Production and characterization of the ^{111}Ag radioisotope for the development of a new generation of radiopharmaceuticals; the Italian ISOLPHARM project

A. Donzella[1,2,*], A. Arzenton[3,4], M. Asti[5], S. Bortolussi[6,2], S. Corradetti[3], G. D'Agostino[7], M. Di Luzio[7], V. Di Marco[8], M. Ferrari[9], A. Gandini[10,2], G. Grosso[11], A. Leso[3], M. Lunardon[11,12], D. Maniglio[13], E. Mariotti[4], A. Salvini[9,2], D. Serafini[3], A. Zenoni[1,2], A. Andrighetto[3]

[1] *Department of Mechanical and Industrial Engineering, University of Brescia, Via Branze 38, 25123 Brescia, Italy*
[2] *Pavia Division, National Institute for Nuclear Physics, Via A. Bassi 6, 27100 Pavia, Italy*
[3] *Legnaro National Laboratories, National Institute for Nuclear Physics, INFN-LNL, Viale dell'Università 2, 35020 Legnaro, Padova, Italy*
[4] *Department of Physical Sciences, Earth and Environment, University of Siena, Via Roma 56, 53100 Siena, Italy*
[5] *Radiopharmaceutical Chemistry Section, Nuclear Medicine Unit, AUSL-IRCCS Reggio Emilia, Viale Risorgimento 80, 42122 Reggio Emilia, Italy*
[6] *Department of Nuclear and Theoretical Physics, University of Pavia, Via A. Bassi 6, 27100 Pavia, Italy*
[7] *National Metrology Institute of Italy, Department of Chemical Sciences, University of Pavia, Viale T. Taramelli 12, 27100 Pavia, Italy*
[8] *Department of Chemical Sciences, University of Padova, Via F. Marzolo 8, 35131 Padova, Italy*
[9] *Laboratoire Hubert Curien, CNRS, UMR 5516, Universit´e Jean Monnet F-42000, Saint-Etienne, France*
[10] *Applied Nuclear Energy Laboratory, Via G. Aselli 41, 27100 Pavia, Italy*
[11] *Department of Physics and Astronomy, University of Padova, Via F. Marzolo 8, 35131 Padova, Italy*
[12] *Padova Division, National Institute for Nuclear Physics, Via F. Marzolo 8, 35131 Padova, Italy*
[13] *Department of Industrial Engineering, BIOtech Research Center, University of Trento, Via delle Regole 101, Mattarello, Trento 38123, Italy*

A fundamental aid in nuclear medicine is the development of radiopharmaceuticals capable of selectively accumulate into a target tissue of the patient's body, allowing either a precise imaging or a focalized treatment, without significantly damaging neighbouring healthy tissues. In the framework of the Italian ISOLPHARM project, carrier-free radioisotopes of high specific activity are studied, with the aim to develop innovative radiopharmaceuticals prototypes [1]. The radioisotopes will be produced with high isotopic purity and high specific activity at the SPES (Selective Production of Exotic Species) facility of the INFN –LNL (Istituto Nazionale di Fisica Nucleare –Laboratori Nazionali di Legnaro, Pd), exploiting the ISOL (Isotope Separation On Line) technique.

In particular, ^{111}Ag was considered as a very promising radionuclide for internal radiotherapy. For its utilization in the ISOLPHARM research activities, the ^{111}Ag radioisotope is produced in a TRIGA Mark II nuclear research reactor and spectroscopically characterized. The radioisotope production is simulated starting from an MCNP6-based reactor model producing the neutron spectrum and flux in the selected irradiation facility. A comparison between experimental results of the activity of irradiated targets and theoretical predictions obtained with different Monte Carlo codes, allows models to be normalized to experimental data. In this way a reliable planning of the ^{111}Ag production for the aims of the ISOLPHARM project is achieved.

References

[1] S. Corradetti & A. Andrighetto (2020), Nuclear Physics News, 30:4, 33-36
doi: 10.1080/10619127.2020.1752100

* Presenting author email: antonietta.donzella@unibs.it

Building a Hybrid Compton Camera System for Improving Hadron Therapy Imaging*

S. Hart[1,2,†], P.Jones[1], L. Pellegri[1,3] , S. Peterson[2],
N. Stodart[4], C. van Tubbergh[4]

[1] *SSC Laboratory, iThemba LABS, Somerset West 7129, South Africa*
[2] *University of Cape Town, Department of Physics, Cape Town, South Africa*
[3] *Department of Physics, University of the Witwatersrand, Johannesburg, South Africa*
[4] *Research and Development Technical Support Department, iThemba LABS, Somerset West 7129, South Africa*

This work investigates building a two-stage Compton camera in terms of energy resolution, efficiency, and geometrical configuration for beam range monitoring in hadron therapy. While development of a clinical imaging device has made tremendous strides, there are challenges to be addressed.

The feasibility of constructing an upgraded Compton camera to complement and enhance the UCT Polaris system is investigated [1]. The scatterer module is a solid-state detector containing two pixelated CZT crystals arranged side-by-side. The absorber module is a monolithic $LaBr_3$(Ce) scintillation detector [2]. This work looks to specifically address the limitations of the Polaris detector: while it has high position-sensitivity (< 2 mm) and excellent energy resolution (< 0.8% at 662 keV), it has mediocre timing resolution ~100 ns) and a maximum dynamic energy range of 3 MeV. This Compton camera prototype looked to overcome the limitations of the CZT detector by maximising on the strengths of the $LaBr_3$(Ce) detector, known for its outstanding timing resolution (< 350 ps), energy resolution (< 2.5% at 1332 keV) and higher maximum detectable energy range. Tracking of gamma-ray scatter events across the device was measured in a parallel-plane geometry using standard gamma-ray sources (AmBe, ^{132}Eu, ^{60}Co and ^{137}Cs) and with a 66 MeV proton beam at iThemba LABS.

A second Compton camera prototype is investigated, assessing the optimal geometrical configuration of compact, low-voltage 14x14x25.4 mm $LaBr_3$(Ce) and SrI_2(Eu) SiPM-readout scintillation detectors to maximise on the strengths of the cutting-edge SiPM technology. These detectors, manufactured by Cape-Scint, have demonstrated excellent energy resolution (~3% at 662 keV), and are known for their fast-timing capabilities. The tracking of scatter events was modeled using the GEANT4 Monte Carlo toolkit to assess the best measurement configuration and timing attributes, followed by measurements with standard gamma-ray sources. Further, two Cs_2LiYCl_6 SiPM-readout detectors have been commissioned to maximise on their neutron detection capability using pulse shape discrimination to distinguish between neutron and gamma events for in situ neutron dose measurements during hadron therapy.

The development of this device would assist in the improvement of hadron therapy safety margins to optimise the dose to cancer cells while reducing the effect to the surrounding healthy tissues and organs at risk. This will improve treatment effectiveness and helping strengthen the application of hadron therapy in the fight against cancer. An overview of the results will be presented.

References

[1] E Draeger *et al*., 2018 Phys. Med. Biol. **63** 035019, doi:10.1088/1361-6560/aaa203
[2] Msebi, L. *et al.*, NIM-A. **1026** (2022) 166195, doi:10.1016/j.nima.2021.166195

* Supported 2023-24 by the Technology Innovation Agency under Grant number 14606/01

† Presenting author email: hrtsha014@myuct.ac.za

A High-Performance Particle Tracker Based on CBM Silicon Strip Detectors for Range Verification in Heavy-Ion Therapy*

Devin Hymers[1,2,†], Sebastian Schroeder[1], Eva Kasanda[2,3], Olga Bertini[4], Vinzenz Bildstein[2], Joelle Easter[2], Johann Heuser[4], Joerg Lehnert[4], Andrea Richard[5,6], Christian Joachim Schmidt[4], Artemis Spyrou[5], Cornelia Hoehr[7], Dennis Muecher[1,2,7]

[1] *Institut für Kernphysik, Universität zu Köln, Köln, Germany*

[2] *Department of Physics, University of Guelph, Guelph, Ontario, Canada*

[3] *Laboratory for High Energy Physics, Universität Bern, Bern, Switzerland*

[4] *GSI GmbH, Darmstadt, Germany*

[5] *National Superconducting Cyclotron Laboratory, Michigan State University, East Lansing, Michigan, USA*

[6] *Lawrence Livermore National Laboratory, Livermore, California, USA*

[7] *TRIUMF, Vancouver, British Columbia, Canada*

The growing societal burden of cancer necessitates improvement in the safety and efficacy of radiation therapy. Scanned heavy-ion therapy provides a precise and highly conformal dose distribution; however robust range verification (RV) methods are needed to ensure correct positioning of the dose-maximum Bragg peak within the patient, in the face of uncertainty in beam stopping powers and patient structures. Filtered Interaction Vertex Imaging (fIVI), which monitors secondary protons produced by beam-patient interactions, is a promising relative RV method for heavy-ion therapy.

To validate fIVI for RV, a ^{16}O beam delivered 12 Bragg peak positions in a 40 mm poly-(methyl methacrylate) phantom. Secondary particles produced during irradiation were monitored using position-sensitive thin silicon detectors. Along with the measured treatment beam axis, events recorded on these detectors were used to reconstruct the sites of origin of these secondary particles. The distal edge of the distribution of these reconstructed points was determined with logistic fits, and the computed translation depth minimizing the discrete χ^2 statistic between two fits was assigned as the range shift between two Bragg peak depths. In all cases tested, the range shift was determined with sub-millimeter accuracy and precision, to a standard deviation of the mean of 220(10) μm [1].

A high-performance system, based on modern strip-segmented silicon detectors originally developed for the Compressed Baryonic Matter (CBM) experiment at GSI, has been adapted for use in fIVI. These sensors are segmented with a 58 μm pitch, cover a large sensitive area of up to 72 cm^2, and achieve count rates up to 250 kHz per segment. This performance meets and exceeds that required to read out expected fIVI event rates on the order of hundreds of kHz per sensor.

This updated system is expected to provide reliable relative RV in each fraction of a scanned heavy-ion treatment plan. Alternatively, the same method would allow RV for the highest energy in a full-field irradiation for ultra-high dose rate FLASH treatment, using a small portion of the prescribed dose delivered before the primary irradiation.

References

[1] Hymers et al 2021 Phys. Med. Biol. 66 245022, doi: 10.1088/1361-6560/ac3b33

* We acknowledge the support of NSERC through the PGS program.

† Presenting author email: dhymers@ikp.uni-koeln.de

Computational image analysis of kidney tissue samples of beagle dogs irradiated with ^{60}Co gamma-rays

Jelena Matković[1,*], Jelena Trajković[1,2], Aleksandra Nenadović[3], Gayle E. Woloschak[4] Tatjana Paunesku[4], Andjelija Ž. Ilić[2]

[1] *Faculty of Physics, University of Belgrade, 11000 Belgrade, Serbia*

[2] *Institute of Physics Belgrade, University of Belgrade, Pregrevica 118, 11080 Belgrade, Serbia*

[3] *Department of Pathological Physiology, School of Medicine, University of Belgrade, 11000 Belgrade, Serbia*

[4] *Department of Radiation Oncology, Northwestern University, Chicago, IL, USA*

The advancements in the computational capabilities, over the past two decades, led to the intensification of research and practical application in the fields of computational image analysis and data classification. In particular, this approach is of interest in medicine, as it promises enhanced diagnostic accuracy and detection of subtle features. Alterations and patterns in medical images can be detected and quantified with precision [1], [2]. Additionally, the approach is markedly time saving and enabling of handling big amounts of data, giving new insights into the disease mechanisms and progression through data patterns and correlations.

Given relatively large quantities of data collected from radiobiology megastudies conducted in the past, we decided to subject some of these archival tissue specimens to computational image analysis in order to study in more detail structural changes in particular organs due to exposures to ionizing radiation. Here, we analyzed solid tissue samples of kidneys in beagle dogs irradiated with ^{60}Co gamma-rays [3]. We performed multifractal analysis [4], [5], of the arrangements and shapes of cell nuclei, as well as tissue architecture in sections stained with hematoxylin and eosin. Although the dosing patterns differed, as well as the resulting days of survival and causes of death (not directly linked to the kidneys), we were able to quantify some of the structural changes present in the analyzed specimens. With the further analyses and more systematic study, we hope to form a base of knowledge on tissue structural modifications and typical values of tissue descriptors in various cases.

References

[1] D. Oprić, *et al.*, "Fractal analysis tools for early assessment of liver inflammation induced by chronic consumption of linseed, palm and sunflower oils," *Biomed. Sign. Process. Control* **61**, p. 101959, Aug 2020.

[2] A.J. Joseph, P.N. Pournami, " Multifractal theory based breast tissue characterization for early detection of breast cancer," *Chaos, Solitons & Fractals* **152**, p. 111301, Nov 2021.

[3] B. Haley, *et al.*, "Past and future work on radiobiology mega-studies: a case study at Argonne National Laboratory," *Health Phys*. **100**, p. 613Y621, 2011.

[4] A.L. Karperien, H.F. Jelinek, H. Ahammer, "Multifractal formalism in image and time series analysis," *Arithmetic Methods in Mathematical Physics and Biology* **109**, pp. 23–45. Polish Academy of Sciences, 2016.

[5] I. Torre, *et al.*, "Scaling properties of binary and greyscale images in the context of x-ray soil tomography," *Geoderma* **365**, p. 114205, 2020.

[*] Presenting author email: jelenamatkovic2@gmail.com

"Comparative analysis of the impact of ionizing radiation on bone-forming cells: a study of DNA repair mechanisms and cellular adaptive responses"*

Magdalena Król[1†], Kamil Kania[1], Piotr Mróz[1], Elżbieta Menaszek[2], Czesław Kapusta[3], Oskar Wasilewski[1], Karol Bizoń[1], Stefan Horodeński[1]

[1] *AGH University of Science and Technology, Department of Applied Nuclear Physics, Kraków, Poland*

[2] *Jagiellonian University, Department of Cytobiology, Kraków, Poland*

[3] *AGH University of Science and Technology, Department of Solid State Physics, Poland*

The study aims to examine the effects of radiation doses from various sources on osteoblasts, which are the bone-forming cells responsible for generating bone tissue. This research investigated the impact of high-energy radiation beams, commonly employed in medical diagnostics and cancer treatment. Understanding the influence of ionizing radiation on bone health was imperative, given that high doses used in radiotherapy can damage osteocytes, osteoclasts, and osteoblasts, thereby disrupting natural bone repair and regeneration processes [1]. The risk of osteoradionecrosis was particularly significant in areas such as the jaw and pelvis, making this investigation critical for improving patient outcomes and developing protective strategies in radiotherapy [2].

The goal of the study is to analyze the effects of different types of radiation (proton, X-ray, and gamma) on osteoblasts by monitoring DNA repair mechanisms and cellular adaptive responses. High-energy radiation beams, similar to those used in medical diagnostics and cancer treatments, were employed. The project utilized preliminary studies with proton beams in collaboration with the Bronowice Cyclotron Center, as part of a research project led by the BOZON physics student research group. Initial findings showed promising results, indicating a need for further research.

The study monitored the levels of GADD45 protein, which is involved in DNA repair, apoptosis pathways, and cell cycle regulation, in NHOst cells (Normal Human Osteoblasts) and MG63 cells (osteosarcoma cells). The results indicated complex cellular responses to radiation, with significant changes in survival rates, cytotoxicity, proliferation, and GADD45 protein levels, depending on the radiation dose and cell type.

To deepen our understanding of cellular responses, additional experiments are scheduled between June and August 2024. These experiments will involve varying irradiation methods and types of radiation beams, delivering doses of 0.25 Gy, 5 Gy, and 10 Gy in multiple fractions to simulate therapeutic conditions. Intervals between fractions will be included to allow for cell regeneration. In addition to the previously employed methods, flow cytometry tests will be applied.

References

[1] J. Willey, Shane A. J. Lloyd *"Ionizing Radiation and Bone Loss: Space Exploration and Clinical Therapy Applications*", Clinical Reviews in Bone and Mineral Metabolism, 2011

[2] Lawrence Berk "The effects of high-dose radiation therapy on bone: a scoping review", pISSN 2234-1900, 2023

* Funding sources: AGH University of Krakow Rector's Grant

† Presenting author email: krolmagda@student.agh.edu.pl

First experimental results of a dual neutron-gamma imaging system for hadrontherapy and nuclear inspections

J. Lerendegui-Marco[1], G. Cisterna[1,2], J. Hallam[3,4], A. Sanchis-Moltó[3] , V. Babiano-Suárez[1,3], J. Balibrea-Correa[1], D. Calvo[1], C. Domingo-Pardo[1], G. de la Fuente[1], B. Gameiro[1], I. Ladarescu[1], P. Torres-Sánchez[1]

[1] *Instituto de Física Corpuscular IFIC IFIC, CSIC-Universitat de València, Spain*

[2] *Universidad de Sevilla, Spain*

[3] *Universitat de València, Spain*

[4] *University of Surrey, United Kingdom*

Compton imaging represents a promising technique for Prompt Gamma (PG) imaging for range verification in hadron therapy (HT) treatments. As for neutron monitoring, a drawback of most of the available systems is that only integral off-field neutron-fluence values are registered but no information is obtained from its spatial origin. Dual neutron and gamma imaging is also of prime interest for nuclear safety and security applications. In this context, we present GN-Vision, a compact and efficient dual imaging system which aims at imaging, simultaneously to the gamma-rays, the spatial origin of low energy (<100 eV) neutrons. The GN-Vision device follows the design of the previous i-TED detector [1], an array of Compton cameras based on large monolithic position sensitive $LaCl_3$(Ce) crystals that were initially designed for neutron-capture experiments at CERN and later applied to HT ion range verification studies [3,4]. In contrast to i-TED, GN-Vision exploits a neutron-gamma discriminating detector together with a passive collimator to achieve neutron imaging, while keeping the Compton imaging of γ-rays (Fig 1).

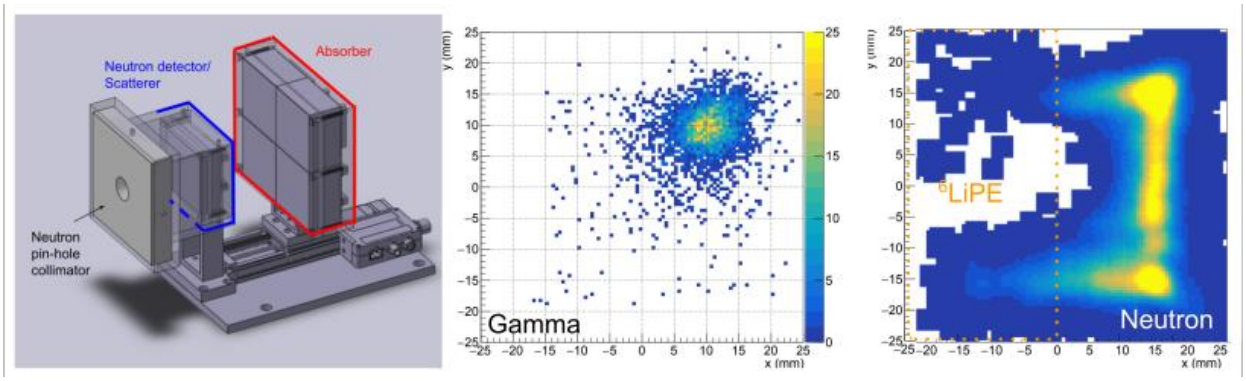

Figure 1: Sketch of GN-Vision (left), first position-sensitive results of a collimated g-ray source (center) and a neutron source irradiating the CLYC-6 detector partially shielded with a 6LiPE absorber (right).

Following the conceptual demonstration of the simultaneous neutron and gamma-ray imaging in a first Monte Carlo study [5], we have been working at IFIC in the technical implementation of the first prototype. By the time of the conference, this contribution will present the latest progresses in the development of GN-Vision, covering the optimization of the collimation system, the advances towards the neutron-gamma discrimination capability in position sensitive CLYC-6 detectors (Fig. 1) and the first proof-of-concept experiments of the neutron imaging capability. Last, the status of the neutron and gamma imaging integration will be reviewed and an outlook will be given on the upcoming field test-measurements.

References

[1] C. Domingo-Pardo *et al*., Nucl. Phys. A **851**, 78-86 (2016), doi: 10.1016/j.nima.2016.04.002
[2] V. Babiano *et al*., *Eur. Phys. J. A* **57**, 197 (2021), doi:10.1140/epja/s10050-021-00507-7,
[3] J. Lerendegui-Marco *et al*., *Sci Rep* **12**, 2735 (2022), doi: 10.1038/s41598-022-06126-6
[4] J. Balibrea-Correa *et al*., *Eur. Phys. J. Plus* **137**, 1258 (2022), doi: 10.1140/epjp/s13360-022-03414-y
[5] J. Lerendegui-Marco et al., *EPJ Techn Instrum* **11**, 2 (2024), doi: 10.1140/epjti/s40485-024-00108-w

Protective Concrete Shielding Thickness Requirements for PET Facilities*

V. Steiner[1], A. Malki[1], C. Ben Yehuda[1], M. Moinester[2,†]

[1] *Department of Nuclear Medicine, Chaim Sheba Medical Center, Ramat Gan, Israel*
[2] *Tel Aviv University, School of Physics and Astronomy, Tel Aviv, Israel*

This experimental study aims to determine the protective concrete shielding thickness requirements in the walls of the positron emission tomography (PET) and PET/CT (computed tomography) facilities at the Sheba Hospital (Israel). Consider the most commonly used PET radiotracer, the 1.4 hour effective life time (physical and biological) radioisotope F^{18}, which emits two back-to-back 511 keV gamma rays (photons) in all directions. After 4 hours, the patient's F^{18} radioactivity falls to about 5% of the typical 10 mCi internal activity injected for PET scans. Shielding is required to protect hospital staff during the entire time that a patient remains in the hospital. Measurements were carried out with photons coming from a 40 mCi activity liquid Fludeoxyglucose (FDG) F^{18} source, held in a 20 mL glass vial, secured in a tungsten container inside a lead-plated transportation box. With this setup, besides 511 keV photons, the "beam" also comprises Compton backscattered 170 keV photons. The attenuation coefficient measured through an Israeli B30 strength ordinary concrete wall (3 meter high, 20 cm thick) having density ~2.3 g/cm^3 is consistent with that of ordinary concrete that has average Z, A values Z=11.1 and A=22.3. The source was positioned at different distances to the wall, and the radiation dose was measured at different distances on the far side of the wall. All measurements were carried out with the same source and collimator. The background radiation level (~0.08 μSv/hr) was subtracted from each measurement. The beam cone aperture angle (FWHM) was 24 degrees. Only the beam disk radius on the wall changed: 1 cm when the source was 5 cm from the wall (narrow-beam) and 64 cm when the source was at 3 m from wall (wide-beam). For each source position, transmission measurements were taken by varying the detector to wall distance from 5 cm to 3 m; and these measurements were averaged. The average photon energy reaching the detector was less than 511 keV, as is the case for the average photon energy emitted from a patient. As the beam disk radius increased, the transmission coefficient increased, starting from the narrowest-beam value. The source activity during each measurement was evaluated using the standard time dependent exponential decay factor. The dose rate was measured by an Atomtex AT6130 Radiation Survey Meter. For the narrowest-beam configuration, having an effective photon energy less than 511 keV, the transfer coefficient through 20 cm of concrete was measured as 3.2%. This corresponds by exponential attenuation to a half-value length HVL = 4.0 ± 0.4 cm. By contrast, an HVL = 3.4 value is calculated using the NIST mass attenuation coefficient μ/ρ value for narrow beam and thin concrete target conditions. For wider-beam configurations, there is an additional "build-up" effect, as more photons reach the detector from multiple Compton scattering. Madsen et. al. [1] reported a transmission factor of 9.0% for 20 cm thick concrete having density 2.3 g/cm^3 at 500 keV for an infinite broad beam geometry; corresponding to a 5.3 build-up factor. Stankovic et al. [2] reported an 8.0% transmission factor for 20 cm thick concrete having density 2.3 g/cm^3 via a MC simulation of 511 keV photons centered on an ordinary concrete cylinder of diameter 1 meter; corresponding to a 4.7 build-up factor. For the largest radius beam configuration, we measured the transfer coefficient through 20 cm of concrete as 8.6%; in good agreement with Madsen et al. [1] and Stankovic et al. [2], considering also the differences between our experimental setup and their MC simulations. Our large-radius transmission coefficient simulates radiation emitted from a patient injected with F^{18}, and is a safe conservative value for shielding considerations. We confirm therefore by experiment rather than MC that thicker concrete shielding (20 cm for PET facilities) is required compared to the thickness calculated using tabulated narrow-beam transmission coefficients.

References

[1] M. T Madsen *et al*., Med. Phys. ***33***, 4 (2006)
[2] S. J. Stanković *et al*.,, Acta Phys. Pol. ***A117***, 812 (2010)

* Funded by the Chaim Sheba Medical Center, Ramat Gan, Israel

† Presenting author email: murray.moinester@gmail.com