Contributions to proton radiotherapy (PRT): annotated bibliography

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1 Before PRT

Born January 6, 1935 in Frankfurt am Main to Ernst Gottschalk (a lawyer) and Rosi (Hamburger) Gottschalk (an art student, later a women's fashion designer). Family emigrated to the USA in early 1938 settling in Washington Heights, New York City where Bernie grew up.[1] Early interest in science, pocket money fixing radios for other tenants of the apartment house.

Attended the Bronx High School of Science, Rensselaer Polytechnic Institute (BS 1955) and Harvard University (PhD. 1962). PhD. work (Karl Strauch, adviser) in medium energy nuclear physics at the Harvard Cyclotron Laboratory (HCL). Befriended then Director Bill Preston and then chief engineer Andy Koehler. PRT just beginning at HCL with RBE experiments (monkeys) and very infrequent neurosurgery treatments (Dr. Ray Kjellberg).

Three-year post-doc at HCL, then taught and rose through the ranks at Northeastern University (15 years), occasional sabbaticals and leaves of absence. Experimental particle physics, electronics, instrumentation, data analysis. Returned to HCL in 1981 as a Senior Research Fellow. HCL by then full-time PRT and, for several decades, treated half the patients in the world, trained numerous early MDs and PhDs. Worked at HCL from 1981 to 2002 when the lab was closed and demolished.

2 At the Harvard Cyclotron Laboratory

Early tasks: assisting in machine maintenance, converting control system from vacuum tubes to solid state, designing and implementing an efficient beam switching system. Among the generally useful circuit ideas we developed for HCL were a standalone (computerless) link for reading and writing arbitrary digital data over a single coaxial cable [1], an improved charge balancing or 'recycling' current integrator [2] and a simple way of resetting charge integrator arrays [3]. Below, describe only contributions which affected PRT elsewhere later on.

2.1 Accelerator Design

Early on, proposed a proton therapy synchrotron to replace the old cyclotron; proposal eventually fell through. Accelerator study not totally wasted because (much later) appointed Deputy Technical Director of the Loma Linda synchrotron project at Fermilab, to advise on clinical requirements. Thus had the good fortune to work briefly for the late Leon Lederman. One publication [4] warning that the proposed machine would have low dose rate. (LLUMC, the first purpose-built hospital based proton center, eventually treated their first patient on schedule three years after ground breaking, beginning an outstanding PRT program. HCL supplied their first contoured second scatterer.)

2.2 Multiple Coulomb Scattering (MCS)

Andy Koehler had long recognized the importance of multiple Coulomb scattering (MCS) to PRT, both for beamline design and dose computation, and had started a multi-year program of occasional measurements. A diode dosimeter was scanned across a measuring plane about 1 m downstream of a carefully measured thin or thick target, and except for increasing automation, that changed little over the years. Shortly after I joined HCL Andy hinted that 'someone' should gather and publish those data.[2]

That grew into a second PhD. thesis. Rounded up and processed the data in a consistent way, compared them with Molière theory and (much simpler) Highland's formula. BG's most important radiotherapy paper and now a benchmark [5, 6]. Showed that, with the possible exception of the thickest high-Z targets, Molière theory is at least as accurate any experiment so far (Fig. 1). We rediscovered that Molière had considered targets of arbitrary thickness (up to 97% of the range), not just thin targets as was generally stated in the (peer-reviewed) English-speaking literature.

[1] This was the diaspora for many Frankfurt Jews, known half-jokingly as the 'Fourth Reich' and the subject of an excellent documentary DVD 'We Were So Beloved'.

[2] You never got more than a hint from Andy.

2.3 Compensated Contoured Second Scatterer

Invented this ca. 1986, replaced the 'annulus' second scatterer of Koehler et al. [7].[3] Flatter dose, higher efficiency. A compensating plastic layer equalizes the energy loss at all radii. The standard for subsequent passive beam spreading systems.

2.4 Upstream Modulator

Range modulation at HCL used a large 'propeller-type' wheel near the patient. Though easy to design (MCS need not be taken into account, and the modulator is independent of the scattering system) this is cumbersome and, above all, contributes to penumbra (dose unsharpness).[4] Realized ca. 1987 that, if the modulator is compensated for equal scattering at all thicknesses by adding some Pb to each step, the modulator could be moved upstream and act as the first scatterer. In addition to improving the penumbra, this greatly reduces modulator size, opening the door to gantry mounting and remote changing.

2.5 NEU and LOOKUP

The design of an upstream modulator and second scatterer to arbitrary requirements is a rather complicated iterative process. The effective origin of scattered protons must be taken into account, especially in compact systems. Wrote a program NEU [5] [9] distributed it (IBA, Mevion), used it to design startup beam spreading systems for TRIUMF, IUCF and LLUMC.[6]

LOOKUP is a wrapper for various routines which we originally wrote for our own use but have since distributed widely as a Windows executable. It has built-in help and solves range-energy, MCS, single and binary degraders, arbitrary degrader stacks, penumbra, and water equivalence [10].

2.6 Collimator Scatter

Patient-specific collimators are widely used, even with pencil-beam scanning, for transverse dose definition. Quite a few protons interact with the collimator but scatter back out, adding to the shallow dose especially. We studied these experimentally and using a homemade Monte Carlo [11, 12]. Never properly published by us but eventually included in our course [13]. Van Luijk et al. [14] a careful study in the open literature.

2.7 Poor Man's Faraday Cup (PMFC)

Years ago the Faraday Cup (FC) determination of physical dose at HCL [15] fell into disrepute. It was an 8% outlier compared to ^{60}Co calibrated ICs. HCL converted to ^{60}Co calibration, and the problem was never definitively resolved. Recently, FCs have assumed new importance with the popularity of pencil beam scanning (PBS) where the FC, adjusted to agree with ^{60}Co, is used for absolute dosimetry [16].[7]

A conventional FC [15] is cumbersome, requiring vacuum and secondary electron suppression. We showed [17] that a 'Poor Man's Faraday Cup' (PMFC), a conducting block wrapped in insulator and an electrostatic shield, counts protons with a charge defect of only $\approx$2%. Those measurements since refined and published [18], the charge defect reduced, and the PMFC commercialized [19].

2.8 Multilayer Faraday Cup (MLFC)

Encouraged by the PMFC, we asked Rachel Platais[8] to construct a multilayer FC. That worked better than expected, considering secondary electrons [20]. We then realized that processes which merely redistribute charge internally do not contribute to the charge integrator signal (Fig. 2).

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[3] An uncompensated form was independently invented [8] by the Uppsala group around the same time.
[4] The diffusing effect of a degrader is greater, the larger the beam passing through it.
[5] Nozzle with Everything Upstream; German for 'new'.
[6] Eventually, significant improvements were made by Damien Prieels of IBA who used NEU to design the IBA passive scattering nozzle. Miles Wagner did the same at Mevion.
[7] Interestingly, [16] finds $\approx$1% agreement between FC and ^{60}Co.
[8] At HCL, cyclotron operators were asked to spend 20% of their time on program-related R&D projects.

The MLFC is a fast and sensitive range verifier [21]. The $\approx 20\%$ of integrated signal preceding the electromagnetic peak also has useful information, as it measures the range distribution of nuclear secondaries and has become a standard test of Monte Carlo nuclear models [22, 23]. Purpose-built MLFCs are used in PRT treatment nozzles, and a stand-alone version has been commercialized [19].

2.9 The IBA Ionization Chamber Electronic Unit (ICEU)

In our final years at HCL we consulted extensively with IBA in the design of the prototype facility at MGH. This included designing and overseeing construction and fabrication of a computer controlled ion chamber electronics unit (ICEU) which oversaw dose delivery and QA. Based on an updated charge-balancing or 'recycling' integrator developed earlier for HCL [2], the ICEU was used in the first dozen or so IBA centers [24].

2.10 Computerized Beam Steering, Skewness

Double scattering systems, used for efficiency and higher dose rate, are sensitive to beam steering. At HCL we had constructed a computer based (IBM 286) feedback system which monitored, by means of a segmented IC, the dose flatness near the patient. For the IBA nozzle, where that was not possible, we found by Monte Carlo studies that the skewness statistic in a strip IC further upstream was linearly related to dose flatness. That was experimentally confirmed later [25], and is used for beam tuning at IBA facilities .

3 In Retirement (2002 - present)

When we retired Harvard University generously gave us a courtesy appointment, Associate of the Physics Department, an office, internet connection and access to online literature. Without these physical assets and this vote of confidence it is unlikely that any of the following would have gotten done.

3.1 Teaching

PRT was clearly destined to expand. Related physics non-trivial but dated (ca. 1930-1970) and not seriously taught in physics graduate courses. With many new persons entering the field there was a clear need to gather the relevant material into a specialized course. Started a book [26] which is still available though outdated. In arrangement with Niek Schreuder, I gave a weekend intensive course before the 2004 PTCOG at IUCF (Bloomington, IN). This was well received and was the forerunner of the training sessions that now routinely precede PTCOG meetings, though it was an in-depth treatment of the physics rather than an overview.

This developed into a 1-week intensive course consisting of 27 PowerPoint lectures which are available at http://users.physics.harvard.edu/~gottschalk and on the PTCOG and MGH websites. I taught this at various venues roughly once a year, to ≈ 20 students each time from many countries, until recently.

3.2 Multilayer Ionization Chamber (MLIC)

This grew out of a consulting contract with MGH to speed up eye beam calibrations. Using a stack of ion chambers as a range verifier is an old idea, but we realized that with proper design such a stack could reproduce water-tank longitudinal scans to clinical accuracy in a very short time, convenient for scattered beams and crucial for scanned beams. The resulting device [27], using an integrator array designed by us and inherited from HCL, is still in use in the MGH eye beam. See the eponymous lecture in [13] for details, performance and design tips. The MLIC was later commercialized, with advice from us, as the IBA 'Zebra' [28].

3.3 Neutron Dose Controversy

In a celebrated paper Hall claimed [29] that scattered proton beams (then the standard except at PSI) were 100× worse than scanned beams vis-a-vis unwanted neutron dose. There were a number of flaws in that paper, chiefly that it relied on measurements in a proton beam that was, indeed, only 1% efficient as we soon pointed out [30]. Bottom line: in a typical scattered beamline most of the external neutrons are from protons stopping in the patient-specific collimator, which can be minimized by good design (selectable beam sizes). In a well-designed scattered beam the external neutron dose is 1 mSv/Gy or less and the unwanted equivalent dose to the patient is, in most geometries, considerably less than the unwanted dose from the primary protons [31].

3.4 Scattering Power

Scattering power is the rate of increase, with depth, of the angular spread σ_θ^2 of a proton beam due to MCS. Unlike stopping power, the analog for energy, an accurate formula for stopping power must take the history of the beam into account as well as conditions (beam energy, stopping material) at the POI. In a 2010 paper [32] we compared all scattering power formulas then in use, introduced *scattering length* (similar but not identical to radiation length) and found an improved formula (cf. Fig. 3) which has been widely used. Our second most important research paper completing, in a sense, the work begun in [5].

3.5 Preston-Koehler (PK) and Fermi-Eyges (FE) Theory

An early manuscript by Preston and Koehler [33] remains the best theoretical *and* experimental account of the evolution of pencil beams in homogeneous slabs. Andy showed me the MS shortly after I rejoined HCL. It had been submitted ca. 1968 (he did not recall the journal) and rejected because of lack of interest in PRT. PK show that a) the lateral spread σ_x of a pencil beam at end-of-range is proportional to its range with a material-dependent coefficient that they calculate; b) σ_x v. depth for a proton of any energy entering any material is a universal function for which they find a closed expression and c) as a stopping pencil beam is made smaller the Bragg peak disappears: fluence decreases faster than stopping power increases. These results have only become more important with the advent of pencil beam scanning.

Later, following referee comments on an MS I had submitted on penumbra, I turned to Fermi-Eyges theory. Till then primarily used for electrons, actually much better for protons. I became interested in relating the two theories dealing with the same phenomena. Reference [34], lecture notes for my course, makes this connection, rederiving the PK results in FE language and extending them to heavy ions. It covers all of FE theory in a single place and, for the first time, draws the connection between the FE B parameter and the *emittance* of beam line theory, allowing scatterers to be combined with magnetic elements in a natural way.

3.6 Time-Resolved in Vivo Dosimetry

Paradoxically, the sharp distal edge is rarely exploited in PRT because of uncertainty in where the protons actually stop. One of the most active fields of PRT research. In passive beams with a rotating range modulator, the time structure of dose at any given POI can be used to infer the water equivalent path length (WEPL) to the POI. However, that technique, demonstrated successfully with an ion chamber dosimeter [35], becomes noisy when a diode (more practical *in vivo*) is used. Using a fast amplifier reveals a noisy time structure, due to the small active volume of the diode (far smaller than its physical volume), which detects protons singly or in small clusters.[9] We showed [36] that under those circumstances the rms spread in time σ_t of the noisy pattern is a simple and accurate function of the WEPL in a water tank.

Further experiments, using a diode array in a prostate phantom, were even more interesting. When, because of MCS, protons arrive at a POI with different energies, the WEPL (even though a number can be assigned to it) is meaningless because there are multiple paths, and σ_t from that diode must be disregarded. We determined, then, that the higher moments (skewness and kurtosis)

[9] As first explained by E. Cascio.

of the time distribution reveal that protons arriving at that diode are range-mixed [37]. These findings have since been patented [38] and have motivated further work with detectors outside the patient.

3.7 Nuclear Halo

In PRT some 80% of the incident protons[10] slow down and stop by electromagnetic (EM) processes, well understood and relatively simple. The remainder, representing some 15% of the beam energy (integrated dose) deposit their energy outside the compact 'core' of a pencil beam, causing field-size dependent effects. For accurate absolute dosimetry this 'nuclear halo' must be taken into account [16]. Early measurements were very much oriented towards the field-size effects and left an incomplete picture of the halo itself.

We became interested on realizing that the halo radius ought to follow from kinematics and that a useful experiment was possible with existing equipment at MGH. A collaboration cobbled together at lunchtime, and two shifts in the test beam, yielded a comprehensive survey of the halo at 177 MeV [39]. Because it separates different reaction mechanisms (EM, coherent, incoherent) as well as can be, it is an incisive test of Monte Carlo nuclear models [40] (Fig. 4). The most efficient parameterization of the halo for PRT is, in our view, still an open question. Ref. [39] takes issue with the method currently used. This is our third most important publication, particularly for pencil beam scanning.

3.8 Dose Algorithm

We contributed significantly to the 'Hong' algorithm [41]. Although quite accurate and widely used, it has some drawbacks. The beam source size and position are input, and it assumes that the fluence is uniform over the patient collimator. Therefore it needs to be commissioned for each new configuration of the beam, and effects such beam alignment that might lead to dose nonuniformity are ignored. Moreover, all materials are treated as water-like and the actual depth of heterogeneities (such as bone or surgical implants) is folded into an averaged 'radiological path length'.

We have written an algorithm [42, 43] that finds the dose everywhere in some region of interest when known beams irradiate a known heterogeneous terrain including the beam line if desired. It proceeds from first principles, that is, established laws of physics, without using empirical models or fitting parameters. The program structure is identical for scattered and scanned beams (PBS), every structure in the beam line (including collimators) is treated identically, and every material is treated according to its proper stopping and scattering powers. Transverse heterogeneities are handled by dividing pencil beams, as required, using redefinition [44] and/or recursive dynamic splitting [45].

3.9 Peer Review and Book Chapters

In the past ten years we have refereed journal articles (Med. Phys., Phys. Med. Biol, Nucl. Instr. Meth. ...) at about three per year. Careful refereeing takes time and is, in the present system, largely unrewarded.

We have contributed chapters to books edited by Delaney and Kooy [46] and by Paganetti [47] (both editions, the second completely rewritten).

[10] Depending on energy.

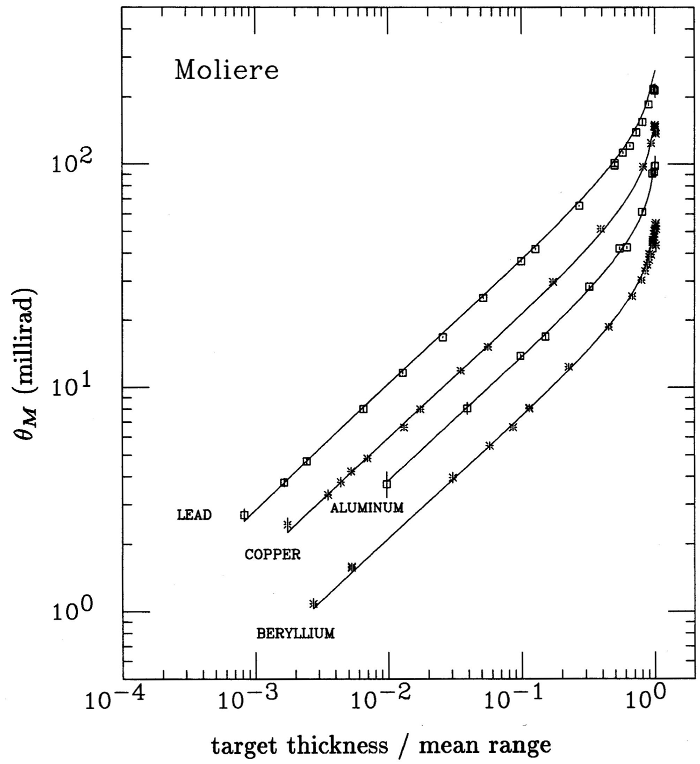

Figure 1: From [5] showing that Molière theory fits thin and thick scatterers over the periodic table.

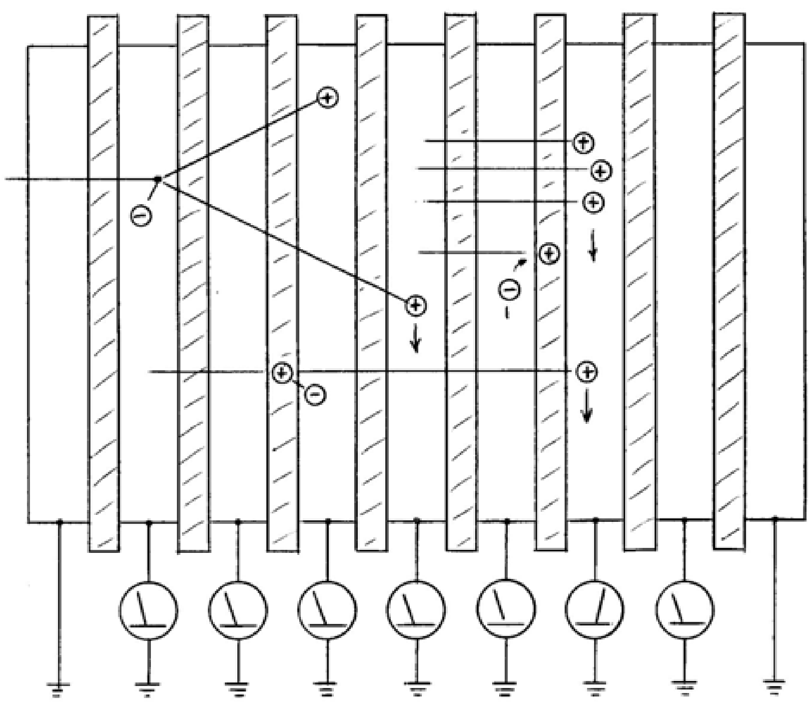

Figure 2: From [13] showing why processes that simply redistribute charge within an MLFC do not affect the output, and protons stopping in insulator count as well as those stopping in conductor.

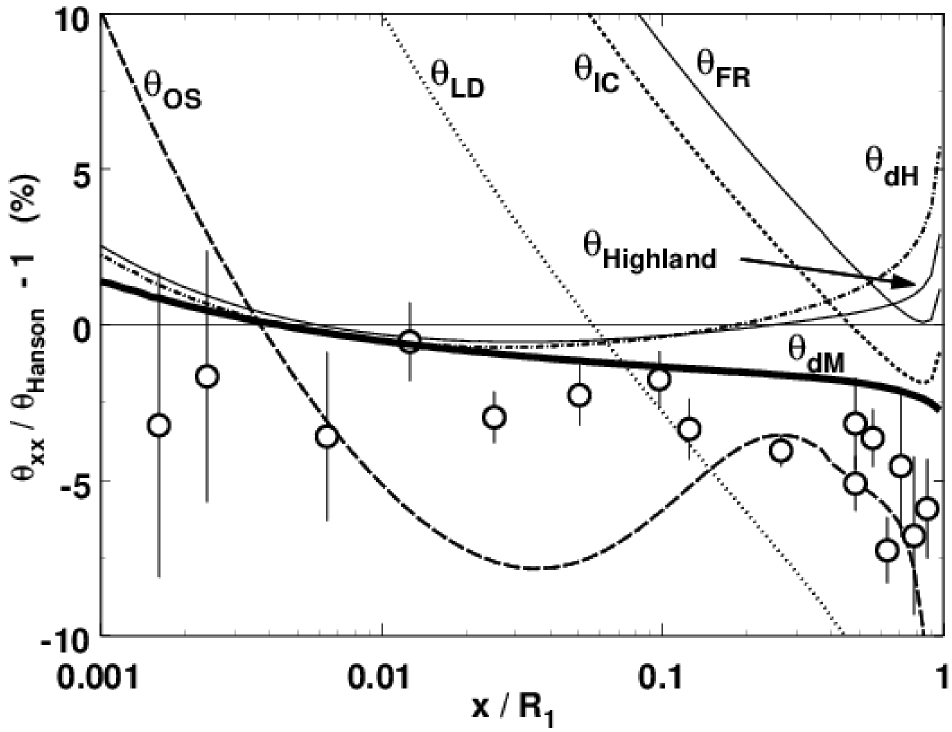

Figure 3: Various scattering powers including ours compared[32] with experiment for Pb.

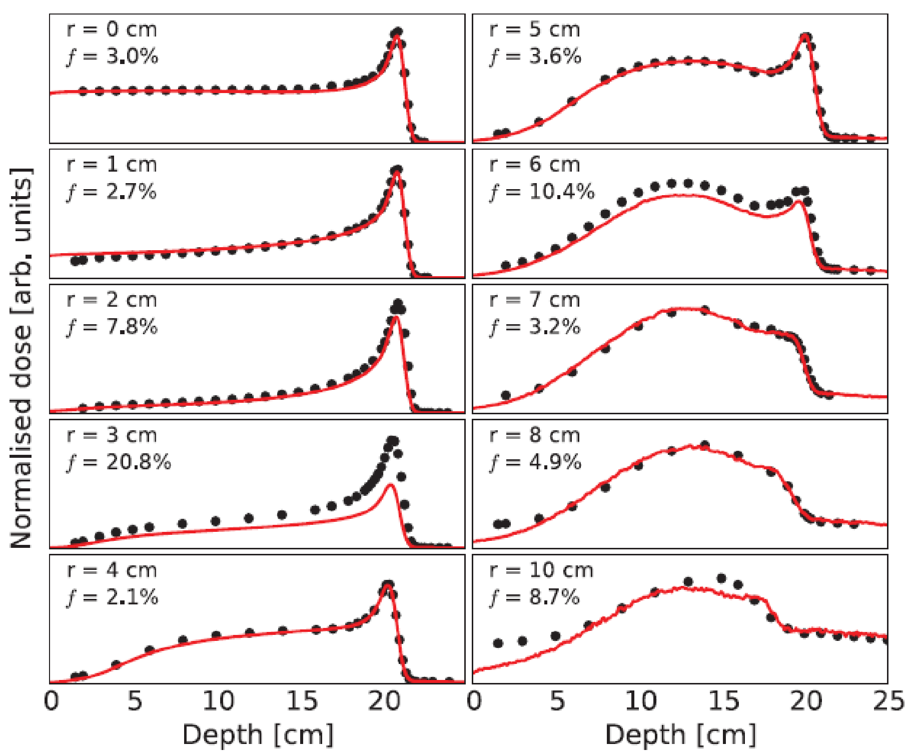

Figure 4: Comparison of Geant4 [40] (red line) with our nuclear halo measurements [39] (points). The comparison is *absolute* (no normalization). Problems at $r = 3$ and $6\,\mathrm{cm}$ remain unexplained.

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$$\Xi(\chi) = \frac{1}{\pi}\,\frac{\chi_c^2}{(\chi^2+\chi_a^2)^2}$$

and in Table 1 the heading α should read α^2 and $\times 10^9$ under χ_c^2 should read $\times 10^6$.

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