivers!***

## 4. Positron Emission Tomography (PET)

### 4,1 PET is a Nuclear Medicine imaging technique

PET generates a 3D-image of the distribution of a positron-emitting radionuclide tracer introduced in the human body with a `marker' molecule. The PET detectors collect pairs of g-rays emitted from the positron annihilation with an electron, and scan through the positions of the radionuclide sources from locations within the human body**:** $e^+$ **<--> $e^-$ ----→ 2 gamma ;** example**:** **$^{18}F_9$ → $^{18}O_8$ + n + + beta$^+$** **(***positron* reference**:** **J. P. Blaser, F. Boehm, and P. Marmier : Phys. Rev. (1949) 75: p.1953 ``***The Positron Decay of $F^{18}$* **").**

- Images of radionuclide activity distribution in 3-dimensional or 4-D space-time within the body are then reconstructed by fast computers to provide physicians with an image of, for example, the patients brain or the whole body. Recently, scans, such as for 3-D reconstructions are typically refined with the aid of higher resolution, local CT (CAT) scans also performed on the patient simultaneously with the PET scanning.

- "A PET image is a 'photograph' of high-energy g-rays emitted from a positron-emitting radioisotope. *Several such* short-lived radioisotopes: *$^{18}F$, $^{11}C$ and $^{15}O$* are made in a cyclotron, and a probe (for example, a drug, or water--*in the case of O-15 of spin 1/2*) is labeled and injected intravenously into a patient. The tracer is imaged in a scanner that comprises a large number of scintillation detectors. The collision of a positron with a nearby electron produces two -rays that are separated by 180 degrees. Two scintillation detectors that are separated by 180 degrees transmit a coincident signal when both are stimulated simultaneously. The photon energy that is absorbed by the detectors is re-emitted as visible light and detected by photomultiplier tubes." (*Nature Reviews Cancer*, 4: 457-469; June 2004). Image resolution is typically 5 to 10mm, which is low but almost adequate for early detection of certain cancers.

*Which Nuclides and Markers can be used for PET/ SPECT detection of AD?*

- FDDNP: binds to plaques and `tangle' deposits in the brain

- PiB= Pittsburg marker : claimed to bind specifically to aggregated Abeta, and $^{11}$C-labeled biomolecules

- $^{18}$F- in FDG analogue of glucose for investigating sugar metabolism and diabetes-related risks of AD. (NaF-- Sodium Fluoride for PET Bone Imaging)

- $^{82}$Rb (Rubidium-82, Z=37) for cardiac PET scanning**.**

**Table 1B: Other Radionuclides for PET Imaging**

- Gallium-68: 1.13h half lifetime, used in: Breast Cancer diagnosis, Heart Imaging, Immunoscintigraphy, Molecular Imaging, Neuroendrocrine Tumors, Pancreatic Cancer, Alzheimer's ?
- Iodine-124: 4.18d: Apoptosis, Cancer Biotherapy, Gliomas, Heart Disease, Mediastinal Micrometastates, Scouting of Therapeutic Radioimmunoconjugates, Thyroid Cancer, Alzheimer's ?
- Iron-52 : 8.28h : in Anemia diagnosis, Human Bone Marrow imaging
- Nitrogen-13: 9.97m: Ammonia Dog Studies, Coronary Artery Disease, Diabetes, Gamma Camera, Heart Disease, Imaging of Heart, Pancreas and Liver, Lupus Erythematosus, Myocardial Perfusion, Pulmonary Ventilation
- Oxygen-15 :122.s : Acute Brain Injury, Arterial Blood Flow, Brain Cancer, Oxygen Utilization, Brain Studies, Cerebral Blood Volume, Cerebral Responses, Coronary Artery Vasospasm, Coronary Reserve, Heart Disease, Ischemic Stroke Disease, Kinetics of Oxygen, Liver Cancer, Myocardial Viability, Oxygen Metabolism, Pain Control, Venous Ulceration, Alzheimer's ?
- Rubidium-82: 1.26m: Heart Disease, Myocardial Perfusion, Sarcoidosis, Alzheimer's ?
- Yttrium-86 : 14.74h: Distribution of Y90, Lung Cancer, Melanoma, Renal Cell Carcinoma
- Zirconium-89: 3.27d: Brain Tumors, Head and Neck Cancers, non-Hodgkin's Lymphoma, Alzheimer's ?

According to Dr. Elliot Kolin, lead radiologist at WMI: *"the NYU research team used PiB-PET with a fluorescent imaging agent called Pittsburgh Compound B that lights up clumps of a protein called beta amyloid (A-beta ) that are a characteristic finding of Alzheimer's disease.***"** Normal A-beta protein does not clump! One notes the presence of modified A-beta clumps, or hydrophobic plaques, also in the frontal areas of the AD brain (most probably advanced AD) in his team's scans.

There are, however, microscopic changes of the neurons in the cortex of AD brains compared with those of the normal brain: the modified A-beta clumps/plaques and/or 'tangles' are characteristic of AD. Such microscopic evidence is at present the only medically accepted (post-mortem) confirmation of the AD diagnosis, because the established Nuclear Medicine techniques currently in use for diagnosis in clinics and hospitals are unable to detect such microscopic changes until the AD is widespread in the brain, which is too late for adequate medical treatment of the disease**.**

*PiB-PET is claimed to detect structural changes associated with AD* ***!***

- **1.** This is quite important because-- if it is firmly established for all AD type-- it may lead to some progress in understanding the disease, and perhaps also other kinds of dementia, hopefully leading to some treatments not at all available today!

- **2.** When combined with other types of PET scans it is hoped to link such structural changes with functional ones as well, and possibly correlate with AD-related cognitive impairement, such as the learning inabilities of AD patients related to short-term memory loss.

- **3.** It has been proposed based on genetic evidence from rare cases of AD--which are inherited--that a specific gene (ApoE) and its **e4** allele are involved: Basun, H., Grut, M., Winblad, B. & Lannfeldt, L. (1995). Apolipoprotein e4 allele and disease progression in patients with late onset Alzhiemer's disease. *Neuroscience Letters*, **183**, 32-34; cited in: A. S. Macdonald and D. J. Pritchard, 2000).

This raises the possibility, or question if in those AD cases that are not inherited through a genetic mutation (activation of e4 ??) in ApoE- the Apolipoprotein E Gene-- might also occur which would be perhaps induced through either metabolic or environmental factors that have not yet been either identified or suspected?

The latter, very important question *cannot* be investigated with the three, already established, Nuclear Medicine techniques discussed above but it is quite feasible by using Near Infrared Microspectroscopy/Fluorescence techniques that are capable of both single cell detection and single molecule imaging, thus making the diagnosis of AD and cancers a real possibility through affordable and noninvasive scanning of human populations, especially those at risk-- above age 60/62, male/female, respectively.

## 5. AD Pathology and Medical Diagnosis

AD Pathology is characterized at least by the following:

- ``(a) senile plaques (deposits on the outside of neurons , consisting largely of the modified protein b-amyloid)—the adopted post-mortem criterion for confirming the diagnosis of AD;

- (b) amyloid angiopathy (deposits of amyloid protein in the arteries of the brain);

- (c) neurobrillary `tangles' (dysfunctional connections between neurons);
- (d) loss of neurons;
- (e) decreased activity of choline acetyltransferase (an enzyme…involved in *synaptic transmission*)";
- (f) mutations in two genes labeled presenilin-1 (PS-1) and presenilin-2 (PS-2), which appear to be associated with AD, though the mechanisms remain so far unclear. (*loc.cit.*)

**5.1. The Apolipoprotein E (ApoE) gene involvement in AD**

- ``The ApoE *e4 allele has been found to confer risk for AD in a* <u>*dose related fashion*</u>,

such that *e4 homozygotes e4 /e4 ) are at a greater risk then e4 heterozygotes e2/e4 ,*

*e3/e4 ), who in turn are at greater risk than those without the e4 allele:"*

*(*Bickeboller et al., 1997; Corder et al., 1994; van Duijn et al., 1995; Farrer et al., 1997;

Jarvik et al., 1996; Kuusisto et al., 1994; Lehtovirta et al., 1995; Mayeux et al., 1993;

Myers et al., 1996; Poirier et al., 1993; Tsai et al., 1994).

- Some studies have observed that <u>the risk depends on age</u>; ApoE *e4 seems to have greatest* effect at ages 60 to 70, tapering off at older ages:

Bickeboller *et al., 1997; Corder et al.,* 1994; Farrer *et al., 1997.*

- (d) It is also possible that the ApoE *e4 allele is associated with an earlier onset of AD (not to be* confused with the <u>*early-onset AD type*</u>—which is inherited, in rare cases, i.e., <u>*e4 homozygotes: e4/e4*</u>).

**5.2. The Modified τ-Protein in AD**

Another hypothesis about AD causes-- that has gained momentum-- is the involvement of a *modified/ shortened tau (t)-proteins* that normally act as spacers between microtubules in the nutrient transport system of the nerve cells; it has been claimed that the modified t-proteins aggregate thus causing the early onset of AD by *`messing up' the nutrient transport system* of the nerve cells that die later for lack of sufficient nutrients.

Moreover, it has been claimed that the Ab plaques appear only at later stages of AD, and also that modified tau's are a better indicator than Ab plaques for early diagnosis of AD.

One notes that the two hypothesis are not mutually exclusive, but one can envisage either 5.1 or 5.2 being the first stage of Alzheimer's, and the question which one occurs first in AD- *if it does indeed occur*-is a very important one for developing an efficient diagnosis and treatment of AD**.**

## 6. Combined Strategies

**6.1.** Combining Techniques**:** PET/CAT, MRI-NMRI/PET, MRI/CAT,…with Modeling**:**

So far still has only limited success, but this is what most often happens in clinical diagnosis because it was an obvious first step, but with the risk of additional radiation doses that are not insignificant for repeated scanning, even if localized, by CAT/CT X-ray tomography.

This is not the case for MRI diagnosis or scanning , but the latter does not have the high resolution of CAT/CT scans.

### 6.2. Novel Strategies

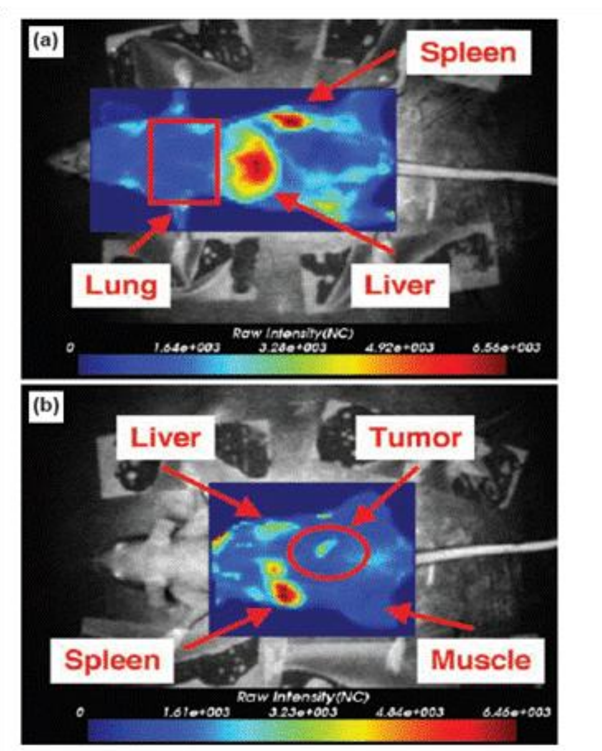
II. Making and using antibodies for modified Ab and t-proteins, combined with

III. **Novel Molecular Imaging, such as FT-NIR Microspectroscopy/SMD Fluorescence techniques/FSSC**, and so on;

IV. Improved AD Supercomputer Modeling, (*maybe also combined with*)

V. Radioimmunotherapy (RIT) and Gene Therapy**.**

***6.2. III. Ilustration of NIRFS Detection of Tumors with NIR-emissive Polymerosomes in Rats***



**<u>Figure 1a</u>. <u>Left a. & b</u>:** NIRFS detection of rat tumors

***(Source:*** Ghoroghchian, P. et al. 2009***. In vivo fluorescence imaging: a personal perspective,*** ***NANOMEDICINE AND NANOBIOTECHNOLOGY*** **,** Vol 1 , ( 2) (March-April 2009), 156-167. DOI: 10.1002/wnan.7**,** ***http://wires.wiley.com/WileyCDA/WiresArticle/wisId-WNAN7.html*** **)**

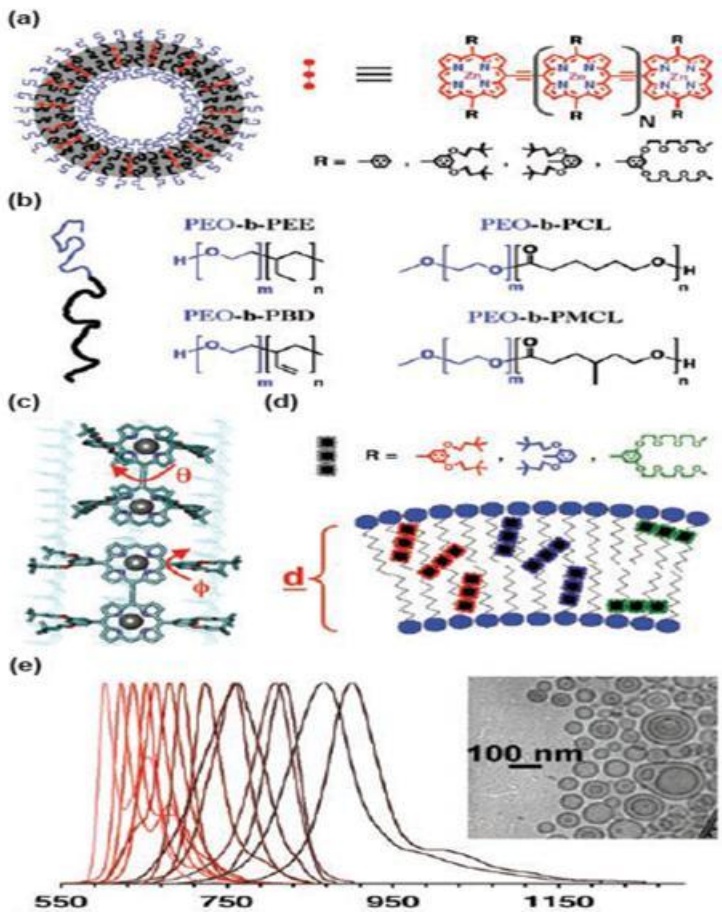



**Figure 1b: <u>Left a. & b</u>: NIRFS detection of rat tumors.**

150-nm diameter nondegradable polymerosomes (composed of a 1 : 1 molar mixture of PEO30-b-PBD46 and PEO80-b-PBD125; 1 : 40 NIRF-to-total-polymer molar ratio) were imaged after tail-vein injection of tumor-bearing mice utilizing a GE eXplore Optix instrument (λex = 785 nm, λem = 830–900 nm).

## *6.3. Major Obstacles to Early Detection of AD*

- *Failed AD Clinical trials in UK with an attempted `vaccination'* of AD patients.
- *The high cost of screening large number of patients by PET/CAT and/or NMRI.*

## 6.4. Possible Answers in the Near Future

- Improved disease modeling and simulations may help, for example, with designing new clinical trials and animal studies that are now needed. This is a low-cost exercise involving minds, supercomputers, data mining and mega-database analyses.
- Novel molecular imaging techniques which are much less expensive than PET/CT and MRI/PET. An example already employed for early discovery of cancers is Near Infrared Fluorescence Spectroscopy (NIRFS).
- RIT or Radioimmunotherapy where the goal is to target with radioisotopes or markers the affected cells or aggregated molecules without harming the healthy cells. This is also known as cell-directed therapy. In cancers, RIT success was achieved with the radioisotopes Irridium-192 and iodine-125 to treat lymphomas and thyroid tumors, respectively.

## *7. CONCLUSION*

FT-NIR/Fluorescence early diagnosis and discovery of AD and cancers is the most promising and powerful approach in comparison with the other, established diagnostic techniques that are expensive and have either low-resolution or expose patients to significant doses of radiation.

## BIBLIOGRAPHY

**``*Early diagnosis of Alzheimer's disease*''** (2010). edited by Leonard F. M. Scinto and Kirk R. Daffner , pp. 875**.**

• Ashburner, M, et al.2000. Gene Ontology: A Tool for the Unification of Biology. The Gene Ontology Consortium, *Nature Genetics*,***25(1): 2529.***

• Baianu, I.C., Editor (2011) **``*Nuclear Medicine, Diagnostic Tomography and Imaging: Early Medical Diagnosis using Nuclear Medicine Techniques*",** *Minuteman Press, USA, pp. 554,* Second Edition.

• Baianu, IC, Editor. 2011. *Complex Systems Biology. Minuteman Press: USA, pp. 545. Ibid.2010. Symbolic Dynamics and Dynamical System Models, Volumes I to III, Minuteman Press, pp. 1,046.*

• Baianu, IC. 2007**.** Categorical Ontology of Levels and Emergent Complexity: An Introduction**,** ***Axiomathes, 17 (3-4): 209-222***

• Baianu, IC. 2006. Robert Rosen's Work and Complex Systems Biology***, Axiomathes, 16 (1-2): 25-34.***

• Baianu, IC.1986. Computer Models and Automata Theory in Biology and Medicine, *Mathematical Modelling*, ***7: 1513-1557. In:***

***Mathematical Models in Medicine, M. Witten, Editor, Pergamon Press: New York. 10***
• Baianu, IC. 1977. *A Logical Model of Genetic Activities in Lukasiewicz Algebras: The Nonlinear Theory*. ***Bulletin of Mathematical Biology,* 39*:*** 249-258*.*
• Baianu, IC, Glazebrook, JF, and Brown R. 2011. A Category Theory and Higher Dimensional Algebra Approach to Complex Systems Biology, Meta-systems and Ontological Theory of Levels. *Conference Proceedings: Understanding Intelligent and Complex Systems. B. Iantovics et al, eds. (accepted, in press)*
• Baianu, IC and Poli, R. 2011. From Simple to Super- and Ultra- Complex Systems: A Paradigm Shift Towards Non-Abelian Emergent System Dynamics, *loc.cit.*
• Baianu, IC. and Glazebrook, JF. 2010. Categorical Ontology of Complex Systems, Meta-Systems and Levels, ***BRAIN** - Special Issue on Complexity in Sciences and Artificial Intelligence, B. Iantovics, et al, editors,* ***1: 118-207***
• Baianu, IC. et al. 2010**. Lukasiewicz-Moisil Many-Valued Logic Algebras of Highly-Complex Systems, *BRAIN. loc.cit, pp. 1- 12***
• Baianu, IC, Brown, R and Glazebrook, JF.2007. Categorical Ontology of Complex Spacetime Structures: The Emergence of Life and Human Consciousness. *Axiomathes, **17: 223–352.***
• Baianu, IC, et al. 2006. Complex Nonlinear Biodynamics: Transformations of Neuronal, Genetic and Neoplastic Networks, *Axiomathes.**16 (1-2): 65—122***
• Baianu, IC and Prisecaru, V. 2005. Complex Systems Analysis of Cell Cycling Models in Carcinogenesis, preprint *arXiv/qbio.OT/0406045: pp.23*
• Baianu, IC et al. 2004. NIR and Fluorescence Microspectroscopy, IR Chemical Imaging and H-R NMR Analysis of Intact Soybean Seeds, Embryos and Single Cells, Ch. 12 in: *Analysis of Oil Seeds, AOCS Publs, pp. 243-278.*
• Bard, J, Rhee, SY, and Ashburner, M. 2005. An ontology for cell types, *Genome Biol, 6(2), R21*
• Bogaard, A et al. 2009. Interaction of Cellular and Network Mechanisms in Spatiotemporal Pattern Formation in Neuronal Networks, The Journal of Neuroscience, 29(6):1677–1687.
Brown, R, Paton, R and Porter,T. 2004. Categorical language and hierarchical models for cell systems, in Computation in Cells and Tissues, Paton, R. et al (Eds.), Springer Verlag, pp. 289-303.
• Casti, JL and Karlqvist, A. 1986. Complexity, Language, and Life: Mathematical Approaches. Springer-Verlag: Berlin, etc. pp.298. (International Institute for Applied Systems Analysis).
• Charles, M., Baianu, I.C. and Prisecaru, V. 2007. Visual Molecular Dynamics (VMD), the Impact of Lectins on Alzheimer's Disease Treatment and Its Side Effects, RAP/YSP Program, YSP Excellent Presentation Award.
• Craft, DL, Weins, LM, Selkoe, DJ. 2002. A Mathematical Model of the Impact of Novel Treatments on the Ab Burden in the Alzheimer's Brain, CSF and Plasma, *Bulletin of Mathematical Biology, **64: 1–21.***
• Fleischaker, G. 1988. Autopoiesis: the Status of its System Logic, *Biosystems, **22(1): 3749.***
• Gnoli, C and Poli, R. 2004. Levels of Reality and Levels of Representation, *Knowledge Organization, **21(3):151-160.***
• Gratton, G et al. 1998. Memory-driven Processing in the Human Medial Occipital Cortex: an Event RelatedOptical Signal (EROS) study, *Psychophysiology, **38: 348-351; Optical Engineering (1995) 34:32-42; Phys. Med. Biol., 4: 308-314.***
• Golubitsky, M, and Stewart, I. 2006. Nonlinear Dynamics and Networks: the groupoid formalism, *Bulletin of the AMS**, 43:305-364***

• Keogh, E K, Mehrotra, S and Pazzani, M.2002. Locally Adaptive Dimensionality Reduction for Indexing Large Time Series Databases, *ACM Transactions on Database Systems, **27(2): 188-228***
• Macdonald, A S and Pritchard, D J. 2000. A Mathematical Model of Alzheimer's Disease and the ApoE Gene. *ASTIN Bulletin, **30: 69–119***
• Mani, S et al. 1997. Dementia Screening with Machine Learning Methods, *AMIA Annual Fall Symposium,Nashville; Differential Diagnosis of Dementia: A Knowledge Discovery and Data Mining (KDD) Approach,loc.cit.*
• Maturana, H., and Varela, F. J. (1980). *Autopoiesis and Cognition: The Realization of the Living. D. Reidel:Boston*
Massoud, T.F. and Gambhir, S.S. 2003. Molecular Imaging in Living Subjects: Seeing Fundamental Biological Processes in a New light, **17 (5): 545-580**
• Nakao, H and Mikhailov, A S.2010. Turing Patterns in Network-organized Activator-inhibitor Systems, *Nature Physics, **6: 544-550***
• Naito A, Kawamura I. Solid-state NMR as a method to reveal structure and membrane-interaction of amyloidogenic proteins and peptides**.** *Biochim Biophys Acta*. 2007 Aug 17,**68**(8):1900-12. Epub 2007 Apr 5.
• Poli, R. 2006. Levels of Reality and the Psychological Stratum, *Revue internationale de philosophie, **61 (2):163-180.***
• Poli, R. 2006. The Theory of Levels of Reality and the Difference Between Simple and Tangled Hierarchies. In: *Systemics of Emergence. Research and Development, Minati , G., Pessa, E., Abram M. eds. Berlin: Springer, pp.715-722.*
• Poli, R. 2002. Ontological Methodology***, International Journal of Human-Computer studies, 56: 639-664.***
• Puri, IK and Li, L.2010. Mathematical Modeling for the Pathogenesis of Alzheimer's Disease, *PLoS ONE, **5(12):e15176***
• Shankle, WR et al. 1997. Detecting Very Early Stages of Dementia from Normal Aging with Machine Learning methods, In Keravnou, E, et al, editors, *Artificial Intelligence in Medicine, AIME97, volume **1211: 73-85, Springer: Berlin.***
• Wallace, R. 2005. *Consciousness: A Mathematical Treatment of the Global Neuronal Workspace Model, Springer: New York.*
• Wallace, R. 2011. The cultural epigenetics of  psychopathology: The missing heritability of complex diseases found? In: *Transactions on Computational Systems Biology XIII, Vol. **6575: 131--170. Editor-in-chief: Priami Corrado.***
• Wallace, D and Wallace, R. 2000. Life and death in Upper Manhattan and the Bronx, *Environment and Planning A, **32:1245-1266.***
• Yamamoto, S et al. 2004. An Ontology for Annotation of Signal Transduction Pathway Molecules in the Scientific Literature: Molecule Role Ontology, *Comparative and Functional Genomics. **5 (6-7): 528-536.***