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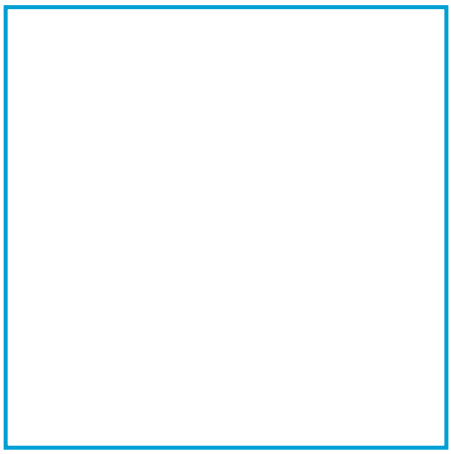
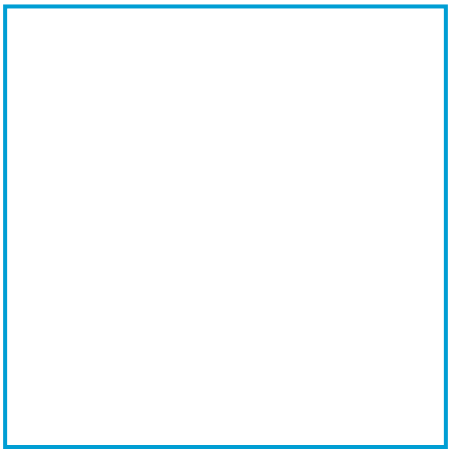
Oktober 2018

Woon Yong Baek, Marion Ute Bug, Volker Dangendorf, Ulrich Giesen, Gerhard Hilgers, Hans Rabus

Metrology for Biological Radiation Effects – Status and Metrological and Research Needs





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Content

Foreword

In June 2016, a two-day international workshop entitled “Metrology of Biological Radiation Effects” was held at PTB in Braunschweig, Germany. The rationale for organizing a workshop on this topic was twofold. First, it was the first year after the completion of the BioQuaRT project (coordinated by PTB department 6.5) which was the only transdisciplinary project funded in the frame of the European Metrology Research Programme (EMRP) that was related to ionizing radiation metrology and extended into the field of biological radiation effects. BioQuaRT is seen as a very successful model for interdisciplinary metrological research and has made promising advances in the field of ionizing radiation dosimetry with respect to biologically relevant quantities. The second rationale was due to the reorganisation of the ionizing radiation division of PTB at the beginning of year 2016 by which the activities on novel radiation detectors measuring track structure, track structure simulations and the ion microbeam of PTB were united in one department.

Workshop participation was by invitation and 16 external experts from institutions in the fields of medical radiation research, radiation protection and fundamental research were invited to elucidate the needs of these communities with respect to the development of metrology for quantifying biological radiation effects. Prior to the meeting, the members of the expert panel were asked to answer a questionnaire, and after the meeting they were invited to provide a written summary of their resume of the workshop and the recommendations they would give to PTB.

The first two parts of the report are a compilation of this dedicated stakeholder input in the context of the workshop. The third part presents conclusions by the authors. This latter part also takes into account the output from similar activities in the radio-oncology field (1st ESTRO Physics Workshop, Glasgow, 17-18 November 2017) and within the European radiation protection networks (EURADOS Stakeholder Workshop, Neuherberg, 30 June 2016; CONCERT Gap Analysis Workshop, Neuherberg, 20 February 2018).

In appreciation of the effort of the expert panel and as a potential reference for the envisaged future European Metrology Network (EMN) on Ionizing Radiation Effects, that hopefully will get the chance to solve the metrological challenges related to biological effects of ionizing radiation in the collaborative spirit that characterized the BioQuaRT project, my co-workers and myself have decided to publish this report including also the input of the other aforementioned stakeholder consultations.

Braunschweig, September 2018

Hans Rabus
Head PTB department 6.5 Radiation Effects

1 Report on the Expert Panel Workshop

1.1 Overview and List of questions to the experts

Sixteen external experts from eight countries and four experts from different divisions of PTB were invited to a 2-day Panel-Meeting in order to provide an overview of current activities and needs in the field of "Metrology for Biological Radiation Effects". The meeting was structured into 3 sessions with a total of 13 presentations covering the areas of **"Radiotherapy with ion beams and its metrological needs"**, **"Medicine and radiobiology"** and **"Metrology and fundamentals"**. Plenty of time for discussions was allowed after each presentation as well as longer **General Discussions** at the end of each session.

The head of PTB's division 6 "Ionizing Radiation", **Jörn Stenger, welcomed the participants** and provided an overview of metrology, in particular the legal tasks and the role of PTB as Germanys National Metrology Institute (NMI).

The main goal of the Workshop is to provide "**Advice on the strategic development of the Department 6.5 (Radiation Effects)"**. Therefore, the following questions were sent to all participants with the request to address them in the presentations or discussions:

1. Which topics of your research or working field would benefit from improving the accuracy of the determination of biological radiation effects?
2. Which physical and radiobiological data are involved in your research and which quantities do require a significant improvement of the accuracy?
3. How would you rate the potential to increase the effectiveness of radiation therapy and the accuracy of risk assessment by a new dosimetric concept based on particle track structure?
4. Which processes leading from the direct physical radiation effect to a biological end point need to be better quantified?
5. Which areas related to biological effects have a large potential for innovation and do require metrological standardization?
6. Which are the most relevant partners for collaboration and how do you see the role of PTB?

1.1.1 Which topics of your research or working field would benefit from improving the accuracy of the determination of biological radiation effects?

CONTE:
In nanodosimetry, the calibration of target size (a specific target size corresponds to a class of biological end-points, for instance a size of 1 nm corresponds to 5%-survival of radio-resistant cells) and afterwards the determination of the scaling factor (for instance 5%-survival is directly proportional to the probability of measuring at least 2 ionizations, with a proportionality factor which depends on the specific cell line) would definitively benefit from improving the accuracy of the determination of biological radiation effects, which at present are affected from a great dispersion.

DÖRR:
Tissue culture and in vivo radiobiology, including patients;

Modeling

GARGIONI:
The topics of my research that would benefit from improving the accuracy of the determination of

i. The use of gold nanoparticles as sensitizers for radiation therapy with photons.
   An accurate determination of the biological effects (corresponding to a dose enhancement in a nanoparticle-enriched tumor) is essential, in order to correct the therapeutic dose accordingly. To this purpose, the definition of a physical quantity related to the quality of the radiation field produced by irradiating a given concentration of nanoparticles in a biological target would be of great advantage.
ii. The biological optimization of treatment plans using tumor-control-probability and normal-tissue-complication-probability models. These models are based on theoretical curves, whose parameters are derived from clinical data and usually have high uncertainties.

GARTY:
There is crucial need to harmonize dosimetry measurements supporting radiobiological experiments, particularly those pertaining to clinical or pre-clinical studies. This was summarized very well in the NIST paper Giuseppe referred to in his talk (1). I think that PTB should take an active role in both supporting and requiring this. I believe that PTB has sufficient expertise to establish standard operating procedures for performing irradiations and dosimetry in both cellular systems and, importantly, for animal irradiations, paying attention to irradiator settings (including, for example, X-ray machine filtration). Within our CMCRC program this activity is also supported by the central lab periodically sending dosimeters (TLD & Film embedded in a phantom) to the irradiation facilities and verifying that the delivered dose conforms to the planned dose. There was a similar program at the University of Maryland(2).
This would likely improve the robustness of outcome studies and facilitate later correlation with new dosimetric concepts.

KRÄMER:
Increasing the accuracy and reproducibility of biological assays would certainly be
a big benefit for radiobiology, radioprotection and radiotherapy.

NEWHAUSER:
My research aims to improve outcomes for cancer patients who receive radiotherapy by reducing radiation-induced late effects, e.g., second cancers. Most second cancers occur outside the “target volume”, where the primary cancer is locations. While the dosimetry is generally adequate for tissues inside the target volume, dosimetric metrology is comparatively primitive and inadequate outside the target volume. The current limitations in metrology lead to large uncertainties in risk projections, and these are obstacle to developing strategies for improving treatment outcomes. In the broader context, improved metrology is needed for a variety of stray radiations from medical procedures, especially for patients who receive photon and proton beam radiation therapies, but also from diagnostic exposures such as the dose to the lens of the eye of interventional radiologists.

ROTHKAMM:

- What contributes to the measured signal?

- How much do the different sources contribute to the observational error?
- Do they matter?
- How do we deal with them?

SCHETTINO:
One of the key activities of the NPL Dosimetry group is to support the implementation of advanced radiotherapy modalities and these include biological optimization. Biological optimization is likely to be the next major step forward for radiotherapy but this requires coordinated and multidisciplinary efforts to determine biological radiation effects. Improved accuracy of the radiobiological measurements is therefore paramount.

UTMDA:
Radiation biology is plagued with uncertainties, many of which are systematic in nature and current assessments show that +- 25% uncertainty in response of biological systems to radiation have to be expected. Effective treatment of cancer relies on accurate information about the patients, the tissues and the expected response of tissue to the treatment. In treatment planning systems, the relative biological effectiveness (RBE) of proton or heavy ion radiation is currently being approximated at best, demonstrated by the fact that the proton RBE is still assumed to be a constant of 1.1. Effective and useful treatments need better quality of underlying physics and biology data in order to improve quality.

1.1.2 Which physical and radiobiological data are involved in your research and which quantities do require a significant improvement of the accuracy?

CONTE:
In my research I measure the stochastics of ionizing processes taking place at micrometric and at nanometric scales. Physical quantities have then to be compared with radiobiological cross sections derived from cell survival curves. The radiobiological quantities are those that would require a significant improvement of the accuracy.

DÖRR:
Organ at Risk subvolume dose/dose distribution

GARGIONI:
In order to understand the physical interactions of nanoparticles with ionizing radiation, my group performs Monte-Carlo particle track simulations. Electron-impact cross-section data for reference materials (such as water or water-equivalent plastic, biological targets, gold) need to be determined with better accuracy, especially for electron energies below 1 keV.

GARTY:
In microbeams there is a need for better specification of the amount of radiation delivered. Specifically, dose is often used by the biologists, while fluence is used by the physicists. In the context of microbeams, due to the small and not always well defined target, the concept of dose is meaningless and fluence does not really provide enough information. Microdosimetric quantities are

also of little use as they typically assume a uniform homogenous radiation field which is not really the case in single particle irradiations.
It would be useful to have a track-structure-based parameter that can be used to describe “radiation quality” in the context of single particle irradiations. Ideally such a parameter would somehow scale with fluence and be numerically equivalent to dose for sparsely ionizing radiations. Such a parameter may also be useful for ion-therapy scenarios.

KRÄMER:
On the physics side, there are depth dose and absorbed dose distributions, and their underlying basic processes such as energy loss and nuclear reactions. While these can be handled pragmatically with sufficient accuracy, their theoretical basis sometimes is weak.
For example, the average ionization potential entering into the usual energy loss formulae is uncertain by several eV, leading to range deviations by about one or two CT voxels.
Theoretical nuclear reaction cross sections can differ from 10% to factors of two, so they often need adaption to experimental data, which reduces their predictive power.
The bigger uncertainty, however, is on the radiobiological side. For the prediction of particle radiation effects, for example the LQ parameters a,b for photon reference radiation are essential, and their accuracy is limited.

NEWHAUSER:
Absorbed dose, radiation quality (e.g., mean radiation weighting factor, quality factor, etc), RBE for carcinogenesis, and “clinical RBE” related to sterilization of tumors. It appears that the metrology for absorbed dose and radiation quality are most urgent. Absorbed dose is a fundamentally solid and highly satisfactory quantity. Hitherto quantities for radiation quality are generally problematic because they are either not measureable, traceable, reproducible, applicable, or relevant. The problems are severe for high-energy neutrons caused by therapeutic proton beams.

SCHETTINO:
NPL Radiation Dosimetry activities span from microdosimetry to radiobiology. As such we are interested in initial physico, chemical and biological processes of radiation-biological sample interaction. Improvement in the measurement of micro and nano-dosimetry as well as in the cellular and animal response is required.

UTMDA:
Our research focuses on several aspects of radiation interaction in tissue, all of which are closely related to modelling the RBE of various ion beams (proton, helium, carbon, …). Foremost there is a large effort to understand the relationship of biological response (cell kill or survival fraction) in in-vitro experiments as a function of dose and linear energy transfer (LET). Secondly, abandoning the concept of LET we aim to understand the dependence of response on local energy deposition density, a direction that has been explored by the developers of the LEM model (Michael Schulz, Michael Kraemer, et al) with promizing results.

1.1.3 How would you rate the potential to increase the effectiveness of radiation therapy and the accuracy of risk assessment by a new dosimetric concept based on particle track structure?

CONTE:
Any possibility to describe and to measure properties of particle track structure (which clearly depict the effectiveness of ionizing radiation), in particular in complex and unknown radiation fields (such as those inside the patient after some penetration depth) would obviously have a great impact to increase both the effectiveness of radiation therapy and the accuracy of risk assessment.

GARGIONI:
As mentioned above, the definition of a physical quantity related to the quality of the radiation field would be desirable. This quantity could be related to given biological radiation effects. Also, accurate, standardized protocols for carrying out biological experiments should be defined in order to investigate this correlation. This would provide traceable biologically-weighted radiation quantities and a well-defined method to compare, for example, radiotherapy outcomes at different facilities.

GARTY:
This is a tricky question. While I think that track structure based parameters can be extremely useful in understanding radiobiological endpoints, I also believe that it would be near impossible to get the medical establishment and regulatory bodies to buy into this approach at this stage.
Before we can start convincing the doctors to buy into new dosimetric concepts, they need to be correlated with a medical or radiobiological outcome. It is not clear to me which of the many endpoints discussed in the meeting and in the literature is the relevant one and I doubt that just one endpoint would be enough. Cell killing may be a relevant outcome but, as seen in Valeria's talk, different cell types would require different track structure paramatrizations. Only after the outcome criteria is established, can we start seriously looking for a dosimetric quantity that will correlate with it. It is likely that multiple parameters would be needed, taking into account the stochastics of the track as well as heterogeneity of the target tissue.
Getting buy-in from the medical establishment would also require qualifying a nanodosimeter as a medical diagnostic device. This is an arduous process and I think that we are nowhere near even beginning it, lacking a convincing connection between track structure and a "relevant outcome". I am not familiar with the situation in Europe but in the US once you have convincing evidence of the usefulness of an assay/device (which we haven't yet done), you are required to demonstrate that the device is manufactured and used under a quality system (e.g. GMP) and that the device is reliable and reproducible. Only after that, efficacy needs to be demonstrated in at least one animal model (typically primates) and in a relevant human population. Lacking this efficacy information, I do not believe that the results reported by the device can be legally used to support clinical decisions.

KRÄMER:
I wouldn't rate this very high, since the uncertainty of risk assessment is due to incomplete biological knowledge, not physics. Particle radiation therapy is already quite effective with the currently applied and validated models, which are based on amorphous track structure. In this context, there's some interest in the physical processes governing the very inner part of a track in condensed matter.

NEWHAUSER:
Clearly new dosimetric concepts and at least one dosimetry quantity (related to radiation quality) are needed for particle therapy and risk assessment. The potential to increase effectiveness in controlling tumors appears modest to strong. The potential to improve outcomes through improved risk assessment appears strong to very strong.

SCHETTINO:
Considering the huge efforts of the last few decades, it is clear that a single quantity is unlikely to be enough to describe radiation effect and risk. Several quantities have been suggested and are being used. Improvement in the measurement of such quantities and their impact on the radiation effect is likely to have a bigger impact than the definition of an extra quantity.

UTMDA:
The potential of a model based on track structures must involve several scientific disciplines in order to improve the quality of response predictions. There is the physics aspect of dose deposition, ionization electron density around the track and the probability of complex DNA damage by direct interaction of those electrons with the DNA. Then chemistry would need to be considered, for example by taking indirect interactions into account, such as the formation of free radicals and their interaction inside the cell nucleus. Finally one needs to consider biological effects other than DNA damage. Questions about the potential of cell kill by rendering biological components ineffective, such as mitochondria etc. The whole concept of modelling biological effectiveness today is a patchwork at best and a comprehensive overhaul is wanted in order to fully understand all aspects.

1.1.4 Which processes leading from the direct physical radiation effect to a biological end point need to be better quantified?

CONTE:
There seems to be a direct link between the direct physical radiation effects (expressed as probability of producing cluster of ionizations larger than a specific quantity in a small nanoscopic volume) to a biological end point. Intermediate processes could mediate the effects without affecting the transmission of statistical properties of the initial interactions to the final observable.

DÖRR:
Molecular pathways in tissues in vivo

GARGIONI:
The chemical processes play a very important role in the chain of events occurring after the direct physical interactions. These processes could become even more important if targeted radiotherapy will become more available.

GARTY:
I do not think it is the job of PTB to go into studying the pathways leading from radiation physics and chemistry to medical outcomes. This would be better done in an academic or national lab setting.

KRÄMER:
Everything which is not basic radiation physics. In particular cellular repair processes or the effects of hypoxia. For example, the non-invasive determination of oxygen content in the tumour microenvironment.

NEWHAUSER:
The initial radiation exposure (absorbed dose and radiation quality) needs to be better quantified. For most medical procedures, dose assessments are largely incomplete, approximate, and lack the accuracy and precision needed for outcome studies of radiation late effects.

SCHETTINO:
The link between the different pathways and processes activated in cells and tissues by the different pattern of energy deposition are still to be elucidated. This is a key step in understanding the mechanisms underpinning biological radiation effects and considerable efforts are being dedicated into this by the research community. The Metrology Institute should help such efforts.

UTMDA:
As mentioned in 4.3, the involved mechanisms envelope physics, chemistry and biology. While physics aspects, such as energy deposition patterns along charged particle tracks are known to a certain degree, many aspects still need to be explored, such as dependence on particle type, target material density, etc. Information about the ionization density on the order of DNA size will be needed in order to accurately estimate the probability of direct damage to the DNA.
To my knowledge, the chemistry involved in RBE modelling has largely been ignored so far and the role of free radicals and their interactions are rough estimates if they are considered at all. My recommendation is to research this topic extensively so that a potentially large fraction of interaction mechanisms can be explained and better taken into account in future RBE models.

1.1.5 Which areas related to biological effects have a large potential for innovation and do require metrological standardization?

CONTE:
Even in simple clonogenic assay, a standardization of the procedure is recommended, in particular for what concerns the specification of physical quantities which characterize the radiation field.

DÖRR:
Molecular pathways in tissues in vivo,
=>biomarkers, biology-based intervention

GARGIONI:
I see a large potential for innovation in nanomedicine and in targeted radioisotope therapy. An accurate correlation between the radiotracer or nanodrug concentration to be injected and the biological radiation effects should be determined and this requires a metrological standardization.

GARTY:

I don't think that, other than work on metrology of the irradiation systems, PTB should get involved in the bioassays.

Since you insist, one field that could use some standardization and better QA is antibody manufacture. The batch-to-batch variations in the performance of antibodies (used in immunolabling) are horrendous, to the point that each lab (that I know) will only work with one brand of antibody and they tend to stockpile antibodies from the same batch (or production year) when they find something that works.I don't know if PTB can realistically get involved in this

In the biodosimetry field there are some assays that have been standardized by ISO and/or IAEA, possibly e.g. ISO 19238 or the IAEA report Cytogenetic Dosimetry: Applications in Preparedness for and Response to Radiation Emergencies. Again, I don't think it would be realistic to have PTB do this in house, perhaps you could farm it out to somebody like Rothkamm.

KRÄMER:
Biological effects themselves and dosimeters and devices measuring them.
In the context of personalized medicine, determination of individual radiosensitivity ("Biomarkers") might play an important role.

NEWHAUSER:
With survival rates approaching 70% in adult cancer patients, clearly great progress has been made in the biologic effects that govern tumor sterilization. Radiation late effects are prevalent and can be severe. The application of physical approaches to reduce late effects has huge potential to improve outcomes for millions of patients each year. The radiation dosimetry and, more generally, metrology urgently need to be extended and standardized to support research and clinical activities that will improve outcomes.

ROTHKAMM:
Biopsy-based prediction of the likely response of a tumour to a molecular targeted treatment combined with radiotherapy

- Based on genetic / epigenetic / expression / kinome… profiling
- Based on functional endpoints (DSBR pathways, cell fate)

SCHETTINO:
Radiobiological measurements require standardization. This is likely to be the single main step with high impact on improving our understanding of radiation biological effects
UTMDA:
Honestly, I think all of the above mentioned mechanisms, ionization, free radicals and the role of biological structures inside a cell need to be re-visited for improved characterization.

1.1.6 Which are the most relevant partners for collaboration and how do you see the role of PTB?

CONTE:
In my opinion the role of PTB must be actively purposeful, in collaboration with other European Metrological and research Institutes.

DÖRR:
MedPhys, RadOncology, Molecular Pathology, Bioinformatics/Modeling

GARGIONI:
There should be two levels of collaboration between the PTB and external partners:

i) National level: with the radioprotection authority, radiobiology labs, radiotherapy centers, and research centers specialized in radiation detector development. The role of PTB should be to provide reference radiation fields (that are already available, including the microbeam facility) for combined physical and radiobiology experiments. These should be carried out under well-defined setups and protocols with the purpose of standardizing in-vitro and in-vivo investigations. Such collaborations should lead to the definition of a "catalogue" of radiation qualities for given biological endpoints (for radiotherapy as well as for radiation protection).

ii) European/international level: with other national metrology institutes and international organizations such as ESTRO, ASTRO, IAEA. The PTB has the duty of leading the process that will result in the definition of new radiation quantities related to biological radiation effects. The national metrology institutes should also provide a calibration facility for portable detectors or, alternatively, a certification facility for radiobiology protocols to be used for in-vitro and in-vivo experiments in unknown radiation fields. Finally, the creation of a common database for accurate electron- or charged-particle-impact cross-section data for use in Monte Carlo simulations should be aimed at. National metrology institutes should provide, in this case, criteria to analyze the consistency of such data prior publication.

GARTY:
I do not think it is reasonable to have PTB heavily involved in outcome research. Based on what I saw PTB has neither the facilities nor the expertise to do any significant biological studies. Certainly this type of work would require a strong radiation medicine/radiation biology program and would be more appropriately be handled by a university or national lab. In the US, for example The Lovelace Respiratory Research Institute (LRRI) and Armed Forces Radiological Research Institute (AFRRI) have been major players in radiobiology in animal systems. I am not aware of the equivalent bodies in Europe but would be surprised if there were none.
Other possible collaborators (in the US) are CRR at Columbia, the MacVittie group at the University of Maryland. The Radiation Emergency Assistance Center/Training Site at Oak ridge, TN – They have a lot of data on accidental exposure "victims"Ruth Wilkins at Health Canada I'll try to think of more. Reinhard can point you at more medically oriented groups in the US

The Role of PTB in my view should be in developing robust parametrizations for track structure that can be correlated with outcome data generated elsewhere. This would require a strong experimental nanodosimetry program supported by (and supporting development of) track structure modeling. It would also be useful to develop a radiation chemistry program (like the, now closed, lab of John Ward and Jaime Milligan in UCSD), if one does not already exist.
As described above, PTB should also take an active role in ensuring that the outcome studies be performed in as rigorous and standardized way as possible.

KRÄMER:
Regarding the Panel title ”Metrology for Biological Radiation Effects”, PTB’s natural partners are sites with research on radiobiology and/or radiotherapy. PTB has some unique experimental facilities (microbeam, low energy beam line, neutron dosimetry) which could offer ”standardized” service.
Likewise, PTB expertise in instrumentation (dosimeters, experimental setups) might be beneficial, for example in the design of devices measuring biological effects (not their surrogates) accurately and in a reproducible fashion.
PTB’s role could also be similar to US-based NIST, i.e. providing standardized data sets.

NEWHAUSER:
In the broadest terms, clearly a multi-disciplinary and multi-institutional approach is called for. Relevant partners in such an approach might include other standards laboratories, universities, and private and governmental research organizations. At some point, collaboration may be facilitated by collaborating with medical physics and health physics professional societies. A few specific examples include might include LSU, NPL (hadron dosimetry), AAPM, HPS, and others. However, “relevance” is of course just one criteria, and other factors will be important, such as potential for sustained successful collaboration, convenience, cost, and so on.

ROTHKAMM:
For metrology:

- Other national metrological organisations (e.g. NPL)
- International networks such as EURADOS

For biological effects:

- EU CONCERT / MELODI for low dose research
- DEGRO and ESTRO for radiation oncology
- Universities and other large research infrastructures (e.g. Helmholtz)

Role: Core resource for physical & radiation biophysical expertise

- Radiation sources
- Modelling
- Data analysis

SCHETTINO:
Other NMI involved in micro-, nano-dosimetry and radiobiology. Established radiobiology research centres in Europe, particularly those with strong and clear link with cancer research and radiotherapy centres.

UTMDA:
The most relevant partners we have right now are the DKFZ and the HIT in Heidelberg. We are in communication with HIMAC and other facilities to gain access to heavy ion beams. The role of the PTB I imagine could be the provision of beam time at the accelerator facility for the accurate determination of the physics parameters of clinically relevant ion beams first, followed by experiments of in-vitro and in-vivo RBE determination. Finally it would be nice to collaborate on the development of novel, improved RBE models.
I am not sure how much of chemistry and biology can be done at the PTB, but a collaboration on RBE would certainly mean to develop the basic infrastructure for such activities.

1.2 Programme of the Meeting "Metrology for Biological Radiation Effects"

PTBs reorganised department 6.5 focuses on selected aspects of radiation effects, and in order to properly address stakeholder needs, an expert panel meeting was organised. The format of the event included representative presentations on specific topics, invited speakers and experts from related fields and ample time for discussions. The programme is shown in Table 1:

Expert Panel Meeting for "Metrology for Biological Radiation Effects"

PTB-Braunschweig, 6. - 7. June 2016

Time			Speaker	Title
Day 1				
12:00	60	Arrival and Lunch		
13:00	15	Welcome & Introduction	Stenger/PTB	**Introduction to PTB and objectives of the workshop**
13:15	30	Tour de Table	Giesen & Bug	
13:45	30	Presentation 1	Rabus/PTB	**Status and visons of department "Radiation Effects"**
14:15	15	Discussion		
			Dangendorf &Hilgers	**Radiotherapy with ion beams and its metrological needs**
14:30	25	Presentation 2	Newhauser/LSU	**Medical radiation exposure and risk**
14:55	10	Discussion		
15:05	30	Coffee Break		
15:35	25	Presentation 3	Schulte / LLU	**Status and future plans of particle therapy and what are the metrological needs**
16:00	10	Discussion		
16:10	25	Presentation 4	Krämer / GSI	**Methods and models for treatment planning in particle therapy**
16:35	10	Discussion		
16:45	25	Presentation 5	Verhaegen /	**Research and stakeholder needs in particle therapy**
17:10	30	General Discussion 1	Rabus/PTB	
17:40		Transport to Hotels		
19:30		Dinner at Pentahotel		

Day 2				
08:30		Pick-up from Hotels		
			Giesen	**Medicine and radiobiology**
09:00	20	Presentation 6	Dörr / Medaustron	**Status and research at MedAustron**
09:20	10	Discussion		
09:30	20	Presentation 7	Rothkamm / UKE	**Assessment of radiation-induced DNA damage and repair**
09:50	10	Discussion		
10:00	20	Presentation 8	Garty / Columbia	**Probing radiation response in single cells**
10:20	10	Discussion		
10:30	40	Coffee Break and Foto		
			Bug & Baek	**Metrology and fundamentals**
11:10	20	Presentation 9	Schettino NPL	**Metrology for biological effectiveness of radiation exposure – NPL activities**
11:30	30	General Discussion 2		
12:00	60	Lunch		
13:00	20	Presentation 10	Villagrasa / IRSN	**Use of experimental data using microbeam irradiation in the simulation of early DNA damage**
13:20	10	Discussion		
13:30	20	Presentation 11	Conte / INFN	**Perspectives for a new metrology of ionizing radiation based on nanodosimetry**
13:50	10	Discussion		
14:00	20	Presentation 12	Dorn / MPIK	**Electron impact ionization of biomolecules as monomers and in water clusters.**
14:20	10	Discussion		
14:30	20	Presentation 13	Tinnefeld / TU-BS	**DNA in new roles: superresolution and fluorescence enhancement**
14:50	10	Discussion		
15:00	30	Coffee Break		
15:30	60	Summary & Discussion 3	Newhauser/LSU & Schäffter/PTB	
16:30	30	Conclusion and Farewell	Rabus & Stenger / PTB	
17:00		Transport to Hotel or Station		**Optional tour of ion accelerator facillity and microbeam**
18:00		Transport to Hotel or Station		

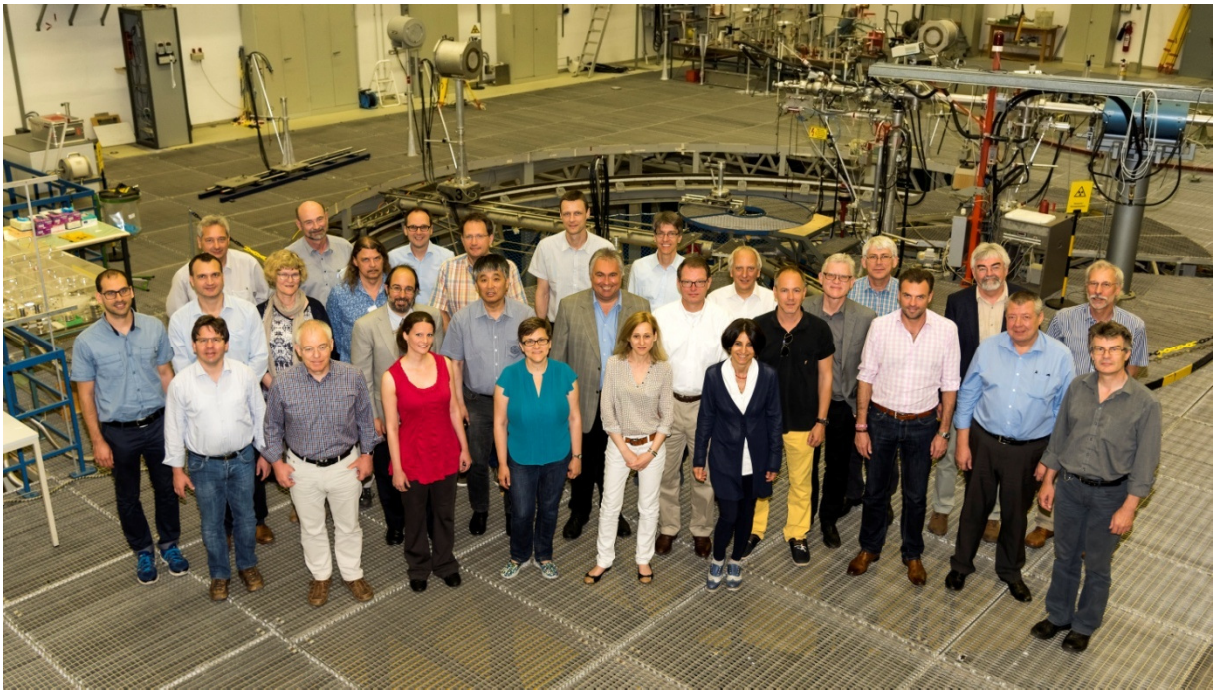


Figure 1: Photograph of participants in the experiment hall of the PTB Ion Accelerator Facility (PIAF).

1.3 Post-Workshop Feedback by the Expert Panel Members

The external experts were asked after the workshop to provide written summaries of their views that are listed below.

CONTE:

All participants have more or less acknowledged that the *dose* alone does not explain the differences in the effectiveness of radiation at biological level.

Hence the need to identify new sizes metrological able to describe and predict the biological effects of exposure to the radiation. A marked reduction of the uncertainties of radiobiological data, however desirable, seems, by their very nature, difficult to achieve.

I recommend a prepositive action by the PTB. We cannot expect that the demand for new metrological procedures comes by the users, in the absence of appropriate and stimulating proposals.

Microdosimetric characterization, for instance, performed not as a protocol procedure but as a supplement to standard dosimetry, is a tool already applicable and could enhance the knowledge of physical aspects of complex and unknown radiation fields, both in radiation protection and radiation therapy contexts. Similarly, nanodosimetry seems to be able to identify measurable quantities that are proportional to specific radiobiological end points. Considered that PTB already has excellent expertise on this field, and one of the few operative detectors worldwide, it should spend a strong effort to develop a new metrology of ionizing radiation based on nanodosimetry.

GARGIONI:

As a medical physicist in the field of radiotherapy, I am daily confronted with the task of improving the dose delivery to patients, in order to control the tumor and minimize side effects. This implies being always concerned with the assessment and understanding of the biological radiation effects. Today, nanomedicine (in particular the use of metal nanoparticles) and radio-immunotherapy are considered as promizing strategies to improve the outcome of radiotherapy with photons. Also, the acquisition of biological information about the tumor and its response to treatment has become easily available by using molecular and multimodal imaging, thus giving radiation oncologists better opportunities to individualize radiotherapy. I therefore believe that the task of improving the accuracy of the determination of biological radiation effects will become increasingly important in the next years.

GARTY:

I think that the goals for this meeting would have been better served had there been a stronger up-front description of current activities and expertise at PTB. E.g. the first day should have been dedicated to talks by PTB personnel about the strengths and weaknesses of their programs.

This would have framed a better context for the expert panel to advise PTB on future directions. This is the format we always use at our advisory committee meetings. The second day could have had expert presentations by people in the fields which PTB is currently working on as well as in “adjacent” fields, followed by discussions on the usefulness of expansion into these fields.

HORNHARDT:

Most of the discussion was focused on new radiotherapies like the application of particle therapy and proton therapy. In personalized radiooncology the aim is to target the tumor but to minimize the side effects in healthy tissues. However, with the increasing number of cancer patients surviving their

primary tumor disease also the risk of developing secondary cancers is increasing. 66% of secondary cancers develop out of the radiation field. So far the radiobiology of charged particles is not fully understood. The knowledge of track structures of different radiation qualities has to be improved, as well as the understanding of biological radiation effects like inflammation, immune response and effects on the microenvironment. However, it has to be asked if only the absorbed dose to the tumor or healty tissues at risk is an adequate measure for the exposure. There is a clear need to better verify the calculated dose from the beam. So far there is no biological control/ marker for different doses (high and low dose) and effects of different radiation qualities in the addressed tissues. Therefore a cooperation of physicists and medical/ biological researchers is necessary. The experiments have to be performed in vitro as well as in animals to improve the knowledge.
There is an urgent need to improve the understanding of the biological effect of a calculated dose. This is important for medical treatment planning and risk assessment for medical applications (radiotherapy and nuclear medicine) as well as for radiation protection for e.g. internal contamination to reduce uncertainties. Especially radiation quality and the radiobiological effectiveness (RBE) was discussed and new concepts are demanded (What is radiation quality and how to measure it?). Some promizing approaches to model the radiation effects on a micro/ nanodosimetric scale were presented and could show a way for future basic research.
The department 6.5 has excellent knowledge and facilities to contribute to this kind of research.

KRÄMER:
Was ich versuchte rüberzubringen ist, dass man in dem angesprochenen Feld ganz ohne Biologie, nur mit reiner Physik, nicht weit kommt. Das heisst aber nicht, dass man jetzt ins andere Extrem fallen sollte, d.h. auf Deubel komm raus zB alle möglichen Tierversuche machen sollte, das können andere besser.
Man muss kein Hardcore-Biologe sein, um biologisch relevante Physik zu treiben, siehe Nobelpreisträger Stefan Hell. Sich ein bisschen mehr in Richtung Biologie zu bewegen wäre allerdings schon notwendig, erst recht, wenn das die Wunschrichtung der Chefs ist. Experimentelle Expertise, zB auch im Apparatebau, wäre ja vorhanden. (ein Conte'sches Nanodosimeter würde ich allerdings nicht als "biologisch" bezeichnen:-)

NEWHAUSER:
The workshop revealed many opportunities and emerging needs for radiation metrology in medical physics, radiation oncology, radiology and nuclear medicine, radiobiology, and basic physics. The major findings and recommendations from the individual presentations were collected, summarized, and presented to stimulate discussion during the closing session of the workshop, which was a moderated discussion including all participants. That summary, prepared by Schaeffer and Newhauser, is given elsewhere. In the remainder of this document, the author provides remarks from the perspective of an individual participant.
The need for new initiatives in radiation metrology is greatest in cancer care. In Germany, Europe, and much of the developed world, the burden of cancer is large and rapidly growing, mainly due to increases in the size and age of the population. As cure rates have surpassed 65% in adults and 80% in children, there is increasing concern about the treatment-induced side effects that occur in long-term survivors. About two thirds of cancer patients receive radiotherapy at some point in their care and radiation-induced late effects are prevalent, with second cancers being of greatest concern. To improve long-term outcomes after radiotherapy, beams of protons and heavier ions are being used because they allow reduction of doses to normal tissues. Germany is a world leader in proton and

carbon ion radiation therapy. Worldwide, there are 27 ion facilities in operation, comprizing a multi-billion euro industry.
The metrology of proton and heavier ion therapies is increasingly important, yet current capabilities are surprizingly insufficient or, in some cases, entirely lacking. For example, to my knowledge, there is no national or international standards laboratory that provides routine calibrations of dosimeters for therapeutic ion beams, *e.g.*, based on a fundamental measurement technique such as calorimetry. It is noteworthy PTB foresaw these needs and took decisive and concerted actions to meet them. Indeed, PTB is to be commended for its many contributions to the metrology of calorimetry (e.g., measurement of heat defect of water) and ionimetry, (e.g., mean energy required to create an ion pair in gases, particle track topology). PTB should continue to develop the metrological capabilities to meet the current and future needs of the radiation medicine.

It is interesting to note a few specific examples of current needs being met by PTB. Today, most radiotherapy dosimeters are calibrated in x-ray beams and a conversion factor is applied to enable their use in ion beams. However, the conversion factors are uncertain because of limited knowledge of basic nuclear data, such as the mean energy required to create and ion pair and stopping powers. Again, PTB has provided leadership by collaborating with researchers at particle therapy centers to find practical solutions to meet pressing clinical needs (e.g., *W* value measurements by Dieter Schardt from GSI and Uli Giesen from PTB, k_Q determinations by Osinga from PTB and Jaekel at HIT). Other example synergistic activities include in-flight exposure measurements in civil aircraft and environmental measurements near radioactive waste containers, to name just a few.
The metrology of stray radiation exposures is generally less developed, especially for radiation therapies and other settings involving high-energy neutrons. The importance and magnitudes of metrological problems in ion therapy have been well documented in the scientific literature, e.g., neutron dosimetry and spectroscopy. For example, the extended Bonner Sphere spectroscopy system developed at PTB is widely considered to be the best of its kind. With an exponentially increasing use of particle therapy in recent years, now is an opportune time to develop the necessary metrology and calibration.
Another longstanding problem across all of radiation protection are the problems with the quantities used to characterize radiation quality. Radiation quality has been defined in various ways by various organizations. Currently most recommended quantities for radiation quality (for radiation protection purposes) include consideration of macroscopic physical characteristics of the radiation field and estimates of its relative biological effectiveness. However, knowledge of the relevant biologic effects is both limited and evolving, resulting in radiation quality metrics that are uncertain and subject to frequent revision. In addition, there are conceptual incoherences between some recommended methods to estimate radiation quality, e.g., $Q(L)$ for charged particles *versus* $Q(E)$ for neutrons. Thus, there is an unmet need for a quantity to characterize radiation quality in way that is measureable, traceable, calculable, has uncertainties that are known, and whose definition and numerical values are independent of radiobiologic considerations. Despite decades of research, there is growing consensus that the radiobiology is astoundingly complex. It is so complex, in fact, that it appears intractable to model the response of human systems with simple, empirical, or even first principles approaches of physics. Given that a model to “bridge” physics and biology cannot be built any time soon, it appears necessary for both communities to utilize other approaches to addressing the needs to specify radiation quality, e.g., as mentioned above.
The written questions posed to the workshop panelists probed the idea of finding a way forward in light of the present-day intractability of modeling clinical radiobiology in humans. Observational

methods, such as epidemiologic studies and clinical trials, may offer the best hope of gaining new knowledge within the next decade. Observational studies seek to correlate exposure with clinical outcomes. As such, high quality measurements of exposure and outcome are essential. As noted above, the metrology for exposure is only partially developed. The quantity absorbed dose is fundamentally solid and highly satisfactory. However, quantities for radiation quality are generally problematic because they are either not measureable, traceable, reproducible, applicable, or relevant. The problems are severe for high LET radiations, such as high-energy neutrons caused by therapeutic proton beams.

With survival rates approaching 70% in adult cancer patients, it could be fairly said that we know how to sterilize most tumors. However, in recent decades, long-term studies revealed a high prevalence of radiation-induced late effects. The application of physical approaches to reduce late effects has huge potential to improve outcomes for millions of patients each year. Prominent examples are the use of heavy ion beams; less discussed but no less relevant are modifications to current x-ray treatment techniques to reduce out-of-field exposures. The radiation dosimetry and, more generally, metrology urgently need to be extended and standardized to support research and clinical activities that will improve outcomes by the application of physical principles and methods. Many strengths of PTB could be brought to bear on these issues, including expertise in neutron dosimetry and spectrometry, proton dosimetry, operational dosimetry, and others. PTB also has expertise and experience that is well suited to developing a new quantity for radiation quality, such as, radiation quality derived from temporal and spatial properties of the track structure and nanodosimetry. Importantly, PTB is well positioned to successfully lead new areas of research and metrology in support of radiation therapy research. In fact, PTB enjoys a strong reputation for leading and participating in multi-disciplinary, multi-institutional research collaborations.

In summary, there is a strong need to continue to develop and extend established metrology for the quantity of radiation absorbed dose, especially for therapeutic beams of protons and heavier ions. In addition, new research and development are needed to develop a more solid foundation of knowledge upon which to construct new quantities to characterize radiation quality. It appears highly likely that this will require improved understanding of how radiation transport on an interaction-by-interaction basis. This should include an improved understanding of how radiation deposits energy deposit in matter on multiple spatial scales, ranging from nanometers to centimeters.

Computational, experimental, and possibly theoretical methods show considerable promise toward new discoveries in this area. The PTB's stellar reputation in radiation dosimetry is a direct consequence of scientific excellence, vision, and engagement in a wide variety of practical metrology projects with external collaborators.

SCHETTINO:

Biological Radiation Effects are the result of a complex chain of physico-chemical-biological events. Improved knowledge and measurements for all elements of the chain are needed.

Due to the complexity of the issue, there is no commonly agreed quantities or parameters which could be used to fully describe the biological radiation effects. Over the past 50 years, a variety of approaches and quantities have been proposed. They all have their benefits and shortfalls. As a result, whilst the medical community continues to strongly rely on the absorbed dose and the Relative Biological Effectiveness (RBE) concept, the research and pre-clinical community is focused on validating alternative approaches such as micro- and nano-dosimetry. It must be noted, that quality assurance and standards in the pre-clinical research is significantly lacking which represents an

obstacle for the validation of the micro-, nano-dosimetry approach and establishing robust links with the biological effects which the clinical community could adopt.
PTB has unique capabilities (i.e. microbeam and microdosimeters) and significant expertise in the dosimetry area. It can therefore contribute to further improve the knowledge of the initial events of energy deposition into biological samples. However, to make a significant impact into the field of Biological Radiation Effect, it would be necessary to link with established radiobiology and pre-clinical research institutions to provide input into the standardization activities of the field, data and analysis for correct radiobiological interpretation and make sure to develop a measurement program in line with the needs and directions of the pre-clinical community.

VERHAEGEN:
Questions… (arizing from 2015 workshop in Barcelona):

- Multiscale model
  - Why is nanodosimetry not sufficient if we agree DNA is the target, is this not a superior approach over LET?
  - Do we still need quantities like LET if we know how to measure/calculate cluster distributions (are only ionizations important?)?
  - Does it make sense to believe in both micro and nano-targets?
- Sensitivity of models to uncertainties
  - May lead to conclusions with high uncertainties
- In radiobiology models (TCP, NTCP) we now mostly feed dose distributions, and an estimate for RBE
  - Do we need much more complex models that have dose&radiation quality information per voxel?
  - Do we need tools such as Damage-cluster-density-Volume Histograms (analogy of Dose Volume Histrogram)?
- Should we do more cell culture experiment?
  - Or have we learned all we can from them?
  - Time for image-guided precision-irradiation of tumor-bearing animals?
  - Or something in between with spheroid tumor models?
  - Is only proton/carbon work important or is there important work to do for photons?
- Use automated microscopy and image analysis (not visual imaging and manual scoring)

Conclusions:

- There's more to proton therapy than proton dose calculations
  - And even these need improvement
    - Cross sections
    - Stopping powers
    - Imaging
- Need for physics input for verification imaging (PET, PG, proto-acoustics)
- Need for physics input in distributions of LET, DNA damage, dose rate, neutron dose,…
- Need to go beyond cell culture experiments
  - Small Animal RadioTherapy (for protons)
  - Much physics input needed here

- Issues in proton dose calculation (slides 14-19)

large uncertainties for transfer of CT# to stopping powers of different tissue types
improvement may be possible by use of dual energy CT
Challenges:

i. accurate collisional and nuclear stopping powers of water and different tissues
ii. Physics input in imaging methods to derive dose calculation quantities

- Imaging for proton (range)verification (slides 20-27)
  Sketch of PET methods, prompt gamma emission, Proto-acoustic imaging;
  These methods are not yet used in the clinics and there is still a lot of work required
  Challenges:
  i. Accurate knowledge of cross section data
  ii. Accurate kinetic energy-acoustic energy transfer data
  iii. Uncertainties/sensitivities
  iv. Dose instead of range verification

- Cluster analysis very likely to be used in addition to dose (slide 33)
  Challenges:
  i. Comparison and standardization of cluster analysis methods
  ii. Experimental alidation necessary

VILLAGRASA:

It is well-known that different radiation qualities (meaning particle and energy) have a different biological impact. This can be measured in vitro irradiating a cellular layer and calculating, for instance, the survival fraction curve of the cells or other biological end-point. Nevertheless, this measurement is always done taking the absorbed dose to the cell layer, as the quantity used to quantify the energy deposition in the target. This representation (biological effect vs absorbed dose) is the base of the impossibility to obtain a single value relating the irradiation to the biological effect. Therefore, it is nowadays impossible to predict what will be the biological consequence of an irradiation if we do not have any measurement of similar irradiation characteristics.

There is a quite broad consensus to understand that this problem comes from the fact that the absorbed dose used to characterize the exposure is a too imprecise description of the energy deposition at the origin of the biological effects because those arise from molecular responses and thus it is the topology of the energy transfer points at the molecular scale (nanometric) that could be directly related to the effect. Even if the absorbed dose keeps to be useful to describe the exposure with regard to macroscopic behaviors, the fact that nowadays we are still unable to define a new metrological quantity relating the IR characteristics to the initial biological effects shows our lack of knowledge in the whole mechanism behind and have important consequences in some applications as in the case of hadrontheray. Besides, this mechanistic knowledge that must be behind the definition of a new quantity could also be very useful in radioprotection in the low dose region. Therefore, and from my point of view, the need of research in this domain makes no doubt and it meets the missions of a metrological laboratory.

The BioQuaRT project in which PTB was the coordinator, has pointed out some candidates for this new quantity that can be measured with a nanodosimeter of the characteristics of the Ioncounter at PTB. Nevertheless, the relation between the nanodosimetric quantities and the biological effect must still be deeply investigated and thus, the expertise on the use and development of the nanodosimeter should be maintained. Taking into account that nowadays only a very few

experimental devices for nanodosimetry exist, this strategic position of the PTB group for the definition and metrological characterization of the new quantity should be preserved.

On this issue, Monte Carlo simulations are an essential tool in the experimental development and understanding of the measured data. Historically at PTB both developments (device and MC simulations) were done in parallel and fed each other. This should always be the case as MC simulations can also be used to go further than the reproduction or prediction of the measured physical data to better understand the mechanism of the biological effects. Even if this type of simulations are not the role of a metrological laboratory, researchers working on the field of nanodosimetry should always keep being involved on these developments by establishing collaborations in research projects with other research groups.

The use of the microbeam in radiobiology experiments offers the opportunity to PTB of establishing research partnerships with other groups investigating radiobiological affects which offers several advantages: PTB has a privileged access to the results needed for the definition of the nanodosimetric quantity and it has the correct dosimetric characterization of the experimental results (often a problem in the biological data when taken from the literature). It has also the possibility of characterizing the used irradiation from the nanodosimetric point of view.

In sum, PTB has nowadays the experimental facilities, devices and simulation skills needed for keeping the research on the physical characterization of ionizing radiation related to the biological effect. There is still a great need of research in this field that should lead to the definition of new quantities and portable detectors needed in some applications of the use of ionizing radiation. In Europe, the PTB group in charge of this activity is leader among metrological laboratories and has an strategic network with other research teams in the field that should be encouraged.

2 Analysis of the Stakeholder Feedback

This second part summarizes statements and recommendations that were extracted from the stakeholder input in form of answers to the questionnaire, presentations at the workshop and post-workshop summaries.

2.1 Statements on Metrological and Research Needs

2.1.1 Statements from the questionnaires

- (Q1) In nanodosimetry, the calibration of target and afterwards the determination of the scaling factor would definitively benefit from improving the accuracy of the determination of biological radiation effects
- (Q1) Increasing the accuracy and reproducibility of biological assays would certainly be a big benefit for radiobiology, radioprotection and radiotherapy.
- (Q1). The current limitations in metrology lead to large uncertainties in risk projections, and these are obstacle to developing strategies for improving treatment outcomes
- (Q1) Effective and useful treatments need better quality of underlying physics and biology data in order to improve quality.
- (Q2) Physical quantities have then to be compared with radiobiological cross sections derived from cell survival curves. The radiobiological quantities are those that would require a significant improvement of the accuracy
- (Q2) Electron-impact cross-section data for reference materials (such as water or water-equivalent plastic, biological targets, gold) need to be determined with better accuracy, especially for electron energies below 1 keV
- (Q2) In microbeams there is a need for better specification of the amount of radiation delivered. It would be useful to have a track-structure-based parameter that can be used to describe “radiation quality” in the context of single particle irradiations
- (Q2) quantities for radiation quality are generally problematic because they are either not measureable, traceable, reproducible, applicable, or relevant
- (Q2) Improvement in the measurement of micro and nano-dosimetry as well as in the cellular and animal response is required.
- (Q2) abandoning the concept of LET we aim to understand the dependence of response on local energy deposition density, a direction that has been explored by the developers of the LEM model with promizing results.
- (Q3) Any possibility to describe and to measure properties of particle track structure, in particular in complex and unknown radiation fields would obviously have a great impact to increase both the effectiveness of radiation therapy and the accuracy of risk assessment.
- (Q3) The definition of a physical quantity related to the quality of the radiation field would be desirable, perhaps related to biological radiation effects. Also, accurate, standardized

protocols for carrying out biological experiments should be defined in order to investigate this correlation

- (Q3) Before we can start convincing the doctors to buy into new dosimetric concepts, they need to be correlated with a medical or radiobiological outcome. Only after the outcome criteria is established, can we start seriously looking for a dosimetric quantity that will correlate with it.
- (Q3) I wouldn't rate this very high, since the uncertainty of risk assessment is due to incomplete biological knowledge, not physics. Particle radiation therapy is already quite effective with the currently applied and validated models
- (Q4) There seems to be a direct link between the direct physical radiation effects to a biological end point
- (Q5) An accurate correlation between the radiotracer or nanodrug concentration to be injected and the biological radiation effects should be determined and this requires a metrological standardization.
- (Q5) Radiobiological measurements require standardization. This is likely to be the single main step with high impact on improving our understanding of radiation biological effects

2.1.2 From the workshop presentations

Panel discussion of session 1

- more accurate values for ionisation potential or stopping power (Krämer)
- important topics at PTCOG: uncertainties (range, dosimetry, ionisation potential); huge differences between LET-paintings and dose-paintings (Schulte)
- top priority to be investigated:
    - Schulte: evaluate ionisation clustering and benchmark against existing models, e.g. LEM
    - Newhauser: solidify metrology of medical exposures by getting a good model of the physical level, which is usable to predict the patient's outcome. The work at PTB should be tied to lay the foundation for the physics and the interface with the biology for medical exposures.
    - Krämer: at a level as close as possible to the final outcome
    - Garty: define exactly what you want to measure or what the number you are measuring is trying to model; before developing the metrology, you need to define your relevant endpoints.

Presentation Rothkamm

- Biological dosimetry requires calibration curves for different radiation qualities – nanodosimetric approach would be helpful

Presentation Verhaegen

- accurate collision and nuclear stopping powers of water and different tissues, accurate knowledge of cross section data; fundamental data are also important for imaging
- Cluster analysis of incidence of DNA SSB and DSB as function of LET: large discrepancies between different simulation codes due to large uncertainties in fundamental physical data
- Cluster analysis very likely to be used in addition to dose; challenges:
    - Comparison and standardisation of cluster analysis methods
    - Experimental validation necessary

Presentation Villagrasa

- simulations without the chemical stage showed a very good correlation with the shape of the biological curve when counting all ionization clusters with a threshold of 50 eV
- the microbeam was one of the main tools to try to understand this mechanism

Presentation Conte

- Nanodosimetry is capable to bridge the gap between physics and radiobiology.
- The main hypothesis, on which experimental nanodosimetry is basing on: “The ionization processes rule the DNA damage”
- Ionizations are a measurable quantity; assumption: the amount of all the interaction processes scale with the amount of ionizations.
- physical quantities are proportional to radiobiological effects: $F_k \sim \sigma_{biol}$

Presentation Schulte

- It appears that the number of clustered (not single) ionizations occurring in nanoscopic volumes is the most important parameter in radiation response
- Ionisation clustering focuses on the starting conditions for all the biology that is following after; as it will be (almost) impossible to model the whole process (= physics + chemistry + biology), so why not focus on the starting conditions with the hypothesis becoming: under equal starting conditions and equal biological systems you should get an equal biological effect
- Optimised particle treatment planning of the future: based on metrology of clustering of ionisations in tumour and normal tissues
- Future metrology/research needs
    - Experimentally validated treatment planning codes that calculate the ionisation clustering levels in standardised nanoscopic volumes
    - Radiobiological studies that validate the equal clustering = equal effect hypothesis in tumour and normal tissue models for the most relevant particles (protons, helium, carbon, oxygen)

Presentation Tinnefeld

- DNA can be used to build structures of various shapes with sizes in the order of 100 nm x 100 nm. Starting point is a circular DNA strand from a phage with a known sequence, the approximate length is 8000 bp (~ 3 µm). Shaping is done by application of specified oligonucleotides having a specified sequence of bases. Due to the specific sequence of the bases, the oligonucleotides will connect to the DNA strand at those points which match to their specific sequence of bases. With this technique the DNA strand can be shaped almost arbitrarily. Additionally, the oligonucleotides can be equipped with some functionality like a fluorescent dye, so one knows exactly where the dye is located on the DNA strand.
- Possible application in radiation physics: DNA-dosimeter: attach DNA nanostructure between two electrodes and measure the change in the electrical characteristics in dependence of the radiation field
- Idea for optical detection of strand breaks: put DNA nanostructure under tension such that it falls apart upon a single strand break and visualize this e.g. by a change of the fluorescence resonance energy transfer

Presentation Dörr

Presentation Dorn

- Collaboration with PTB in measurement of fully differential electron interaction cross sections with biomolecules
- Transfer of technique to measure large biomolecules in relevant surrounding
- Most of the damage caused by ionizing radiation by electron molecule interaction
- Very low energy electrons (< 10 eV), which are below direct ionization level, play also a role
- Experimental data provide data for track structure calculations and an experimental data base. Also provide benchmark for calculations and check if physical processes used are complete and good enough
- Questions:
    - Are data for track structure calculations correct
    - Do we need fully differential cross sections
    - What is the effect of the environment (condensed phase effects)?

Presentation Krämer

- LEM model: Separation of physics from biology
    - Physics: radial dose distribution on micrometer scale; overlap critical target (= cell nucleus) with local dose distribution of ion track

- Biology: Biological effect is taken from known photon response of biological systems (cell cultures); used as input data for local dose effect calculations

- In newer version of LEM 4 also ionization clustering is taken into account
- Recommendation to PTB: go more into biology; development of biological detection devices which are more reliable

Presentation Newhauser:

- Task for a metrology lab (= PTB)
  - Measure the physical properties of the radiation fields applied so to have retrospective a way to relate late effects to doses received in earlier treatments; this implies characterization of the secondary radiation and out of field radiation in therapy and diagnostics.
  - These parameters should be measured with standard procedures and uncertainties should be assigned
  - This will provide the input data for epidemiologists who later will come up with risk models; this in turn will enable improvement of radiation treatment planning to minimize late effects, while preserving maximum tumor control

Presentation Schettino

- Clear and rigorous definition of "radiation quality" required
- Are we able to characterize a radiation field in such a way that if the characterizing quantities do not change, the biological effect is the same?

2.1.3 Statements from the workshop discussions

HORNHARDT:
We need more interdisciplinary approaches:
In a new project we include microbeam and track stucture calculation in a new project. This will provide and represent the full picture. We (biologists) need to get more information of what can be provided by PTB and the physicists.

SAUERBREY:
Of what we have heard these days the tasks are only part in the realm of PTB and what they can do. For me it is not completely clear what has to be measured. But if there is anything to do it calls for on an European level of collaboration. Collaboration with institutions with capabilities which PTB does not have. Helmholtz centers may be a good partner and I can offer to start such a discussion.
ICSD oder DSB clustering?

Newhauser:
How would then one take into account the additional steps between damage and the appearance of the tumor? It seems that the clustering is focusing to initial damage …
Schulte: No, it is focusing on the starting conditions for all the biology that is following after. Biology will depend on the genetic profile, it will depend on many things. I believe it is very difficult to simulate all of the biology, and to model all of it. So why not focusing on the starting conditions, and then the hypothesis becomes: under equal starting conditions and equal biological systems you should get an equal biological effect.

SCHULTE:
I mentioned by priorities in my talk. Important would be evaluating the ionization clustering, which was also mentioned by F. Verhaegen. The clustering should be evaluated against existing models like LEM, also considering the different LEM versions as version 1 is used clinically but version 4 is offering improvement. Also, Rob Steward's approach with RBE based on DSB clustering. This should be evaluated as described by F. Verhaegen during his talk. There should be a collaborative approach with good physics support.

GARTY:
Thinking about metrology for radiobiology, you should pay attention to define exactly what you want to measure or what the number you are measuring is trying to model. Because you can get one parameter which could correlate fantastically with killing of the tumor but there is no reason to believe that this could be related to acute early or late effects or the formation of secondary tumors. I find it hard to believe that one number is enough. This is the problem with RBE, everyone uses the term RBE depends on the endpoint. And the RBE for DSB formation, for dicentrics or for micronuclei are all different. So before developing the metrology, you need to define your relevant endpoints.

SCHULTE Presentation:
" - Although not fully proven, it appears that the number of clustered (not single) ionizations occurring in nanoscopic volumes is the most important parameter in radiation response.
- The change in cluster yields (in particular those larger than 2-3 ionizations per DNA segment) per unit dose has a striking resemblance to the LET dependence of RBE, but better reflects differences between particles of the same LET."
"Summary of Future Metrology/Research Needs
- Experimentally validated treatment planning codes for calculating high and low macroscopic doses in particle therapy beams
- Experimentally validated treatment planning codes that calculate the ionization clustering levels in standardized nanoscopic volumes
- Radiobiological studies that validate the equal clustering = equal effect hypothesis in tumor and normal tissue models for the most relevant particles (protons, helium, carbon, oxygen)"

Schulte summary (Newhauser):
-Validation of treatment codes and models.
-Validation of microscopic and nanoscopic dose distributions.
-Radiobiological studies to validate e.g. nanodosimetric approaches to biological effects
-Develop new approaches to biological effectiveness than just the traditional

Verhaegen summary (Schäffter): need for

- better cross sections, stopping powers, imaging
- verification imaging
- physics input (LET, DNA damage, dose rate neutron dose,..
- go beyond cell experiments: small animal radio therapy for protons

(this was requested by many participants to overcome the present shortcomings in the radiation action concepts.´

2.1.4 Statements from the post-workshop feedback

- The dose alone does not explain the differences in the effectiveness of radiation at biological level.
- There is the need to identify new metrological quantities capable to describe and predict the biological effects of exposure to the radiation.
- A marked reduction of the uncertainties of radiobiological data, however desirable, seems, by their very nature, difficult to achieve.
- nanodosimetry seems to be able to identify measurable quantities that are proportional to specific radiobiological end points
- The knowledge of track structures of different radiation qualities has to be improved, as well as the understanding of biological radiation effects like inflammation, immune response and effects on the microenvironment
- Another longstanding problem across all of radiation protection are the problems with the quantities used to characterize radiation quality. Radiation quality has been defined in various ways by various organizations.
- there is an unmet need for a quantity to characterize radiation quality in way that is measurable, traceable, calculable, has uncertainties that are known, and whose definition and numerical values are independent of radiobiological considerations
- research and development is needed to develop a more solid foundation of knowledge upon which to construct new quantities to characterize radiation quality.
- Biological Radiation Effects are the result of a complex chain of physical-chemical-biological events. Improved knowledge and measurements for all elements of the chain are needed. Due to the complexity of the issue, there are no commonly agreed quantities or parameters which could be used to fully describe the biological radiation effects.
- quality assurance and standards in the pre-clinical research is significantly lacking which represents an obstacle for the validation of the micro-, nanodosimetry approach and establishing robust links with the biological effects
- Nevertheless, the relation between the nanodosimetric quantities and the biological effect must still be deeply investigated

2.2 Recommendations of the Expert Panel

2.2.1 Recommendations from the questionnaires

- (Q1) There is crucial need to harmonize dosimetry measurements supporting radiobiological experiments, particularly those pertaining to clinical or pre-clinical studies. PTB should take an active role in both supporting and requiring this. PTB has sufficient expertise to establish standard operating procedures for performing irradiations and dosimetry in both cellular systems and, importantly, for animal irradiations, paying attention to irradiator settings (including, for example, X-ray machine filtration).
- (Q4) I do not think it is the job of PTB to go into studying the pathways leading from radiation physics and chemistry to medical outcomes.
- (Q5) I don't think that, other than work on metrology of the irradiation systems, PTB should get involved in the bioassays.
- (Q6) PTB should be to provide reference radiation fields (that are already available, including the microbeam facility) for combined physical and radiobiology experiments. These should be carried out under well-defined setups and protocols with the purpose of standardizing in-vitro and in-vivo investigations. the creation of a common database for accurate electron- or charged-particle-impact cross-section data for use in Monte Carlo simulations should be aimed at.
- (Q6) I do not think it is reasonable to have PTB heavily involved in outcome research. Based on what I saw PTB has neither the facilities nor the expertise to do any significant biological studies.
- (Q6) The Role of PTB in my view should be in developing robust parametrizations for track structure that can be correlated with outcome data generated elsewhere. This would require a strong experimental nanodosimetry program supported by (and supporting development of) track structure modeling
- (Q6) PTB should also take an active role in ensuring that the outcome studies be performed in as rigorous and standardized way as possible.
- (Q6) PTB has some unique experimental facilities (microbeam, low energy beam line, neutron dosimetry) which could offer "standardized" service.
- (Q6) PTB's role could also be similar to US-based NIST, i.e. providing standardized data sets

2.2.2 Recommendations from the workshop presentations

- There is crucial need to harmonize dosimetry measurements supporting radiobiological experiments, particularly those pertaining to clinical or pre-clinical studies. PTB should take an active role in both supporting and requiring this. PTB has sufficient expertise to establish standard operating procedures for performing irradiations and dosimetry in both cellular systems and, importantly, for animal irradiations, paying attention to irradiator settings (including, for example, X-ray machine filtration).

- PTB should be to provide reference radiation fields (that are already available, including the microbeam facility) for combined physical and radiobiology experiments. These should be carried out under well-defined setups and protocols with the purpose of standardizing in-vitro and in-vivo investigations. The creation of a common database for accurate electron- or charged-particle-impact cross-section data for use in Monte Carlo simulations should be aimed at.
- The Role of PTB in my view should be in developing robust parametrizations for track structure that can be correlated with outcome data generated elsewhere. This would require a strong experimental nanodosimetry program supported by (and supporting development of) track structure modeling
- PTB should also take an active role in ensuring that the outcome studies be performed in as rigorous and standardized way as possible.
- Considered that PTB already has excellent expertise on this field, and one of the few operative detectors worldwide, it should spend a strong effort to develop a new metrology of ionizing radiation based on nanodosimetry
- Taking into account that nowadays only a very few experimental devices for nanodosimetry exist, this strategic position of the PTB group for the definition and metrological characterization of the new quantity should be preserved
- The use of the microbeam in radiobiology experiments offers the opportunity to PTB of establishing research partnerships with other groups investigating radiobiological affects which offers several advantages: PTB has a privileged access to the results needed for the definition of the nanodosimetric quantity and it has the correct dosimetric characterization of the experimental results (often a problem in the biological data when taken from the literature). It has also the possibility of characterizing the used irradiation from the nanodosimetric point of view
- Historically at PTB both developments (device and MC simulations) were done in parallel and fed each other. This should always be the case as MC simulations can also be used to go further than the reproduction or prediction of the measured physical data to better understand the mechanism of the biological effects. Even if this type of simulations are not the role of a metrological laboratory, researchers working on the field of nanodosimetry should always keep being involved on these developments

2.2.3 Recommendations from the post-workshop feedback

- a prepositive action by the PTB; we cannot expect that the demand for new metrological procedures comes by the users, in the absence of appropriate and stimulating proposals.
- Considered that PTB already has excellent expertise on this field, and one of the few operative detectors worldwide, it should spend a strong effort to develop a new metrology of ionizing radiation based on nanodosimetry
- There is no biological control/ marker for different doses (high and low dose) and effects of different radiation qualities in the addressed tissues. Therefore a cooperation of physicists

and medical/ biological researchers is necessary. The department 6.5 has excellent knowledge and facilities to contribute to this kind of research

- In dem angesprochenen Feld kommt man ganz ohne Biologie, nur mit reiner Physik, nicht weit. Sich ein bisschen mehr in Richtung Biologie zu bewegen wäre allerdings schon notwendig, erst recht, wenn das die Wunschrichtung der Chefs ist. Experimentelle Expertise, zB auch im Apparatebau, wäre ja vorhanden.
- The metrology of proton and heavier ion therapies is increasingly important, yet current capabilities are surprizingly insufficient or, in some cases, entirely lacking. PTB should continue to develop the metrological capabilities to meet the current and future needs of the radiation medicine.
- PTB also has expertise and experience that is well suited to developing a new quantity for radiation quality, such as, radiation quality derived from temporal and spatial properties of the track structure and nanodosimetry. Importantly, PTB is well positioned to successfully lead new areas of research and metrology in support of radiation therapy research.
- PTB has unique capabilities (i.e. microbeam and microdosimeters) and significant expertise in the dosimetry area. It can therefore contribute to further improve the knowledge of the initial events of energy deposition into biological samples. However, to make a significant impact into the field of Biological Radiation Effect, it would be necessary to link with established radiobiology and pre-clinical research institutions
- Taking into account that nowadays only a very few experimental devices for nanodosimetry exist, this strategic position of the PTB group for the definition and metrological characterization of the new quantity should be preserved
- Historically at PTB both developments (device and MC simulations) were done in parallel and fed each other. This should always be the case as MC simulations can also be used to go further than the reproduction or prediction of the measured physical data to better understand the mechanism of the biological effects. Even if this type of simulations are not the role of a metrological laboratory, researchers working on the field of nanodosimetry should always keep being involved on these developments
- The use of the microbeam in radiobiology experiments offers the opportunity to PTB of establishing research partnerships with other groups investigating radiobiological affects which offers several advantages: PTB has a privileged access to the results needed for the definition of the nanodosimetric quantity and it has the correct dosimetric characterization of the experimental results (often a problem in the biological data when taken from the literature). It has also the possibility of characterizing the used irradiation from the nanodosimetric point of view

3 Conclusions by the authors of this report

This section reproduces the view of Marion Bug on the key outcome of the workshop, a summary of key statements and recommendations by Gerhard Hilgers and conclusions on the future strategy of department 6.5 by Woon Yong Baek. The fact that these texts are listed explicitly does not imply that they are not endorsed by the other authors.

By the time of the workshop, Marion Bug was a PostDoc and leader of working group “track structure simulation”. In the meantime, she is working in the acoustics division of PTB. Until the reorganization of 2016, Gerhard Hilgers used to be the leader of the working group “nanodosimetry”. From January 2016 to April 2017 Woon Yong Baek was deputy head of department “radiation effects” and leader of the working group “condensed phase effects”.

3.1 Marion Bug: Summary of the expert panel workshop (January 2017)

- **Interdisciplinary approaches** should be opted for on an international level of collaboration with skilled partners (Hornhardt, Newhauser, Rothkamm, Sauerbrey, Schulte, Verhaegen)

- **Metrology for radiobiology (Garty, Hornhardt, Rothkamm, Schettino), medical exposure (Newhauser, Verhaegen) and epidemiology (Newhauser, Schulte)**
  Dose calculation and radiation quality description for validation of biomarkers (Hornhardt, Rothkamm). A description of radiation quality which is related to the DSB formation would be important as it is often observed in the clinics that equal dose distributions lead to very different RBE distributions (Verhaegen). “There is a quite broad consensus to understand that … the absorbed dose used to characterize the exposure is a too imprecise description of the energy deposition at the origin of the biological effects because those arise from molecular responses and thus it is the topology of the energy transfer points at the molecular scale (nanometric) that could be directly related to the effect.” (Villagrasa). However, quality assurance and standards in pre-clinical research are lacking and, therefore, disable the validation of micro- and nanodosimetric approaches and establishing robust links with biological effects (Schettino).
  Biological endpoints of interest have to be exactly defined and the respective RBE has to be separately studied, as the outcome of one endpoint cannot be directly related to another (Garty). For standardization activities and analysis of radiobiological data, a measurement program needs to be developed in line with needs and directions of pre-clincal community (Schettino).
  Dosimetry and description of radiation quality for radiobiological experiments should be improved (Hornhardt, Rothkamm). For example, Schettino states that 93% of published biological experiments are not reproducible because there is not enough information. In his point of view, this is due to the lack of metrology in radiobiological work, which NPL aims to improve. Also the NIH plans on reviewing new publications to ensure consistent reporting on the dosimetry (Garty).
  Particularly in low-dose delivery, as for example in radiation protection, dosimetry has to become more accurate (Schulte, Villagrasa).
  Medical exposures requiring solidified metrology are out-of-field dose (Hornhardt, Newhauser) and neutron exposure (Newhauser), both having a high potential to lead to secondary cancer induction in conventional and hadron therapy. Also nanomedicine (in

particular the use of metallic nanoparticles) and radio-immunotherapy as promizing strategies to improve the outcome of RT with photons (Gargioni) would profit from standardization.

- **Track structure related quantity** of high interest
  Required for validation of codes and models for RT with respect to nano- and microscopic dose distributions (Schulte, Villagrasa) and to develop new approaches to biological effectiveness (Schulte). Also Verhaegen has the opinion that "ionization cluster analysis is very likely to be used in addition to dose" (Verhaegen) with challenges being their experimental validation and a standardization of the cluster analysis methods.
  Monte Carlo simulation tools are indispensable to understand the biological data, but have to be validated (Verhaegen, Villagrasa) and their basis data have to be determined with low uncertainty (Krämer, Verhaegen, Villagrasa).
  "There is an unmet need for a quantity to characterize radiation quality in way that is measureable, traceable, calculable, has uncertainties that are known, and whose definition and numerical values are independent of radiobiologic considerations. Despite decades of research, there is growing consensus that the radiobiology is astoundingly complex" (Newhauser)
  Schulte's hypothesis: under equal starting conditions and equal biological systems you should get an equal biological effect. Hence, the complex biological processes may not have to be simulated in detail. As a first step in the DNA damage formation, ionization clustering should be evaluated against existing models like different versions of LEM or DSB clustering (Schulte, Verhaegen) within a collaborative approach.
  Different opinion Krämer: cell-kill painting in hadron therapy to directly observe the biological endpoint without any quantity in-between. This argument was waived by U.Schneider whose opinion is that cell killing is still far away from tumor tissue as inflammation processes and the complex microenvironment in the tumor influence on the biological outcome.
  "PTB also has expertise and experience that is well suited to developing a new quantity for radiation quality, such as, radiation quality derived from temporal and spatial properties of the track structure and nanodosimetry. Importantly, PTB is well positioned to successfully lead new areas of research and metrology in support of radiation therapy research."(Newhauser)

- Even **basic data** required: cross section data with uncertainties (e.g. related to PET imaging) and stopping powers of water and biological tissue and physical input related to the track structure or DNA damage (Verhaegen). A large source of uncertainty is, for example, the ionization potential used in the Bethe-Bloch equation (Krämer), where a difference in 2 eV corresponds to half a millimeter in range, which is significant.

3.2 Gerhard Hilgers: Important points from the workshop (January 2017)

3.2.1 Statements

- more accurate values for ionisation potential or stopping power
- accurate collision and nuclear stopping powers of water and different tissues, accurate knowledge of cross section data; fundamental data are also important for imaging
- Cluster analysis of incidence of DNA SSB and DSB as function of LET: large discrepancies between different simulation codes due to large uncertainties in fundamental physical data
- fully differential electron interaction cross sections with biomolecules provide data for track structure calculations and an experimental data base. Also provide benchmark for calculations and check if physical processes used are complete and good enough
- What is the effect of the environment (condensed phase effects)?
- The dose alone does not explain the differences in the effectiveness of radiation at biological level.
- There is the need to identify new metrological quantities capable to describe and predict the biological effects of exposure to the radiation.
- The main hypothesis, on which experimental nanodosimetry is basing on: “The ionization processes rule the DNA damage”
- Ionizations are a measurable quantity; assumption: the amount of all the interaction processes scale with the amount of ionizations.
- physical quantities are proportional to radiobiological effects: $F_k \sim \sigma_{biol}$
- Ionisation clustering focuses on the starting conditions for all the biology that is following after with the hypothesis becoming: under equal starting conditions and equal biological systems you should get an equal biological effect
- Clear and rigorous definition of “radiation quality” required; there is an unmet need for a quantity to characterize radiation quality in way that is measureable, traceable, calculable, has uncertainties that are known, and whose definition and numerical values are independent of radiobiological considerations
- define exactly what you want to measure or what the number you are measuring is trying to model; before developing the metrology, you need to define your relevant endpoints.
- Future need: radiobiological studies that validate the equal clustering = equal effect hypothesis in tumour and normal tissue models for the most relevant particles

3.2.2 Recommentations

- There is crucial need to harmonize dosimetry measurements supporting radiobiological experiments, particularly those pertaining to clinical or pre-clinical studies. PTB should take an active role in both supporting and requiring this. PTB has sufficient expertise to establish standard operating procedures for performing irradiations and dosimetry in both cellular systems and, importantly, for animal irradiations, paying attention to irradiator settings (including, for example, X-ray machine filtration).

- PTB should be to provide reference radiation fields (that are already available, including the microbeam facility) for combined physical and radiobiology experiments. These should be carried out under well-defined setups and protocols with the purpose of standardizing in-vitro and in-vivo investigations. The creation of a common database for accurate electron- or charged-particle-impact cross-section data for use in Monte Carlo simulations should be aimed at.
- The Role of PTB in my view should be in developing robust parametrizations for track structure that can be correlated with outcome data generated elsewhere. This would require a strong experimental nanodosimetry program supported by (and supporting development of) track structure modeling
- PTB should also take an active role in ensuring that the outcome studies be performed in as rigorous and standardized way as possible.
- Considered that PTB already has excellent expertise on this field, and one of the few operative detectors worldwide, it should spend a strong effort to develop a new metrology of ionizing radiation based on nanodosimetry
- Taking into account that nowadays only a very few experimental devices for nanodosimetry exist, this strategic position of the PTB group for the definition and metrological characterization of the new quantity should be preserved
- The use of the microbeam in radiobiology experiments offers the opportunity to PTB of establishing research partnerships with other groups investigating radiobiological affects which offers several advantages: PTB has a privileged access to the results needed for the definition of the nanodosimetric quantity and it has the correct dosimetric characterization of the experimental results (often a problem in the biological data when taken from the literature). It has also the possibility of characterizing the used irradiation from the nanodosimetric point of view
- Historically at PTB both developments (device and MC simulations) were done in parallel and fed each other. This should always be the case as MC simulations can also be used to go further than the reproduction or prediction of the measured physical data to better understand the mechanism of the biological effects. Even if this type of simulations are not the role of a metrological laboratory, researchers working on the field of nanodosimetry should always keep being involved on these developments

3.3 Woon Yong Baek: Conclusions for the future research of department 6.5 (March 2017)

3.3.1 Preface

Department 6.5 "Radiation Effects" carries out multidisciplinary research on radiation effects in different length and time scales. The goal of the research is to obtain fundamental insight into the mechanisms of radiation damage to biological systems, to elucidate the interplay of different processes leading to the formation of a biological effect and so to develop a predictive model for radiation damage based on traceable, measurable quantities. The main targets for this research are the optimization of treatment planning in modern radiotherapy such as hadron therapy, IMRT, nanoparticle-enhanced treatment and personalized radiation treatment as well as radiation protection in complex radiation fields appearing in space, air craft, high energy accelerators and out of field exposure in radiation therapy.

3.3.2 State of the art

Great advances have been achieved in dose delivery technologies in the last decade. Image-guided dose delivery systems of newest generation allow a multiadaptive radiation therapy with a precise dose application tailoring the molecular environment of tumors. The technical advances have clearly outpaced the progress in the biological optimization of the treatment planning. As not the applied dose itself but its biological effect is decisive for the success of the treatment, the benefit from the impressive innovations in the dose delivery technologies will remain limited without the improvement of the biological optimization. Along with the high uncertainties in current radiobiological measurements, this improvement is not least hampered by the lack of a proper quantity to describe the biological effectiveness of various radiation types.

Linear energy transfer (LET) is still mainly used to characterize radiation qualities and to compare their relative biological effectiveness although its shortage in describing the tissue response to radiation exposure is well known since several decades. There is general consensus that the biological effectiveness of charged particles depends essentially on their track structure at nanometric level. This is in line with the fact that no single quantity has yet been proved to be generally adequate as a descriptor for radiation action in biological systems. It cannot be excluded that different biological effects emphasize different characteristics of track structure. It is therefore reasonable to find a generic descriptor for the biological effectiveness of various radiation types that is based on the radiation track structure.

The results of the research carried out so far, especially in the framework of the BioQuaRT project, suggest that ionization cluster size distribution (ICSD) and quantities based spatial correlation between ionization clusters are a promising approach to the generic descriptor of the biological effectiveness of ionizing radiation. As it is not a single quantity but a distribution, it contains substantial information on the radiation tracks, enabling the extraction of a number of track-structure-related parameters. Radiobiological measurements conducted at the microbeam facility of PTB revealed that the yields of the studies biological endpoints are strongly correlated with these parameters. The degree of the correlation between each parameter and the yield may depend on the cell types and the biological endpoints.

3.3.3 Proposed research directions

The nanodosimetric method based on ICSD and their spatial correlation will be further developed conceptually as well as instrumentally. A track-imaging detector will be built in order to measure the

three-dimensional track structure over a spatial extension corresponding to a micrometer in tissue. The spatial resolution will correspond to a few nanometers. The ultimate goal is to build a portable instrument that can be used in clinical practice, especially for the characterization of the secondary radiation fields produced by therapeutic beams.

On the one hand, the nanodosimetric detector has the preeminent advantage that it provides a comprehensive picture on the radiation tracks. On the other hand, it has the drawback of measuring only the physical stage of the radiation action. This weak point will be covered by a radiation detector that directly measures the radiation damage in DNA. This so-called DNA dosimeter quantifies the radiation damage by means of the impedance change in nanoscale biomaterial based on DNA-origami. The chemical and early biological stage of radiation-induced damages in biological systems may be selectively investigated using this detector. Noteworthy that the DNA dosimeter measures the integral effect of ionizing radiation while the nanodosimetric detector enables the analysis of the track structure, complementing each other.

On the conceptual side, we will, in close operation with biological and medical research groups, establish a descriptive model for biological effects that unravels the physical part of the radiation action from the biological one to a great extent. Such model, based on quantities derived from radiation track structure and nanodosimetric measurements, would enable a more unique representation of biological effectiveness in dependence of radiation quality, and consequently an extrapolation of radiobiological and epidemiological results to new radiation modalities.

This new model incorporating observable correlation between physical quantities and biological effects will contain parameters that depend on the cell types and biological endpoints. Systematic radiobiological measurements are required to determine these parameter values. The microbeam facility of PTB is well suited for this purpose as it allows a precise delivery of single particles at subcellular level and therefore, the investigation of biological effects of individual radiation tracks.

The microbeam facility will be furthermore used to elucidate biological mechanisms involved in signaling pathways for DNA repair and their dependence of radiation quality. This is pivotal to understand how tumor and normal tissues respond to radiation damage. The understanding of the spatial organizations and of the temporal evolution of the repair network is a key step to control the response of tumor and normal tissues to radiation and helps find a molecular signature or a surrogate marker for the individual radiosensitivity.

Monte Carlo simulations will play an essential role in the research activities of the department. It will be employed to check the detection efficiency of the nanodosimetric detector, to interpret the measured radiation track image, to derive and coordinate the relevant quantities from the track structure. Event by event Monte Carlo simulations are also necessary to evaluate molecular-level-effects on radiation action. This is of particular importance for molecular targeted radiotherapy or therapies involving radio-sensitizing agents where the molecular nature of the tumor and of its environment has a decisive influence on the biological effects.

While the development of efficient and accurate codes for Monte Carlo simulations has reached a high level of standard, the reliability of the simulation results is heavily suffering from inaccurate input data. Unfortunately, the simulation of track structure of charged particle in biological systems is mostly based on the interaction cross sections of their molecular components in gas phase. A theoretical and experimental method will be de developed in order to take into account the possible dependence of the interaction cross sections on the aggregate state of the target medium.

Department 6.5 will be also engaged in research topics regarding the conventional dosimetry. For instance, the stopping power of water for carbon ions in the Bragg peak area is being measured for the first time using a sophisticated experimental technique. These data are important for the estimate of biologically effective dose in tumor volume.

Recently, there is increasing demand for standardization of dosimetry in radiobiological measurements. Numerous radiobiological studies have been carried out up to now. However, the reproducibility and comparability of their results are limited, not least due to the lack of standards for the characterization of the radiation field at the biological probes. Department 6.5 will engage in the development of a methodology to establish the traceability of radiobiological measurements. The nanodosimetric detector may be an appropriate tool for this purpose.

3.3.4 Funding and cooperation

Department 6.5 will intensify cooperation with other institutes like HGF in order to benefit from external expertise in the ongoing research activities. Within the framework of the existing networks such as Helmholtz Association and KVSF, it will endeavor to take a joint approach to current research topics, to start research initiative and to receive external funds. Department 6.5 aims to finance the major part of its research activities by third-party funds and its research activities will be evaluated by external experts at regular intervals.

3.4 Hans Rabus: Vision for the future of department 6.5 (March 2018)

3.4.1 Executive Summary

This chapter of the report outlines the envisioned strategy for the development of PTB department 6.5 “Radiation Effects” considering recent stakeholder feedback including the expert panel workshop “Metrology for biological radiation effects” and from the following sources:

- EURADOS Report 2017/2 summarizing the feedback from a Stakeholder workshop for consultation on the EURADOS Strategic Research Agenda [1].
- The keynote lecture of A. Ahnesjö at the discussion session of the 1st ESTRO Physics Workshop “Science in motion – micro- and nanodosimetry”, Glasgow, 17 and 18 November 2017 [2].
- The current version of the Strategic Research Agenda (SRA) of the Multidisciplinary European Low-Dose Initiative (MELODI) [3].

Driven by the challenges of facilitating biology-based treatment planning in radiation therapy of cancer and of improving the assessment of low-dose risk in radiation protection, the following metrological challenges are addressed:

- *1: Providing metrology support for Monte Carlo simulations and* biophysical modelling *by*
  - Collaboration with the developers of Monte Carlo codes suited for micro- and nanodosimetry simulations.
  - Developing and performing experiments for validation of the results of advanced track structure simulations (i.e. including pre-chemical and chemical phase) at different stages after the physical radiation interaction.
  - Investigation of the effects of the aggregate state on the radiation interaction cross sections and related quantities.
  - Active engagement in EURADOS working groups 6 “Computational Dosimetry” and 7 “Internal dosimetry”.
- *2: Developing concepts and detectors for improved radiation* measurement quantities *by*
  - Solidification of the nanodosimetric dose-response relationship.
  - Performing benchmark experiments at the cellular and tissue level for the correlation of radiation interaction with initial and late radiobiological endpoints.
  - Collaborations with strategic partners to jointly develop a basis for novel quantities in radiation metrology and establish detector standards and standard procedures.
  - Collaboration with clinical partners interested in developing track-structure based treatment planning and of detectors suited for its verification.
- *3: Developing metrology underpinning* radiobiological assays *by*
  - Developing procedures for the standardization and assessment of uncertainties of radiobiology experiments with ion beams
  - Establish flow-cytometry at the microbeam for better characterizations of cell populations.
  - Collaboration with the German collection of microorganisms and cell cultures (DSMZ, Braunschweig) which is actively involved in standardization and testing of cell lines.
  - Engagement in standardization committees at the national and international level.
  - Promoting the establishment of a European Metrology Network for “Ionizing Radiation Effects”.

3.4.2 Drivers

Radiation Therapy – Biology-based treatment planning

> "*You should not see [the lack of legal tasks assigned to department 6.5] that pessimistic. In 20 years all treatment planning in radiation oncology will be based on biology, and there is a demand to develop the metrology to underpin this development.*" (Jürgen Debus, Medical Director of the Heidelberg University Medical Centre, at the 68th convention of the PTB Advisory Committee, 11 May 2017, Braunschweig.)

As indicated in above quote, the development of biology-based treatment planning in radiation oncology is one of the development branches of stratified or personalized medicine. Since the formulation of the ESTRO[1] Vision 2020 for the realization of personalized radiotherapy of cancer, published in 2012, the discussion sessions at the Annual ESTRO Meetings have been addressing this issue, and it also has been a focus topic for the 1st ESTRO Physics Workshop.

As was summarized by A. Ahnersjö in his keynote lecture at this event [2], current activities aiming at biology-based treatment planning are almost exclusively relying on modelling approaches. A number of models have been published in recent years that relate radiation interaction with matter on the microscopic scale (track structure, microdosimetry, nanodosimetry) to predictions of biological outcome, such as cell survival or even tumor control probabilities. As was also highlighted by the expert panel, experimental validation of these models or of the numerical tools employed are lacking even for the predictions of aforementioned physical radiation quantities which are expected to be ultimately used in radiation oncology as additional treatment planning target quantities owing to their independence of biological factors such as individual radiation sensitivity.

Radiation Protection – Low-dose risk

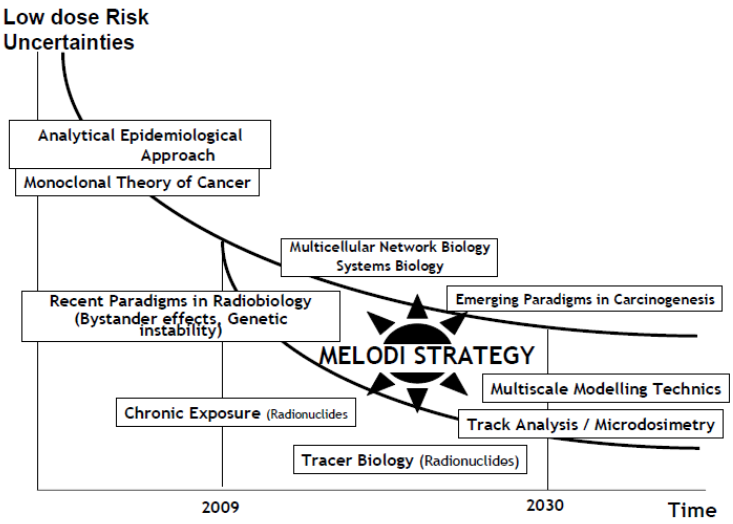
The Multidisciplinary European Low-Dose Initiative (MELODI) is a European Platform dedicated to low-dose ionizing radiation risk research. The purpose of the MELODI Association is to integrate national and European activities in low -dose and low -dose rate radiation research, to define priority scientific goals and to facilitate effective implementation of research. The Strategic Research Agenda (SRA) of MELODI identifies these priority goals and the specific resources, infrastructures and training capabilities needed to further develop low -dose risk research. Among the 44 members of MELODI are radiation protection authorities, 5 European DIs and the 4 European Associations of Radiation Medicine (EANM[2], EFOMP[3], ESR[4], ESTRO[1]). The roadmap of MELODI (see figure) mentions the fundamentals of radiobiology as well as multi-scale modelling technics and track analysis and microdosimetry as essential tools for realizing the goal of reduced low-dose risk uncertainties.

[1] European Society for Radiotherapy and Oncology

[2] European Association of Nuclear Medicine

[3] European Federation of Organisations for Medical Physics

[4] European Society of Radiology



MELODI Road Map taken from the final report of the High Level Expert Group on European Low Dose Risk Research [4].

3.4.3 Challenges

Aforementioned stakeholder needs involve three kinds of challenges for the field of metrology that were highlighted at the expert panel workshop and in the other documents mentioned above, including the MELODI roadmap on low-dose research:

1. To develop and underpin the uncertainty assessment and, thus, the validation of the models and the numerical tools, e.g. Monte Carlo track structure codes, used in the radio-oncology (and radiation protection) research community.

2. To investigate which microdosimetric or nanodosimetric radiation quantities are best suited as a measurand of radiation quality, i.e. the radiobiological effectiveness and to develop suitable detectors for their measurement in primary realizations as well as in clinical practice and for establishing a traceability route.

3. To underpin the augmentation of radiobiological assays in terms of reliability, reproducibility, solid measurement uncertainty assessment and model-based data interpretation.

Across all three challenges, there is a need for standardization of procedures and for tangible as well as written standards which by itself may be considered as a fourth, overarching challenge. In the following, however, the planned activities related to standardization are treated under the targets addressing above challenges.

3.4.4 Targets and implementation

This section describes how the department 6.5 is addressing the aforementioned challenges. Owing to the broad scope of the challenges of which some require transdisciplinary approaches, all actions involve collaboration with key partners and networks, where the role of department 6.5 will be to take care of the metrologically relevant aspects.

1: Providing metrology support for Monte Carlo simulations and biophysical modelling

This target involves several aspects that are addressed by pursuing the following activities:

a. Collaboration with the developers of Monte Carlo codes suited for micro- and nanodosimetry simulations.

Following the respective recommendation from the external review of ionizing radiation metrology in 2013, the collaboration with the Geant4-DNA developing group at IRSN has been extended to an active partnership in the international GEANT4-DNA collaboration, where the implementation of cross sections measured and/or evaluated at PTB as new classes in Geant4 give PTB a high visibility in the community (comparable to LLNL[5]).
Further collaborations have been developed in the recent years with the groups developing the PARTRAC code at HMGU[6] and Uni Pavia and with the TOPAS developer group at MGH[7].

b. Developing and performing experiments for validation of the results of advanced track structure simulations (i.e. including pre-chemical and chemical phase) at different stages after the physical radiation interaction.

The so-called DNA dosimeter approach – originally invented at PTB as prototype detector with true nanometric dimensions allowing the direct detection of lesions in DNA – will be further developed together with collaborators at University of Jyväskylä and Ludwig-Maximilians-Universität München as well as PTB departments 3.1 and 2.4 to measure the indirect radiation effects from radical species formed in water radiolysis. This will allow testing the uncertainty of parameters used in the simulations, such as chemical reaction constants etc.

c. Investigation of the effects of the aggregate state on the radiation interaction cross sections and related quantities.

This will involve the experimental determination of electron emission and fragmentation cross sections of biomolecules clustered with water molecules as well as measurement of the stopping power for carbon ions in water. The latter data are an important benchmark for the validity of approximations made in the simulation codes, while the former data can be used as input for Monte Carlo codes. Collaborations exist with theoretical groups at the University of Alicante and University of Bordeaux and experimental groups at University Frankfurt am Main and Max-Planck-Institute Heidelberg. The efforts will be leveraged by participation in the proposed COST action "Energy deposition in complex biomolecular systems" (under review).

d. Active engagement in EURADOS[8] working groups 6 "Computational Dosimetry" and 7 "Internal dosimetry".

Within EURADOS working group 7, task group 7 "Microdosimetry" is also focused on simulations and has close collaboration with task group 6.2 "Computational micro- and nanodosimetry". Both task groups are undertaking exercises aimed at investigating the comparability of different track structure codes and assessment of uncertainties of simulation results.
The department head, Hans Rabus, is leading EURADOS task group 6.2 and is currently candidate for the future WG 6 chair with the aim to extend the scope of the WG towards experimental validation and towards taking a lead role within EURADOS in addressing the challenges identified in a recent gap analysis [5] as highest priority in the EURADOS SRA, namely investigating the link between track structure and biological effects.

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[5] Lawrence Livermore National Laboratory, Livermore, California, USA

[6] Helmholtz Center Munich for Environmental Health, Neuherberg, Germany

[7] Massachusetts General Hospital, Boston, Massachusetts, USA

[8] European Radiation Dosimetry Group

e. Engagement in standardization activities related to reporting of simulation results and specification of model predicted outcomes.

This is to some extent within the scope of EURADOS activities, but it is envisaged to carry this further into the conventional international standardization scheme. A first initiative in this direction has been initiated by the Multi-scale Monte-Carlo Modeling Lab at MGH and is currently pursued in a collaboration of MGH, PTB, HMGU, IRSN and Uni Pavia.

2: Developing concepts and detectors for improved radiation measurement quantities

Activities for this target will build on the achievements of the BioQuaRT project [6-12], such as a multi-scale model for the relation between track structure and biological effects [7] and findings that, for particular target sizes, nanodosimetric parameters of track structure linearly correlate with the yield of cellular radiobiological effects (presently referred to as universal curve), where the target size depends on the biological endpoint and the proportionality constant depends, primarily, on geometrical properties of the cell type [9-11].
The achievements of BioQuaRT have stimulated the development of similar multi-scale models by other groups [13-15]; the importance of several length scales involved in the induction of biological radiation effects have been experimentally shown in the joint research project "Verbundprojekt LET" of several Helmholtz Centers [16].

This target will be addressed by the department with the following activities:

a. Solidification of the nanodosimetric dose-response relationship.

A key instrument for this will be the PTB "Ion Counter" as the only nanodosimeter worldwide that can be operated as a "transfer detector". Concrete goals are:

- *Closing data gaps in the universal nanodosimetric curves for radiation qualities typical for the entrance region of clinical ion beams where the issue of biological effectiveness (for side effects) is also of high relevance. Experiments of this kind require access to an ion accelerator facility providing clinical ion beams and will presumably be performed in collaboration with MedAustron[9] (under review at the MedAustron research panel).*
- *Testing the validity of the universal curves by performing nanodosimetric measurements in the mixed radiation field of a clinical ion beam (presumably also MedAustron).*
- *Establishing a rigorous uncertainty budget for nanodosimetric measurements including the uncertainty of the target size. This will require more detailed modelling of the measurement process in the nanodosimeter to be performed in collaboration with the mathematics department 8.4. (DFG proposal to be finalized).*

b. Performing benchmark experiments at the cellular and tissue level for the correlation of radiation interaction with initial and late radiobiological endpoints.

A key instrument for this will be the Ion microbeam to perform experiments from which the path can be established from controlled single hits by low-LET protons and high-LET alpha particles to measured double strand breaks (e.g. γH2AX and 53BP1 foci), misrepair and survival and tissue reactions.

[9] MedAustron – Austrian Ion Therapy Center, Wiener Neustadt, Austria

This work is or will be done in collaboration with radiobiology groups such as from the IST[10] (ongoing Master thesis), IRSN[11], BfS[12] and others. This kind of activities are also included in a potential research topic for the 2018 EMPIR Call SI Broader Scope and funding proposals in preparation to be submitted to the SNF[13] (collaboration with PSI[14] and UZH[15]) and the EURATOM Call NFRP-2018-8*.*

c. Collaborations with strategic partners to jointly develop a basis for novel quantities in radiation metrology and establish detector standards and standard procedures.

Strategic partners among NMIs/DIs are NPL, CMI and SCK.CEN. Non-NMI/DI partners regarding detector development include CMRP[16], CNM[17], INFN[18], PoliMi[19] and University of Santiago. Clinical partners include Christie[20], dkfz[21], MedAustron[9], MAASTRO[22] and UKE[23].
A potential research topic related to the establishment of novel radiation quantities has been submitted to the 2018 EMPIR Call Health.

d. Collaboration with clinical partners interested in developing track-structure based treatment planning and of detectors suited for its verification.

This will involve developing a track-imaging detector to enable measurements of three-dimensional track structures over a spatial extension corresponding to a micrometer in tissue with a spatial resolution of a few nanometers. This will be complemented by endeavors to build a portable instrument that can be used in clinical practice, especially for the characterization of the secondary radiation fields produced by therapeutic beams.

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[10] Instituto Superior Técnico, Loures, Portugal

[11] Institut de Radioprotection et de Sûreté Nucléaire, Fontenay-aux-Roses and Caderache, France

[12] Bundesamt für Strahlenschutz, Neuherberg, München

[13] Schweizerischer Nationalfonds, Swiss Federal Agency for Funding Science

[14] Paul Scherrer Institute, Villigen, Switzerland

[15] University of Zurich, Medical Physics and Radiation Research - Research Group of Prof. Uwe Schneider.

[16] Center for Medical Radiation Physics, University of Wollongong, Wollongong, New South Wales, Australia

[17] National Center for Microelectronics, Barcelona, Spain

[18] Istituto Nazionale di Fisica Nucleare, Italian Nuclear Research Center, Legnaro, Catania and Rome, Italy

[19] Politecnico di Milano, Milan, Italy

[20] Christie NHS Foundation Trust, Manchester, United Kingdom

[21] German Cancer Research Center, Heidelberg, Germany

[22] MAASTRO Clinic, Maastricht, The Netherlands

[23] University Hospital Hamburg-Eppendorf, Hamburg, Germany

Clinical partners interested in these activities include Universität und Klinik Hirslanden Zürich and Center for proton therapy at PSI[14] with whom a common funding proposal is already in preparation.
Further partners with expressed interest are MRI[24], MedAustron, Loma Linda University and MD Anderson Cancer Center. The disrupted collaboration with dkfz / University of Heidelberg will also be resumed.

3: Developing metrology underpinning radiobiological assays

This target requires to a large extend transdisciplinary collaborations. It involves several aspects that are addressed by the department with the following activities:

a. Developing procedures for the standardization and assessment of uncertainties of radiobiology experiments with ion beams
Experience from the BioQuaRT project has already shown that metrologically well characterized irradiation conditions enable new insight into radiobiological assays including a more profound uncertainty assessment [12,17,18]. Further developments have been started as follow-up activities to BioQuaRT regarding measurement-model based quantification of yields of DNA strand breaks by scoring foci [19,20]. These activities are conducted in collaboration with IRSN, IST (ongoing jointly supervised Master project) and University of Pavia. They will benefit from the investigation and improvement of the spatial resolution of the microbeam using the new tandem accelerator.
In addition, regarding the standardization of assays, two key activities have already been agreed with the respective partners:
1. An intercomparison with IRSN regarding irradiation of cells at ion microbeams to be conducted as soon as the IRSN microbeam is fully operational.
2. An intercomparison with University of Namur comparing irradiation of cells using a broadbeam setup and an ion microbeam.

b. Establish flow-cytometry at the microbeam for better characterizations of cell populations.

In the frame of a doctoral thesis together with departments 3.1 (Metrology in Chemistry) and division 8 (Medical Physics and Metrological Information Technology), it is planned to establish flow-cytometry at the microbeam for better characterizations of cell populations before and after irradiation as well as measurements of fluorescent markers. First pilot studies are planned for the detection of biomarkers with higher sensitivity and selectivity by mass spectrometry at department 3.1.

c. Collaboration with the German collection of microorganisms and cell cultures (DSMZ, Braunschweig) which is actively involved in standardization and testing of cell lines.

In this context, the microbeam facility will, furthermore, be used to elucidate biological mechanisms involved in signaling pathways and DNA repair and their dependence of radiation quality. Studies involve specialized and unique cell lines where proteins of interest are genetically fused with fluorescent proteins. This is pivotal to understand and simulate how tumor and normal tissues respond to radiation damage.

[24] Klinikum rechts der Isar, Technical University Munich, Munich, Germany

d. Engagement in standardization committees at the national and international level.

The goal is to promote the translation of the insights already gained and to be obtained from the preceding activities into standards. Colleagues from other departments in division 6 that are experienced in standardization work have already been consulting on this. One straightforward topic could be a standard on ion microbeams as a reference field. Further topics are or will be elicited in imminent meetings with the WHO BioDoseNet and ISO working groups active in the standardization of biological dosimetry.

e. Promoting the establishment of a European Metrology Network for "Ionizing Radiation Effects".

At the expert panel workshop "Metrology for biological radiation effects", some of the identified stakeholder needs were beyond the scope of current metrology and/or beyond the capabilities of a single NMI, namely development of reference cells systems or reference procedures for cell assays, research for markers of individual radiation sensitivity and of reference irradiation facilities for radiobiological experiments, in particular for (small) animal irradiation. Addressing these needs can only be achieved with a network of NMIs/DIs and external partners from the larger research associations such as Helmholtz Society in Germany. This requires a coordinated approach as is requested for the envisaged European Metrology Networks that EURAMET is about establishing. Ideas for such a network have been independently proposed by PTB and the French LNHB at EURAMET workshops in Berlin (December 2017) and Paris (January 2018). In a bilateral meeting between PTB and LNHB it was agreed that the two initiatives should be joined and that the lead would be with PTB. It was also agreed that the scope would probably not be limited to biological effects of ionizing radiation, although this would be the most urgent area to be addressed. NPL (UK) and SCK.CEN (Belgium) and IRSN (France) have also indicated their interest in establishing such a network, and the European Biodosimetry Platform RENEB has indicated its endorsement. The department will actively promote the formation of such an EMN by liaizing with further partners with the goal to have an initial consortium by the opening of the 2019 EMPIR call for potential network topics and to be able to propose the EMN to the EURAMET general assembly in 2019.

3.4.5 The role of the ion microbeam in this strategy

The ion microbeam is involved at all targets mentioned above:

- RE Target 1: The measurements for the validation of advanced track structure codes will mostly be performed at the ion microbeam, as the targeted irradiation of the DNA based structures will be a decisive experimental condition.

- RE Target 2: The cell and tissue model irradiations for the benchmark experiments correlating radiation tracks and early and late biological effects will be conducted at the microbeam exploiting the fact of its large available LET range as well as the advantage of a vertical beam that enables irradiation of tissue samples floating in medium. Furthermore, the microbeam will also be necessary for irradiating novel detectors and detector components to characterize the spatial variation of their response or their sensitive volume dimensions. Such investigations require a good targeting of the test radiation and a radiation quality that is characterized by a small range of secondary electrons in the micrometer range. This can best be achieved by protons of higher energy such as those provided by the cyclotron accelerator. These capabilities can also be used for testing detectors and detector components for other applications such as dosimeters for conventional dosimetry.

- RE Target 3: The microbeam is the ideal tool for establishing standardized radiobiological assays as the well-defined irradiation conditions remove a number of uncertainty contributions prevailing in other types of irradiation setups. This kind of activities will constitute the majority of the use of the microbeam within the research agenda of the department.

Benchmark of the microbeam:

	Laboratory	Location	Ion species	Energy range
Inside Europe	CENBG	Bordeaux, France	p, He	1 – 3.5 MeV
	GSI	Darmstadt, Germany	C to U rarely p, He, Li	1.4 to 11.4 MeV/u
	Ion Beam Center	Surrey, UK	p to Ca	p: 4 MeV He: 6 MeV O: 12 MeV
	IRSN (start in 2018)	Caderache, France	p, He	p: 1- 4 MeV He: 1 - 6 MeV
	PTB	Braunschweig, Germany	p, He	2 - 20 MeV
	SNAKE	Munich, Germany	p, He, Li, Be, B, C, O, F, Si, Cl, I	p: 4 – 28 MeV He: 1.4 – 10.5 MeV/u Li – O: 1 – 8 MeV/u Si, Cl: 1 – 4 MeV/u I: 0.5 – 2 MeV/u
Outside Europe	IMP	Fudan, China	p, He	6 MeV
	IMP	Lanzhou, China	C	Several to 100 MeV/u
	JAERI	Takasaki, Japan	He, C, Ne, Ar	He: 12.5 MeV/u C: 18.3 MeV/u Ne: 13 and 17.5 MeV/u Ar: 11.5 and 13.3 MeV/u
	RARAF	New York, USA	p, He	1 - 5 MeV
	RIKEN[25]	Wako, Japan	p, He	1 - 4 MeV
	SPICE/NIRS	Chiba, Japan	p	3.4 MeV

Table 1: Charged-particle microbeams for targeted irradiation of living cells. The list is based on reports on the facilities at the last two microbeam workshops (period from 2010 to 2013) [21,22].

[25] According to Volkhard Mäckel (2018), the operation of the microbeam, collimated by glass capillaries, was stopped and the installation disassembled after he left, and the group leader retired.

4 Annex 1: Protocols of Presentations and Discussions

4.1 Protocols Introduction

4.1.1 Hans Rabus – Status and Visions of Department 6.5 "Radiation Effects"

- Outline of the department history (2003 until today) (slides 2-4)
- Introduction of current working groups (6.51 – 6.54) and related tasks (slides 5-9)
- Forecast for ionizing radiation metrology in medicine (debates at ESTRO meetings) (slide 10)
  - Personalized treatment to minimize toxicity (side effects)
  - Should absorbed dose in treatment planning and QA be complemented by another quantity to describe radiation effects of densely ionizing radiation?
- Introduction to relation of absorbed dose / microdosimetric quantities / nanometric targets (slides 11-13)
  - Graph of imparted energy per mass of voxel where expectation value is equal to absorbed dose only for large voxels;
    for smaller voxels an increasing spread in imparted energy is observed.
    This spread starts already at larger voxel sizes for densely ionizing radiation (neutrons, protons, ions) compared to x-ray radiation
  - Microdosimetric quantity frequency mean lineal energy depends strongly on voxel size -> is there a voxel size for which this quantity is proportional to $1/\alpha$?
    This was investigated by Kellerer et al. 1980-1990s
    -> extrapolation from measurable sizes towards target diameters 1-10 nm
    -> Idea of nanodosimetry born
  - Problem for nanometric target sizes: no secondary electron equilibrium
- Discussions in medical community (literature review): (slides 14-16)
  - Chaikh et al.:
    - Need for implantable nanodosimeters for real-time measurements
      Rabus: nanodosimeters as devices to measure absorbed dose in nanometric volumes do not make sense (for above reason)
    - Improvement of quality assurance in radiation therapy by miniature in-vivo real time measurements devices
      -> goal: determine delivered dose with better accuracy to increase local tumor control probability and reduce side effects
  - Cunha et al.:
    - Studied feasibility of implantable miniature dosimeters by Monte Carlo simulation to measure absorbed dose
    - Rabus: Exactly the problematic outlined above and known for 30 years (slide 16)
      ->dosimeters have to be large enough to measure absorbed dose;
      particularly, for densely ionizing radiation, dosimeter size has to be larger than for photons
    - Rabus: nonetheless, if goal is to measure distribution of imparted energy instead of only the expectation value, this distribution could be used to estimate reaction of biological system
- Aim of department 6.5
  -> Track structure based metrology of ionizing radiation

- Status in the community (slide 17)
  - Relevant target size relied on belief
  - Generally, simulation results providing early stage of physical system response are being related to late biological endpoints
    -> ignoring chemical and biological processes inbetween
  - Simulation tools taking biological effects into account
    -> usually not very clear on which data models and parameters are based on
  - Track structure codes generally homemade developments which are not widely distributed and often are used by single persons
- Recent work of our department to improve track structure based metrology:
  EMRP JRP "Biologically weighted quantities in radiotherapy" (2012-2015) (slides 18-19)
- Forecast on future of ionizing radiation metrology from current perspective (slide 20)
- Requirements to achieve these new developments from current perspective to stimulate questions and discussion in this panel (slide 21)

Questions and Discussion

Schettino: Can PTB do or be involved in animal experiments?

Rabus: Not at this time

Schettino: To have an impact in clinical radiobiology, the track to go is via animal experiments and metrology institutes such as PTB or NPL have the same limitations to that

Krämer: What are your perspectives in establishing radiobiological competence at PTB compared to other institutes performing already research in this direction? Is there a PTB for biology?

Rabus: No national institute for biologogy exists but there is competence, for example, at BfS

Krämer: Such an institute should consider that due to ethics restrictions in Germany, performing animal experiments is much more difficult that using cell experiments. By the current model used at PTB (restricted to the physics), your are far away from the clinics.

Schulte: Along this line, there seems to be only little collaboration between different radiobiological efforts. This is the case in Europe and also in the USA.

Rabus: I have the same impression

Schulte: Do you think there are enough radiobiological institutions in Europe?

Rabus: I think, we have enough radiobiological institutions driven by radiation protection and performing basic research in Europe.

Cordes: I think, there are many institutions concentrating on radiotherapy and radiooncology while there are only a few on radiation protection and epidemiology

Newhauser: A follow-on comment: 2 or 3 years ago, an article dealt with the funding of physics, biology and oncology research in USA. They reported that about 80% of awarded grants (about 200 in total) had a biology component. It was not in the paper but deeper inspection showed that only very few radiobiologists were actually funded. So I think that there is a crisis at least in

the US in the field of radiobiology and particularly in the research funding. With this in mind, I wonder if it could be a benefit to perform international research trying to solve this problem. If the situation for funding is similar in Europe and radiobiology is a priority, then there would not have to be more resources allocated to it. But the more unified and stronger the voice lobbying for resources, the more effective an international effort would be.

Garty: A lot of the work seems to be on the physical aspects of dosimetry measuring dose and variations in dose. Something to keep in mind is that people react individually to radiation treatment. A few, maybe 5%, would have severe effects where dose should be limited. Another group of people under-respond and more dose is needed for a better tumor control. But this is very difficult to get into the mind of the regulatory bodies and convince them that dose is not sufficient. For example, the DNA repair capacity can be measured in a blood test, which is an indication about the sensitivity of that person. We have to think about how to include this into the metrology and convince the regulatory bodies to support this approach.

Schettino: I think, one of the key points is the word “metrology”. There is a fair number of radiobiological institutions worldwide. But they do basic research and very few approach the issues with the same metrology or regular standards as we do from the physics point of view. This has to change. We have to get them on board and get them to apply the same standard. 4 years ago in the US, NIST reviewed the number of radiobiological papers and found that only 7% of them report any standard on the dosimetry. This means that 93% of this work is not reproducible because they didn’t give enough information in the paper. This gives an idea of the lack of metrology in radiobiological work. This does not mean their work is bad, they have different issues, different agenda, more related to basic research. But if we want to address the metrological issues, we need to get them on board to use the same standards. In the UK, major funding for radiobiological research goes into this direction. The plan is to implement a sort of regulatory, mandatory check for all funding requests and papers with radiobiological work. NPL would have the task to provide support in dosimetry so that any lab can fulfil the required standard. I think, such a plan should be pushed at the European and worldwide level.

Garty: A comment to Schettino: The NIH is implementing something similar, where the centers for medical countermeasures agains radiation have established a common core that harmonizes dosimetry across all projects within this program and they also plan on reviewing all papers to ensure proper and consistent report on the dosimetry.

Schäffter: I find particular interesting in your (Rabus’) project the different levels starting at physics level, then the chemical level where you have free radicals and finally the biological level with interacting cells and in the end, a clinical level. However, you and other people suggest to implant the physical level directly on the clinical level, which seems strange to me. I would not measure nanodosimetry in the patient, but rather measure the overall effect.

Rabus: The rationale behind this is the same as the conventional absorbed dose approach. Basically, the oncologist prescribes a dose distribution in order give a specific dose to the tumor and spare the surrounding tissue based on their sensitivity. The idea behind this is that there is a relation between the absorbed dose and the biological effect. The way to do this at the moment is to take a CT of the patient, contour the target volume, calculate the treatment plan. And then you use your equipment to place the patient and the beam to perform the irradiation as calculated in the plan. I am no specialist, but it seems to me that people rely on a proper

alignment of the patient and then you will get the dose where it is supposed to be. The use of image-guided radiotherapy already offers a better confidence or correct local dose deposition. But it still seems as shooting into the dark. It would be interesting to see in more detail how the dose is distributed in the irradiated volume. I think this is what these suggestions are about.

Schäffter: I agree, but I would also look into the biological level not only on the clinical level.

Rabus: I agree that it would be beneficial for the treatment if we could perform a direct measurement at the biological level.

Güttler: My division is involved in metrology for chemistry, covering many areas and the medical aspect is one of them. Another one are the food risks where we collaborate also with external institutions. They usually distinguish between risk assessment and risk control. It seems to me of great importance to draw a line here and decide in which direction you go. This is because the approach is very different, in risk assessment you need more resources and knowledge from partners outside of your institute. I see the side of PTB more in the risk control. Would you have any ideas of how to draw a line there in your field?

Rabus: Before I answer your question, I would like to clarify that in ionizing radiation we even have an additional aspect. On the side of radiation protection we are basically concerned about risk limitation. Risk assessment is usually no concern for metrology of ionizing radiation. And we have the intentional use of ionizing radiation to kill cancer. Here we have another kind of risk limitation to the healthy tissue. So, it is not clear to me where to draw the line. There are generally two issues: the treatment of tumor cells without damaging the healthy cells too much. There we have an issue, mentioned by Garty before, regarding the distribution among individual radiation response. So the risk has to be determined based on this distribution, so that a significant part of the population may get an ineffective treatment or strong side effects. In my point of view, assessing the individual radiosensitivity would be something like risk assessment. It may benefit the radiooncology community the most, if we could come up with a measurement of the individual response and adapt the treatment accordingly. I hope to have answered your question. In any case we need to interact with the radiobiology and –oncology communities.

Schulte: I agree from my practical experience. One aspect is to deliver the absorbed dose with tight control within a few percent. I think this is well established with standardization, for example via phantom measurements. But there is fairly little on the side of low doses, which are usually not measured but they determine the second cancer risk. A lot of work has to be done there to even get the absorbed dose correctly. There is also fairly little on radiation quality assessment, because we are not clear on what to assess. There is limited amount of in-vivo verification of absorbed dose delivery in particle therapy. Methods are just evolving now, showing the delivered dose during or after the treatment. So, all kinds of risk assessment are implanted on various levels in radiation therapy. Regarding the issue of risk control, an improvement of risk models is necessary. This requires data collection, developing risk models and getting proper parameters, where we, for example, are lacking centralized data collection. It is really a multidimensional problem that has to be addressed. In my point of view, a few people should keep the overview and coordinate, while experts should develop methodologies in various areas. Keeping the overview may be a task of PTB.

Krämer: Before discussing details on the physical level, oncologists should be consulted on what they need. I remember that in our carbon-ion pilot project, almost everything was fine from the point of view of a physicist. But the harder work is to convince the oncologists to implement that into the treatment planning system. For example, the HIT clinic still uses the LEM model version 1, which is far outdated (there is a version 4 already). But even though there is a better version, the doctors rely on their experience on how much dose is required. Their major interest is that the tumor is successfully treated and that there is progression-free survival for an extended period of time. Simply put, this is their detector. You have to find oncologists who are willing to implement your new data and developments into the clinical practise.

Newhauser: I think that's correct. Having worked on research with some oncologists I would say that their concern is that they do not want to harm the patients by using calculations which are not rock solid, traceable, built on solid dosimetry and metrology. Another issue is the risk projection, the fundament on which is the physics which is then projected on the clinical level. All of this has to be validated, which probably is the task of the epidemiology community. But epidemiologists and also radiobiologists often are not interested in the details of the physical metrology. As these fields emerged individually, it is within reach to combine them in a way that, I believe, could lead to clinical systems which clinicians would use. I think it is our task to integrate this knowledge, to make sure that uncertainties are known and models are not overused.

Cordes: I am in line of what you said. As a physician, I would like two things: We want to verify that the prescribed dose arrives at the correct position and can be tracked. The second issue is that the treatment is reproducible, which is not only a concern of patient positioning, but also for the localization of the tumor within the patient in each fraction. These rather big challenges need to be solved.

Hornhard: From the radiobiological point of view I would say that it is sometimes difficult to connect physics and biology. But on the other side, in biology things are often not as clear as in physics. Our aim is to get biomarkers to describe effects after exposure, but they are difficult to find due to the broad range of individual reactions. Of course it would be helpful if physicists could contribute to dose calculations which would improve the validation of biomarkers.

Giesen: We heard last week from Oliver Jäkel that about 20% of tumors cannot be cured. Whenever I saw presentations of physicians or medical physicists at a conference, they compared Kaplan-Meier curves and were arguing about few percent of improvement if this or that was changed. So they actually have a measure and are interested to improve treatment modalities. Or is my impression wrong?

Schulte: In fact, for some tumors there is quite some progress with tumor controls rizing from 20% to 80% or so. This improvement occurs step-wise over a longer time period. A good example is Hodgekin's disease which we could cure once we had MV-therapy. Another example are head-and-neck tumors where adding chemotherapy to the radiation had a very beneficial effect. But there is still a number that we cannot cure and there was no progress within the last years. These are either tumors which are discovered late and became treatment resistant or those, which are inherently resistant. Both kinds of tumors cannot be cured with low-LET radiation. For these tumors we need something better.

Verhaegen: There are also a lot of new kinds of therapies coming, for example the stimulation of the immune system. Also, the treatment becomes more and more complex: To really achieve an individualized treatment, we may also have to take into account the other modalities than radiation. For example, as was mentioned before and is frequently applied, the combination of radiation and chemotherapeutica, where there is also an individual response to the chemo with individual effects on the immune system. So the treatment is going to become very complex in the next decade and we have to think what we could do to significantly contribute to such a complex treatment.

The other thing is that we have confused the physicians already quite a bit with quantities like dose-to-medium and dose-to-water and so on. In my experience, most physicians do not understand the difference between the two and are not willing to change the way they prescribe. If you would offer them a treatment planning system based on dose-to-medium instead of dose-to-water it would probably be not accepted in the clinics.

4.2 Protocols Session 1: Radiotherapy with ion beams and its metrological needs

4.2.1 Wayne Newhauser: Medical Radiation Exposures and Risks

Essentials from Talk:

Success of radiation treatment of cancer constantly improving

As survival rates increase, late radiation exposure effects like secondary cancers, fertility effects, cardiac attacks become more and more important

Task for a metrology lab:

- Dose: All constituents of dose must be calculated/measured accurately, the direct therapeutic dose as well as the healthy tissue / out of field dose. Latter is still unknown in the clinic
- Radiation quality: RBE for carcinogenesis. Would take decades to find out. But should be possible to measure the physical properties of the beam so to have retrospective a way to relate late effects to doses received in a treatment in a diagnostic exposure.
- This involves spectrometry of N, p, X/G etc to characterize the secondary and out of field radiation fields
- This doses and field parameters should be measured with standard procedures and uncertainties should be assigned
- If all this will provide the input date for epidemiologists who later will use these data to come up with risk models (e.g. quoting number or cancer incidences per unit dose of certain quality)
- That in hand turn will enable to improve radiation treatment planning to minimize these late effects, still preserving maximum tumor control
- Will be a long tough project and needs to be interdisciplinary, involving fields from Physics, epidemiology, oncology, informatics and biology

Discussion:

Krämer: While improving scatter contribution in dose calculation, the normal TPS's have pencil beam algorithm, so you need to feed the data your measured/calculated yourself. The providers depth dose profiles are not so good as they should be.

Newhauser: That is true. The (TPS's) input data are only measured out to a certain distance. We use these input data to generate kernels. In principle they work then also further out of field. No reason why the TPS cannot perform better. We tried to figure out why the TPS do not work better, but is mainly proprietary information needed which the supplier does not provide. Interest is also low – manufacturers says that two-sigma outside is not of interest – so you can measure what you want they do not take it.

Dörr: What is with diagnostic imaging dose, which may or may not be related to the treatment? How shall we deal with this?

Newhauser: Excellent point which need to be addressed. Estimates say that this imaging component can be up to 8 % of therapeutic dose. Can be handled in the same spirit of the therapeutic dose, has to be measured and/or calculated.

Dörr: But also imaging doses outside the treatment period, earlier in life, have to be considered

Newhauser: This is harder to do, at least in US there is no registry. Some European states have registers where all these doses are collected. (Denmark?). No universal acceptance to keep record of this information and share it. Hope this changes, possibly by government regulation.

Schulte: You talked of low dose modelling out of field. Verification is missing. MC and analytical models need verification

Newhauser: True. In the 2nd hour of my talk I will address this. This was neglected for a long time but a lot of interest grew in the last years. There is a rush now to fill the void of missing verification. Many modelling with Monte Carlo or based on MC are derived analytical models, based on data of poorly known accuracy. It is essential that modelling is put on more solid footing, that is measurable, traceable, reproducible. Strength and task for PTB and metrology labs who know to do this and make service available to clinics. Both, dosimetry and spectrometry e.g. to understand the spectral neutron fluences.

Schäffter: You mention a top priority on cross field studies of effectiveness and cost effectiveness of studies, large trials (2000s of patients), outcome, survival, side effects, quality of life. Question: We as metrology institute should we link to these large studies to or make a strong dosimetric measurement impact in in the large studies where we can see later what the effect of proper dose calculation could be?

Newhauser: Interesting question but I have no ready answer. Possible solution: In the US, if you want to run a clinical trial, it requires certain things before you become eligible for that. One of

that is to get dosimetry in shape, including an external audit. Some of these audits are done with phantoms developed for this purpose.

Whether PTB would support individual user or a national epidemiology study group is not clear. But as larger the number of institutions involved as faster results can be obtained. The way how this must by obtained must be quick, reliable and not very obtrusive. Best way is to use current methods for calculating therapeutic dose might be extended and suitable also for out-of-field dose.

Schäffter: I see 2 categories: normal clinical papers, doing 30 patients and showing some effects. But this will be forgotten in the end. Then there are the landmark papers. All people make a paradigm shift. Neoadjuvent therapy was example (remark VD: a form of combination therapy which uses e.g. radiation or chemotherapy to reduce tumor mass before a final surgery). Given the limited resources of PTB one should focus on one of these big trials.

Newhauser: Agreed, but not necessary exclusive. No point of dragging everybody into this if they do not want to participate. Another way would be a legislative approach. In diagnostic radiology, now one is obliged to estimate organ doses. This can be contemplated also for therapy. Would probably not work in the US at present.

Dangendorf: Probably in Europe a legislative approach would work, in US you better try an economical incentive.

4.2.2 Reinhard Schulte: Status and Future Plans of Particle Therapy and what are the Metrological Needs

Historical remark:

His first meeting at PTB was in winter 1990 with a few people to discuss how PTB could contribute to metrology in proton therapy, and he is happy that nanodosimetry keeps going.

Due to its large uncertainties, RBE is not a quantity suitable for precise metrology.

Slide 23 states:

" - It appears that the classical RBE concept, which is based on dose modification leading to the same cell survival for different radiation qualities, breaks down considering the many factors that influence radiation response.

- A new concept(s) is (are) needed that relates the new radiobiology to radiation quality."

Slide 25 states:

" - Although not fully proven, it appears that the number of clustered (not single) ionizations occurring in nanoscopic volumes is the most important parameter in radiation response.

- The change in cluster yields (in particular those larger than 2-3 ionizations per DNA segment)per unit dose has a striking resemblance to the LET dependence of RBE, but better reflects differences between particles of the same LET."

Slide 26 states:

“Underlying Premise: Equal Clustering = Equal Biological Effect in Normal Tissues.”

Slide 27 states:

“Underlying Premise: Equal Clustering = Uniform Biological Effect in Tumors.”

Slide 28 states:

“A concept of Future Metrology in Particle Therapy planning and Delivery

Optimized particle treatment planning of the future:

- Based on metrology of clustering of ionizations in tumor and normal tissues

- Maximize uniform biological effectiveness to the GTV by maximizing the number of large ionization clusters

- Prevent toxicity by nit exceeding the number of large ionization clusters in normal tissue delivered at threshold doses of low LET radiation schemes (isoeffective to 2 Gy fractionation)”

Slide 29 states:

“Summary of Future Metrology/Research Needs

- Experimentally validated treatment planning codes for calculating high and low macroscopic doses in particle therapy beams

- Experimentally validated treatment planning codes that calculate the ionization clustering levels in standardized nanoscopic volumes

- Radiobiological studies that validate the equal clustering = equal effect hypothesis in tumor and normal tissue models for the most relevant particles (protons, helium, carbon, oxygen)”

Discussion:

Krämer: I was a little bit wondering, because once the US was leading country in particle therapy, it is where it all started. It is completely lost now?

Schulte: Yes, somebody has to start it, and after funding it for forty years they thought it is enough, so let the others do it. Now they are trying to catch up.

Krämer: Astonishing that is completely … for 20 years now

Schulte: Not photon therapy, but proton therapy started on the wrong foot

Baek: You emphasize the role of ionization cluster, but there are many studies indicating that the ionization cluster can be different from the clustering of DSB, and DSB’s are the main reason for the radiation damage. Isn’t it better to characterize in terms of DSB clustering index?

Schulte: I thought about this back and forth, but if you want a physical metrological quantity, it should not be the clustering of DSB's, it should be the clustering of ionization. That's my answer, and meaning that there must be a correlation between the clustering of DSB's and the clustering of ionizations, and of course that may be a fairly complex relationship, and it could be that the very large clusters, there is so much recombination, of radicals, that you get less effective, which is probably true, so you have to find probably a range of cluster sizes that is most relevant. I agree, it is not so black and white and simple.

Newhauser: Just one question, how would then one take into account the additional steps between damage and the appearance of the tumor?

Schulte: You come to second tumors now? You relate the clustering to the second tumors?

Newhauser: It seems that the clustering is focusing to initial damage …

Schulte: No, it is focusing on the starting conditions for all the biology that is following after, it will depend on the genetic profile, it will depend on many things, it may even depend on the barometric pressure, I am trying to be provocative. I believe it is very very difficult to simulate all of it, to model all of it, so why not focusing on the starting conditions, and then the hypothesis becomes: under equal starting conditions and equal biological systems you should get an equal biological effect. That's all I am saying.

4.2.3 Michael Krämer: Methods and models for treatment planning in particle therapy

Video: Radiation Effects_day1_3 01:20:30 – 01:52:50

Essentials from talk:

GSI pursues pragmatic approach to get things done for immanent treatment planning in HI therapy

Slide 78, RBE problems:

- alfa/beta dependence on many factors (cell, tissue, endpoint, ion)
- nonlinearity of RBE (linear/quadratic behavior)
- slight difference in repair (result in large difference in dose/dose relation

Conclusion: no ab initio correlation between dose and biological effect is possible

All this led to development of LEM Model: Separation of Physics from Biology

Physics:

- Required is radial dose distribution on micrometer scale,
- cell nucleus is considered as critical target,
- overlap critical target with local dose distribution of Ion track (obtained from radial dose profile)

Biology:

- Biological effect is taken from known photon response of biological systems (cell cultures)
- Parametrize with the alpha/beta values from linear quadratic dose response curve
- Use tiese data for inut to local dose effect calculations.

Fluence (not Dose or RBE) is now uses as input data in treatment planning

Reproduces quite well also response to tissue due to 50 years of experience in photon treatment

Slide 10:
-In newer version of LEM 4 also ionization clustering is taken into account (DNA loops)
-Compare number of isolated lesions to cluster damages and make photo equivalent
-This goes into direction suggested by Schulte in his talk but GSI believes that problem is already solved.
-Statement about RBE: In treatment planning RBE is not calculated but survival or lethal effect instead.
RBE in mixed beams is problematic because RBEs cannot easily been merged

Slide 12:
-Verification: BIO-Phantom, this tests everything: Physics and Biology
- Result show large error bars: lack of reproducibility in existing biological systems.
- Task for metrology institute: developing more reliable cell system

Some slides for emerging therapy modalities: He (less fragmentation as C, less scattering than p)

Metrological problem: variation of radiation sensitivity of cell lines, depending on time, need for understanding of these variability and correction

File 22: Treatment in Hypoxic environment
-Measuring oxygen enhancement ratio (OER)
- OER for x-rays: 1 - 3,
- higher dose averaged LET reduces OER
- Implementing in treatment planning can control/correct OER
-verification with hypoxia chambers (control oxygen content in cell culture)

Conclusion: Dose and RBE are not good quantities if OER is included. Cell survival is new metrological quantity.
Open issues: how to measure Hypoxia in treatment: (Imaging with PET?)

Slide 26:
Microscopic explanation of OER: Include Chemistry into TRAX code.
Due to diffusion the detailed track structure might not play such a role,

Summary: Recommendation to PTB:
Go more into biology
Development of biological detection devices which are more reliable
Segmented hypoxia chambers

Discussion:

Schettino: Did you also verify LEM in tissue response and Tumor micro environment

Krämer: With own experiments not for tissues, only from literature values when available

Schettino: You use biological data for input and validation. How important are the uncertainties of these? Usual biological data have uncertainties of 20 -30 %, which is obscene from metrological point of view. How important is it to get more reliable data

Krämer: slide 20 show 2 different survival curves for same cultures. Uncertainties can even be larger. Desirable to find a marker in the tissue or cell culture which allows to better determine the alfa/beta and not just an uncertainty. If these values can be determined better one can plug them directly in the TPS.

Schettino: So it is required to measure more precise the biological data.

Krämer: Exactly, we need to know better the biological effect, and not what is the RBE or the Dose.

Baek: What is difference in RBE when going from LEM1 to LEM4.

Krämer: LEM 1 underestimates in the tumor and overestimated in the healthy tissue. This is the "(good direction", because in increases tumor control and reduces healthy tissue effects.

Baek: What are the numbers?

Krämer: Forget the RBE, this is not a fixed quantity. One has to make the full calculation. But it can be easily 20 to 30 %. We overestimated e.g. RBE in entrance channel by factor 1.5. For Protons 1.8

Baek: There are not only chronic but also acute hypoxic tumors. And oxygen contend varies in space and time. How to deal with?

Krämer: If imaging can provide these data in space and time the TPS can calculate its effects almost in real time.

4.2.4 Frank Verhaegen - "Research needs for hadron therapy clinics"

- Overview of plans for dutch University Medical Centers and specifically for the ZON-PTC (slides 2-9)
- Introducing the state of the art in photon radiotherapy (slide 10)

  F. V. points out that only few clinics apply response assessment. Also, particularly beneficial for photon therapy is the use of a portal imager for a verification of the correct dose received by the patient (DGRT, dose guided RT), which showed that in reality there are often discrepancies between the planned and delivered dose delivery. But this cannot be used in proton therapy as these are stopped within the tissue.
- Outline of national grant "PROTECT"

  Specifically addresses:
  - Project 1: Improvement of treatment planning. Currently, these systems still use tissue composition published in the 1980s, but a tissue composition should be considered on the individual basis
  - Project 2: Imaging methods for in-vivo verification

Which both require physics input
    - Outline of issues not covered by “PROTECT” but nonetheless important (slide 13)
- Issues in proton dose calculation (slides 14-19)
    - large uncertainties for transfer of CT# to stopping powers of different tissue types
    - improvement may be possible by use of dual energy CT
    - Challenges:
        - accurate collisional and nuclear stopping powers of water and different tissues
        - Physics input in imaging methods to derive dose calculation quantities
- Imaging for proton (range)verification (slides 20-27)
    - Sketch of PET methods, prompt gamma emission, Proto-acoustic imaging; These methods are not yet used in the clinics and there is still a lot of work required
    - Challenges:
        - Accurate knowledge of cross section data
        - Accurate kinetic energy-acoustic energy transfer data
        - Uncertainties/sensitivities
        - Dose instead of range verification
- Radiation quality effects in proton beams (slides 28 ff) - Outline and possible approaches:
    - Going beyond the dose concept (not yet established in clinical practice)
    - Significant increase of RBE at distal end of spead out Bragg peak (well known but not used in clinics) (slide 28)
    - Cluster analysis of incidence of DNA SSB and DSB as function of LET using Geant4-DNA and the Monte Carlo damage simulator (MCDS) or codes like PARTRAC (slide 29) -> large discrepancies between different simulation codes due to large uncertainties in fundamental physical data
    - MCDS limited but nonetheless useful for a basic estimation (slide 30)
    - RBE calculations for low-energy photons from an electronic brachytherapy source using MCDS and application to determine an RBE map in breast tissue (slide 31) -> RBE increased over the whole tissue -> this issue is published and accepted but not applied in clinical practice Challenge: Emphasis on how this can be used in the clinic
    - Cluster analysis very likely to be used in addition to dose (slide 33) Challenges:
        - Comparison and standardization of cluster analysis methods
        - Experimental validation necessary
    - LET painting with protons (slide 34)
    - A single model to predict biological no evidence of disease as a function of tumor control probability using dose and alpha- and beta-parameters for a specific patient (slide 35)
    - Small animal radiotherapy in pre-clinical research (slides 36-38)
    - Dose rate effects (slide 39)
        - High dose rate: no biological effect observed
        - In VMAT, a lot of the dose is given with a very low dose rate below 1 Gy/min -> investigate detector- and patient responses to low dose rates
    - Neutrons in proton beams (slide 40)

Questions and discussion

Schäffter: You mentioned different imaging techniques and I know that there is a lot of research in this area. What is the metrology aspect related to imaging?

Verhaegen: In the three techniques I mentioned, a lot of physical input is required as the signal, whether it's a gamma or a protoacoustic signal, always has to be predicted. For modeling this signal, accurate physics input is mandatory. This predicted signal is compared with the measured signal. So I think that there is work to do for centers like PTB to improve the accuracy of this prediction. Because at the moment the data such as cross sections for a lot of reactions in tissues are not well known and have large uncertainties. The question is if a center like PTB could do some work for real human tissue, which would be extremely useful. This is open for discussion.

At the moment, I would say that the people developing the imaging modalities are not so ambitious. Most people just want to verify the particle range. That's of course important, but in principle, if your absolute cross sections are correct, you can verify the whole dose distribution in the patient. Without having to put a detector inside the patient, you would have a nearly direct way of measuring the dose distribution in 3D or even 4D if detectors are fast enough. I have not talked about improving the physics related to the detectors but on the interaction data side.

Krämer: I have a question regarding the DSB determination. I remember there was a map of RBE which you calculated from DSB. How do you know that the RBE are the same as for tissue? It is a completely different endpoint.

Verhaegen: Yes, that's of course correct. First you have to decide what kind of RBE you want to calculate, because it not only depends on dose but very much on the endpoint. We don't really know which endpoints to use. For example, results on DSB formation were previously published but I am not sure about how this is related to the patient response. It is no surprise that people are not using this endpoint in the clinics but sometimes you see two completely equal dose distributions but very different distribution in RBE then at least, people should be worried and think of DSB formation probabilities at least. I believe, that dose does not tell you everything.

Schulte: I have concerns about using imaging for in-vivo dosimetry where you seem to heavily rely on response of detectors during treatment. In this case you would only find out a mistake after the treatment. Could you quickly abort the irradiation if you realize during treatment that something is not right?

Verhaegen: If I make the analogy to photon therapy but what is still in the research phase is similar but heavily based on the portal imaging. People would like to interact during treatment but also verify the delivered dose distribution after treatment in detail. In our clinic we operate such a system which logs the delivered dose distributions, which are analyzed automatically. If a parameter falls below a specific threshold, there is an alert. The Holy Grail is to do something similar for ion treatment.

4.3 Panel discussion of session 1

Newhauser: My question is for M. Krämer regarding nuclear stopping powers. If you do a multiscale simulation in particle therapy, where you want to use the correct stopping powers all the way until the ion is completely stopped, are you satisfied with the conditions of the evaluated stopping power tables or do you think more work needs to be done for nuclear stopping powers and stopping powers in general?

Krämer: Nuclear stopping powers are usually ignored because they are relatively small and occur only at the very end on the ion track. I think, for clinical environments where the uncertainties of about half a millimeter, considering the nuclear stopping power will not lead to any difference. As far as the stopping power is concerned, a large uncertainty source is the ionization potential used in the Bethe-Bloch equation. For water, you use 75 eV which is recommended by the ICRU but we decided to use 77 eV because this matches our measurement. These 2 eV difference corresponds to half a millimeter in range which is significant. For us, it is not of primary importance but if there would be a more accurate value of the ionization potential or the stopping power available. This would be more my concern that the nuclear stopping powers.

Hilgers: I have seen that there is work being done on substituting the dose painting by LET painting. Would it be an improvement to go a step further and use, let's say, ionization density painting or interaction density painting?

Krämer: I propose cell-kill painting because in the end, you are interested in killing the tumor. In my opinion, there is no quantity in-between needed, such as LET or ionization density.

Uwe Schneider: If you look at cell killing in the tumor, you look at a complex environment, inflammation processes and the microenvironment of the tumor. Therefore, looking at cell killing of single cells is also far away from a real tumor.

Krämer: My opinion is that if you can treat a cell culture in the right way, then this is as close as you can get apart from performing animal experiments, of course.

Giesen: R. Schulte, could you please summarise the general direction of developments at the recent PTCOG meeting?

Schulte: This is not easy to summarize as it was a large meeting. The number of proton therapy centers is still increasing and there seems to be an almost exponential rise in number of patients treated. The trend is towards more compact facilities, smaller number of treatment rooms per facility. There is surprizingly little talk about neutrons even though there is an emphasis on pediatric treatments. There are even some centers only for pediatric treatment and for most centers are about 25% pediatric cases.
There were a lot of presentations on range uncertainties or dosimetric uncertainties and discussions on the ionization potential value. Discussions showed that there is a need for imaging for treatment planning and imaging verification, an

improvement of biological data, and the implementation of better RBE values in the treatment planning system. Presentations of LET-painting were used as an alert showing the huge differences to dose-painting deliveries.
As the number of patient centers is increasing, there are more and more unexperienced centers and there is a concern that mistakes in treatment planning occur, particularly by not considering the rise of LET at the track end. Therefore, I think that using, for example, LET-painting helps to alert people not to use high-LET radiation close to highly sensitive organs. These are my major impression.

Schäffter: Since I was asked to give a summary of this meeting tomorrow, I would like to ask the external speakers of this session: If they would be Hans Rabus and they should investigate in metrological issues, what would be your top priority?

Schulte: I mentioned by priorities in my talk. Important would be evaluating the ionization clustering, which was also mentioned by F. Verhaegen. The clustering should be evaluated against existing models like LEM, also considering the different LEM versions as version 1 is used clinically but version 4 is offering improvement. Also, Rob Steward's approach with RBE based on DSB clustering. This should be evaluated as described by F. Verhaegen during his talk. There should be a collaborative approach with good physics support.

Newhauser: The common thread that I heard through the talks today was a need for solidifying the metrology of all medical exposures. Via the absorbed dose or ionization clustering or LET, you try to get a good model of the physical level. This level is used to predict the patient's outcome. The work at PTB should be tied to a sizable, worthy problem and I would advocate to lay the foundation for the physics and the interface with the biology for medical exposures. Examples would be the out-of-field dose, neutron exposure, radiation quality of both the therapeutic and stray exposures. This will affect the quality of life of a lot of people. In the US, such problems get a lot of attention from society and I think there will be a sustained effort over decades to deal with this problem.

Krämer: I would advise to enter at a level as close as possible to the final outcome, probably on the level of cell experiments.

Verhaegen: I think that institutes like PTB or NPL should seriously look into animal experiments, where actually physicists have a lot to contribute. To paint a dose in something as small as a tumor in a mouse's lung which is moving much faster than humans breathe, technological challenges have to be solved. I think, PTB would be a good institute to establish an animal experiment facility due to the amount of technological knowledge present. We set up our facility 8 years ago for photon therapy and learned a lot from the collaboration with biologists and oncologists and contributed to a lot of physical problems to be solved. My advice would be to invest in attracting people with highly specialized knowledge. By performing animal experiments, you can answer a lot more relevant questions in research than you could with cell cultures.

Garty: Thinking about metrology for radiobiology, you should pay attention to define exactly what you want to measure or what the number you are measuring is trying to model. Because you can get one parameter which could correlate fantastically with killing of the tumor but there is no reason to believe that this could be related to acute early or late effects or the formation of secondary tumors. I find it hard to believe that one number is enough. This is the problem with RBE, everyone uses the term RBE depends on the endpoint. And the RBE for DSB formation, for dicentrics or for micronuclei are all different. So before developing the metrology, you need to define your relevant endpoints.

4.4 Protocols Session 2: Medicine and radiobiology

4.4.1 Wolfgang Dörr, MedAustron:

Radiation Effects_day2_1 00:31:31 – end

Essentials from talk:

MedAustron: First proton beam in August 2016
MedA has section for patient treatment and nonclinical research, latter W.D. contributes with research for Applied and Translational RAdioBiology (ATRAB)

Supported by Radiation Physics group (Georg)and Basic Physics group (Sihver),
->very important for doing radiobiological experiments in a proper way

Workplan:
-Characterization the biological effects of ion beams and photons
-Validation of treatment planning algorithms (Dose delivery, RBE for different end points in Tumor and normal tissue, SOBP and entrance channel
-radiation effects in normal tissue
- Identification of morbidity biomarkers -> individualization of treatment planning
- development of biology based strategies to reduce morbidity and increase tumor response

Endpoints:
example rectum, various endpoints for complications (bleeding, incontinence, ulceration...)
shift from view “organ at risk” to “endpoint at risk”
define radiation effect parameters and target structures for each endpoint
Task for 10 – 15 years

Investigating tissue:
Focus on particle therapy: SOBP, Entrance channel, dose inhomogeneity
In healthy tissue and tumor
This is done using:
-Cell culture studies
(Important capability to control oxygen contend in sample)
-Tissue culture studies using Tumor tissue
-In vivo studies (animals)

Biological Modelling (PTB can contribute here)

- cellular endpoints
- in vivo endpoints
- TPS validation and RBE modelling

Last slides, dealing with questions by PTB organizers:

Which topics of your research or working field would benefit from improving the accuracy of the determination of biological radiation effects?
Dörr: All parts, better determination of dose improves results and models
Tissue culture and in vivo radiobiology, including patients;
Modeling

Which physical and radiobiological data are involved in your research and which quantities do require a significant improvement of the accuracy?
Dörr: Organ at Risk subvolume dose/dose distribution

How would you rate the potential to increase the effectiveness of radiation therapy and the accuracy of risk assessment by a new dosimetric concept based on particle track structure?
Dörr: No ready answer, I am not expert I this

Which processes leading from the direct physical radiation effect to a biological end point need to be better quantified?
Dörr: Molecular pathways in tissues in vivo, which will be studied by MedAustron

Which areas related to biological effects have a large potential for innovation and do require metrological standardization?
Dörr: Molecular pathways in tissues in vivo, =>biomarkers, biology-based intervention
Animal studies, cell studies at PTB?

Which are the most relevant partners for collaboration and how do you see the role of PTB?
Dörr: Medical Physicist, Radiation Oncologists, Molecular Pathology, Bioinformatics/Modeling

Discussion:

Schulte: Which cell lines to be investigated (human, mouse)

Dörr: Human cell lines, mouse specific tumor cell lines

Krämer: huge work program, what are priorities.

Dörr: first cell culture experiments for validation of treatment planning systems,

Krämer: should be done before the first patient arrives

Dörr: not possible due to financial and organizational issues

Cordes: how to improve in vivo tumor models, differences between animal and human cell lines. animals are killed too fast by aggressive tumors.

Dörr: Orthotopic (vd: cells in usual environment), non-Xenografts (non-human cell lines in mice) – we need mouse tumors to study tumor response in mice, relevant end points: this means

tumor cure, not shrinkage or genetic changes after 2 weeks as done by many people. On top of that I don't know.

Cordes: last slide: identification of molecular path ways. In tissue and in vivo. How to do? We did not even manage in cell culture (method wise).

Dörr: Huge task, large variability. Requires network of collaboration, 5000 researchers are needed.

Schettino: intension to investigate stem cells and is there a role for stem cells?

Dörr: For tumors there is a role but we do not any studies. For late responding tissues I don't know and we are doing some studies. For early responding tissue we are doing studies. Problem is that we do not have proper stem cell marker.

Giesen: what are possibilities at PTB microbeam? Tissue, co-cultures and tumor micro environment was mentioned. With microbeam selective irradiation of target matrix is possible and does this make sense.

Dörr: Possibly! Only thing is in co-cultures you miss major components like immune system, macro phages, endothelial cells. Strong interaction between macro phages and endothelial cells. Cannot be modelled with in vitro models. Only solution: animal studies.

4.4.2 Kai Rothkamm – Assessment of radiation-induced DNA damage and repair

Until 2015 head of a lab for biological dosimetry at Public Health England

(slide 5) Specific biomarkers or assays which can be used as markers for radiation exposure can be found for any process between initial ionization and tissue response. Main interest in formation of DNA double strand breaks (DSB) which can be detected by γ-H2AX foci. DSB are the precursor of chromosome aberrations, which are themselves used as biomarkers.

Addresses discussion after the previous talk of V. Conte: unrepaired DSB are not so problematic, but misrepaired DSB lead to rearranged chromosomes (e.g. formation of dicentrics) where cells finally cannot go through mitosis. A large local amount of DSB is, for example, the case after high doses of irradiation, leading to a joining of the loose ends and therefore a high probability of such chromosome rearrangements. The local DSB formation is likely proportional to the formation of ionization clusters. This explains the linear quadratic increase of number of chromosome aberrations with dose.

(slides 6) Since last year he is head of a lab at UKE, Hamburg, working in the field of experimental radiation oncology. The overall aim of the group is to use DSB repair as a target to enhance tumor cell killing. The concept used here is called synthetic lethality, where it is known that if one pathway of repair is deficient in the tumor, the tumor will be addicted to a second pathway while the normal tissue still has both pathways open. The tumor cells can then be sensitized by targeting the second pathway.

Slide 7: Repair pathways, most important need is to understand how they are regulated (what are the conditions for a specific pathway to used after a DSB)

- NHEJ – non homologous end joining: classical end joining pathway

- Alt-NHEJ – alternative NHEJ: less often used in normal tissue, but occurs in a number of tumors, where for example PARP1 inhibitor could be used to sensitize these tumor cells
- HR – homologous recombination: plays role in replication processes; can only be used in already replicated systems where templates of DNA are available
- SSA – single strand annealing

A large role for selection of a pathway has resection, where nucleases digest part of DSB ends and reveal a single-stranded end; without resection, only the NHEJ pathway is open. Resection regulation is not yet completely understood

Slide 8: Biological dosimetry

- most work is performed on lymphocytes where the problem is that these cells are relatively but not completely evenly distributed over the whole body. Therefore, it is difficult to include the distribution of the lymphocytes in case of a non-uniform exposure to determine the radiation exposure.
- Exchange between lymphocytes and peripheral blood
- Historic exposure: translocations in predecessors of lymphocytes can be used as a marker for radiation exposure. Complex procedure
- Issues: Calibration curves required for different radiation qualities – nanodosimetric approach would be helpful

Slide 9: Issues in targeting of DSB repair

Slides 10-19 response to our questions

Q2. Example: measured foci formation in 400 patients showed systematic patterns due to external factors such as antibody batches (slide 13).

Slide 14: variability between scorers for chromosome aberration data even with long years of experience.

Slide 15: Results from colony assays looking of the effects of an EGFR-inhibitor where the process of plating the cells has a significant effect.

→ issues related to cellular endpoints believed to be "rock-solid"

Q3. How are ionizations distributed, what is the impact on DNA damage formation, how does that relate to repair?

ECM – extracellular matrix

Q5. Standardization for functional endpoints needed -> DSB repair, involvement of specific pathways, what happens afterwards in a specific tumor, link to epigenetic profiling?

Questions and Discussion

Schulte: My question is related to molecular targeted therapy, which is also a way of personalization. Do you think there is a way to combine molecular and radiation targeting to increase the efficiency of radiation therapy?

Rothkamm: I think this is a promizing field, because we can see for example in the combination of PARP1 inhibitor treatment for patients with breast cancer works very well for patients with NHEJ-deficiency. Based on our data, we think that a lot of tumors should be sensitizeable using PARP-inhibitor because they rely on Alternative NHEJ. The cells would not die due to the PARP inhibitor treatment but would in addition need the challenge of the radiation. The combination leads to a failure of the cell to properly repair the damage. The challenge here is for the oncologists to develop targeting therapy including both, molecular and radiotherapy. I think this is a very promizing area.

4.4.3 Guy Garty: Probing Radiation Response in single cells or "What can we learn from Microbeams"

Summary of talk:

Staff: 7 physicists / 2½ biologists

Accelerator facility is dedicated 100% to radiobiology.

Monday + Friday: maintenance etc., Tuesday – Thursday: irradiations

HVEE Singletron 5.5MV

Radiation types: H+, He++, coming soon: C6+ (and other heavier ions) @ 2.5 MeV/AMU, 4.5 keV (Ti-K) X-rays, 30 keV neutrons, UV microspot

Resolution at present: target ≈ 300nm, image ≈ 250nm

Intended resolution in the future (in progress): target ≈ 75nm, image ≈ 75nm.

Discussion:

Schettino: It is nice to see you continuously improving the micro beam. Regarding the solenoid, you got a four-tesla magnet. I guess some of the magnetic field will get to up the cell, which will be very close.

Garty: The cells are very close, but the magnetic field on the axis falls of pretty fast. Actually, our main concern is the magnetic field going into the stage that holds the cells. We have done measurements of the magnetic field, but the solenoid is actually very well shielded with a thick steel plate on top of it. I not exactly remember but I believe the cells see less than 100 Gauß.

Schettino: So, you are not concerned about the effect of the magnetic field on the secondary electrons and so on?

Garty: No.

Schettino: And if you use the solenoid, are you still able to scan the beam?

Garty: With the solenoid you are not able to deflect the beam.

Schettino: Will the throughput of cells drop?

Garty: No, because the stage we are using is pretty fast. So, we still will be able to irradiate several thousand cells per hour, which is what we normally do.

Schulte: I really like the idea of the 75nm spot. It gets you to the chromatin fiber level. It would be nice to create just one single complex break in one chromatin fiber, but the

cell still has a three-dimensional structure, and you would hit other fibers too. So, my question is, just an idea, can you spread out a cell so thin, that all the chromatin would be in a single layer, essentially? It might be a question to a biologist.

Garty: Yes, it might be a question to a biologist. What you basically need is to spread the cell and to find a chromatin fiber that doesn't have others above or below it. It may be possible to spread it thin and then go to a fiber at the very edge.

Stenger: Could you briefly comment on the PTB's micro-beam or compare yours and PTB's micro-beam under more strategic considerations and explain what you see as the unique points of our beam and what PTB may focus on in the future.

Garty: I am not that familiar with your beam. I looked at the poster yesterday. I will be able to do that after the tour that is this afternoon.

Giesen: Our micro-beam is a small part embedded in a larger system and we get only a small part of the total beam time, whereas for you your micro-beams are your main business and you have a radiobiology group in house. How much of your work is related to basic fundamental radiobiology?

Garty: Most of it. We are funded as a user facility, so we are supposed to spend roughly half the time on developing technologies and half the time on doing service or collaborative experiments with biologists, both from Columbia and from outside, and we have researches coming from all over the world to use the micro-beam. It is a service facility that is available.

Giesen: And how much time do you spend for research for therapy, RBE, etc. or for technological projects?

Garty: Mostly the work we do is for basic research.

Schulte: I assume, the users have to apply for research funding and they put in some budget to come to your user facility. So how is your institution funded?

Garty: It is mostly funded by the NIBIB, including the salaries of the staff. In principle we charge user fees, but we haven't turned back anyone who had good science and couldn't pay. We ask people to put us in their grants and sometimes they do and sometimes they don't. The grant will end in three or four years. We are looking for other funding mechanisms to keep the systems running, and we might have to be stricter with the user fees.

Schulte: So, then the users will pay your salaries.

Garty: And then the users will pay your salaries.

Schulte: It is not like a government institution like PTB?

Garty: It is not a government institution.

Nicht erkennbar: Do you think, you could use the beam itself for imaging at high resolution, if the energy would be a little bit larger?

Garty: Actually, we have been thinking about doing some kind of micro-PIXE, but we don't have any plan for doing that at the moment. And if the beam energy is a bit too low, that's another million dollars to invest in that.

4.5 Protocols Session 3: Metrology and fundamentals

4.5.1 Giuseppe Schettino: Metrology for biological effectiveness of radiation exposure, NPL activities

Video: Radiation Effects_day2_2 00:33:46 – 01:12:40

Essentials from talk:
NPL activity similar to PTB's activity
Strong link to hospital (commissioning, audit of dosimetry)
Support of new modalities in radiation therapy
Biological optimization in treatment planning

Report of NPL activities on:
- High-Z nanoparticles
- Proton beam effectiveness
- Radiobiology for MRI-guided RT
- What is radiation quality and how to measure

High-Z nanoparticles (NP)

- Enhance effect of photon radiation,
  Effect much larger than just due to effect of enhanced dose,
  > this is obstacle for translation to clinical diagnostic and therapy
- NP alter/amplify cellular response
  1 % NP double the dose, but tumor response measured in mice is much larger (than just double)
- Also with MV this effect is observed (not explainable only by dose enhancement)

Radiobiology pf NP:
Physical effect: radiation quality is changed (Auger cascade)
Chemical effect: NP react with cell molecules and radiation products (enhance scavenger effects or so, not clear)
Biological effect, interaction with DNA, modify cell cycle, modify metabolism)

How to characterize NP effect:

- Physics simulation (microscopic and nanoscopis dose distribution)
- Radiochemistry essay
- Biological essay

Quantify NP effects:

- Lots of data but very confusing because not clear how to quantified effect
- NPL tries to standardize the way of quantification
- Is NP medical device or drug (impact on approval, license, cost)

Proton Therapy Effectiveness:

BIOQUART collaboration (Squid as nanocalorimeter, known here, not detailed further in talk)

RBE for protons,

Error in SOBP > 20 %)

NIST Report(J.Research of NIST, Vol 108) “Importance of Dosimetry and Standardisation in Radiobiology”: Only 7 % or radiobiological papers refer to dosimetry standards and QA, so data cannot be reproduced.

Another paper (Radiation Research 185 (2016) reports that only 1 out of 5 labs can deliver dose within 5 % of target (*V. D.: deliver? or quote the dose better 5 % uncertainty?)*

NPL develops tools to improve pre-clinical dosimetry (animal irradiations)

animal irradiators differs from MV facilities in energy and beam size _> code of practice in dosimetry does not work

NPL attempts:

- to determine dose and RBE in SOBP of proton beams including error bars
- RBE in fractionated irradiation at different LET or proton
  Different fractionation can produce different RBE (“ with fractionation you can achieve any RBE you want”)

MRI Guided RT (Doing Dosimetry in strong magnetic field) (not further elaborated)

Summary:

What is Radiation Quality?

Various concepts; Term is not strongly defined,

if not defined, how can we define how to measure RQ

Relevant quantities in the eighties: microdosimetric quantities

But: Initial physical effect (radiation interaction, ionization) in < 1 ns) is so far away from final biological outcome (in size and time (from ns to years), in between so many different pathways and complicated biological effects.

We need to know the details of the initial process, but also the processes in the middle

There is no evidence of proportionality between initial processes and final outcome due to complicated intermediate steps.

We have to define what is RQ / RBE

Multidisciplinary approach in a wider community (not only physicists, but also chemists, biologists)

More rigorous methodology

Discussion:

Krämer: Radiation quality is a fuzzy quantity. We need energy of the beam and everything is determined.

Schettino: That what I mean: Each of us has own idea what Radiation Quality is. For you it is the energy of the beam. Somebody else will tell you that it is the risk. The long term risk? The short term risk?

Krämer: It is a fuzzy quantity for which I have no use in radiation therapy. For me Radiation quality is beam spot size, how clean is the beam, energy spread etc

Schettino: One needs to agree on a definition and then it is clear what we need to measure,

Baek: We do research with nanoparticles. Can we conclude from talk (probably the fact that the biological effect is much larger than just the dose enhancement) that effect is also increased for particles and not only for photons?

Schettino: All research is done with photons. Dose enhancement with protons is very small. Possible effect is rather from effect on cellular path ways. (i.e. biology, not physics). It depends also on nanoparticles, specific to nanoparticle and radiation (effect of material, shell…)

Conte: Nanoparticles (NP) influence effectiveness of radiation. Makes it sense to make a microdosimetric characterization of the radiation field near NP's?

Schettino: Yes, makes sense. Our interest is not in a specific nanoparticle product, many different NP in size, material. Our interest is in methodology to characterize NP behavior. Its important to come up with a microdosimetric characterization of the radiation field around NPs.

Conte: Should not be too difficult – similar to microdosimeter for BNCE, instead of doping the shell with B we dope with Gold or other NPs.

Conte: Another question: Radiation quality. Most link RQ to effectiveness of radiation action on living systems.
As physicists we need to identify those physical parameters of radiation which better relate to the final biological effect.
To Krämer: For a given particle type (e.g. C) and energy there should be a fixed physical effect, e.g. 2 different ions must have always the same effect.

Krämer: But the effect depends on so many things.

Conte: Forget whatever is in between. Are we able to characterize radiation in such a way that if such quantities (VD: intermediate processes) do not change, the effect is the same? E.g 2 carbon ions of same energy: can they behave differently (in the sense: cause different outcome?)

Krämer: This depends on the experimental setup. This is another comment to the earlier statement that only 7 % of the papers can be reproduced because they specify the full experimental conditions. In our modelling we try to compare data of different groups, but what is mostly missing is a sufficient description of the experimental setup. At best you can get a

"keV/micron" which is absolutely useless, it is an average value. You need to specify the setup.

Villagrasa: Are you planning to make experiments to obtain data for (chemical) radicals which can be integrated to simulations.

Schettino: we have done it already, done it in bulk solution, not cells, case studies with few typical nanoparticle products. Not yet published.

Conte: Gerhard: Can the (PTB-) ion counter be used to measure effect of nano particles?

Hilgers: Not at the moment without larger modifications

4.5.2 Carmen Villagrasa: Use of experimental data using microbeam irradiation in the simulation of early DNA damages

- The presented work is from a collaboration between biologists and physicists at IRSN and was performed in order to understand the mechanism of DSB induction and to determine relevant parameters.

- Introduction of relation between absorbed dose and biological effectiveness (slide 2)

- Principle of the simulation of early DNA damages with Monte Carlo methods (slide 3)

- Geometrical description of the DNA within a nucleus on a molecular level (slide 4) was designed to allow the comparison with cell experiments if the cells are in a specific cell cycle phase (G0/G1 phase). The cell cycle phase at time of irradiation can be controlled in the biological experiments.

- Summary of physical and chemical stages (slides 5-7)

- Microbeam experiments (slides 8-13)

o One observed foci is a projection along the particle track but the number of DSB along this track cannot be derived from the experiments.

o Issues related to modeling

- Results on comparison of early damage obtained from experiment and simulation (slides 14-15)

o In experiment, LET increase from 23 keV/um to 90 keV/um leads to increase in mean number of foci, while the mean value drops for an even higher LET of 160 keV/um.

o In simulations, first approximation: all ionizations along the track will give a direct SSB

-> overestimation of expected foci number

- Probability of foci per track (slide 15 lower graph): overestimated simulation results if assumed that all ionizations lead to an SSB

- Change of criteria of how the DNA can break: e.g. linear probability for an SSB between 0 at 5 eV and 1 at 37.5 eV (red curve) as used in PARTRAC or using a threshold for energy deposition leading to an SSB of 17.5 eV as in KURBUC code (black curve) leads also to better agreement with radiobiological experiments

- Perspectives: investigation of the influence of the chromatin structure (slide 16)

Questions and Discussion

Krämer: The results you show on slide 14 are not looking so bad and particularly the larger variance observed in the experiment seems to be missed in the simulations.

Conte: Do you have an estimation of the uncertainty of the radiobiological data? Particularly the interpretation of the maximum value and the drop at higher LET depend on the uncertainties.

Villagrasa: I didn't plot it, but we determined the uncertainty related to the experiment and you have the relative spread in the population, which is characteristic of the radiation. The repeatability of the experiment was very good and in this graph (slide 15) are pool data.

Conte: Could it be that you have a systematic underestimation of the number of foci due to more likely superposition of foci with increasing LET? I expect more a saturation effect than a decrease with higher LET.

Villagrasa: I don't think so because the endothelial cells were only 2µm in diameter and you will be able to distinguish if you have one or more than one foci by stack imaging. I also believe that it is a saturation effect.

Conte: Another comment: I also find that the agreement of experiments with the simulations including all ionizations is not so bad at least regarding the shape.

Villagrasa: Yes. We have also performed simulations without the chemical stage and looked at the clustering of ionizations. Actually we found a very good correlation with the shape of the biological curve when we count all ionization clusters with a threshold of 50 eV. But of course, we have to consider the chemical stage in reality.

Cordes: Currently, there is a big interest in understanding DSB reduction and repair in different chromatin regions. The chromatin distribution of hetero- and euchromatin in 3D cell cultures and tissue is very different compared to 2D cell culture systems. What is the basis on which you are simulating the chromatine models?

Villagrasa: We were planning on using monolayers of different chromatin structures, but we will adapt the protocol based on this knowledge.

Schäffter: I would like to turn the focus again on the purpose of this meeting. Would you advice PTB to work further on the development of such models in Geant4-DNA which is open source and used by a lot of academic groups? In which aspects could the metrology enter in this tool?

Villagrasa: The BioQuaRT project, in which this multi-scale tool has been developed, was founded by metrological institutes with the objective to define new quantities. This is fundamental research work because we aim to understand the underlying mechanisms. But fundamental research is also the basis for metrology. In this case, the microbeam was one of the main tools to try to understand this mechanism.

Giesen: As you are from the French metrology institute, what is your motivation to proceed with this work? And what are your plans?

Villagrasa: This work fits well with an internal project at IRSN called ROSIRIS, which has the objective to investigate secondary effects of radiation therapy. This project started in 2009 as a long-term project. These projects at IRSN are meant to feed our expertise in case of radiotherapy accidents with new knowledge of, for example, how radiation quality could be taken into account in the case of an accident.

Giesen: Do you also see a role of your work to better interpret the data in biological dosimetry and is there a motivation to use these data for investigating low-dose risk, which is also a great issue in radiation protection?

Villagrasa: Of course, these fundamental knowledge of the mechanism behind the radiation action and tools we develop are applicable not only to an investigation of secondary cancer induction but also to low dose risk problems.

Zimbal: In Cadarache you are setting up a new microbeam with biological infrastructure but only with a 2 MV Tandem accelerator, so you do not get the LET range which you can access here at PTB? Could you comment on the difference or on the reason for setting up this new facility?

Villagrasa: I am not involved in this project but I know that the new microbeam in Cadarache is meant to be complementary to the microbeam facility in Bordeaux. Both facilities should cover a large LET range, but the facility in Bordeaux has a strong focus on material studies.

Newhauser: I think the work you do to get the base of knowledge, as you call it, is terrific. I am wondering about other applications, for example cataract genesis. The ICRP has recently lowered the occupational dose limits and the NCRP will probably follow shortly. I think the mechanistic processes in cataract genesis need considerably better understanding. I know that some work in this direction is performed at IRSN, could you comment on this?

Villagrasa: The work at IRSN so far involves only biological studies. A next step in our simulation tool is the implementation of repair mechanisms so that we can take into account the different repair mechanisms present in different cell types. But with this we are limited by human resources.

U. Schneider: One important aspect of your work is the geometry of the chromatin structure. Did you try different models because there are competing models “on the market”?

Villagrasa: Generally, in the simulations it is quite heavy to change such a complex geometry. For now, my PhD student has developed a tool called DNA fabric, which enables to change the geometry relatively easily on the level of chromatin fibers. He published his results showing changes in DSB clustering in heterochromatin and some kind of euchromatin structure. So we start to look into these differences, but only on the fiber level. The next step will be to create a nucleus with different chromatin regions.

4.5.3 Valeria Conte: Perspectives for a new metrology of ionizing radiation based on NANODOSIMETRY

Historical remark:

20-25 years ago nanodosimetry started with a group of scientists, who decided to try to measure the ionization interaction in a nanometer sized volume using gas detectors with a sensitive volume containing the same mass content as a DNA segment.

Nanodosimetry is capable to bridge the gap between physics and radiobiology.

Slide 5: The main hypothesis, on which experimental nanodosimetry is basing on: "The ionization processes rule the DNA damage"

Ionizations are a measurable quantity; assumption: the amount of all the interaction processes scale with the amount of ionizations.

Slide 9: "There are unique relations between the cumulative distributions F_k of the ICSD's (= ionization cluster size distributions) and their mean M_1 that do not depend on the nanodosimeter type and site size."

Slide 15: "V79 cells irradiated by protons and ^{12}C ions: same cell - different ion species - different end points Radiobiological effectiveness at high dose corresponds to the incidence of simple DSB (F_2), at low dose corresponds to the incidence of complex DSB (F_3)"

The results for CHO cells and T1 cells are similar to the results for V79 cells. They all are radio resistant cell lines. For XRS5 cells (radio sensitive mutant cell line of CHO) (Slide 21): "Radiobiological effectiveness corresponds to the incidence of SSB (F_1)"

Slide 19: F_k is linearly proportional to σ_{biol}

Slide 23: "Measurable physical quantities are proportional to radiobiological effects: $F_k \sim \sigma_{biol}$ "

Future perspectives:

- extend this comparison to other endpoints
- extend this comparison to complex radiation fields (to see whether we are able to measure something which is related to radiation effectiveness in a complex radiation field)
- construct detectors suitable for practical use, including development of proper calibration procedures if necessary

Discussion:

Schulte: I have heard this before, that is why I am not so excited, but each time I hear it I get excited again. Let me make a suggestion for something that can be tested as well. My suggestion is you test it on hypoxic cell survival, and my prediction is that probably F4 or F5 will correlate. There are nice data for hypoxic cell survival, I believe from GSI. You could find out whether a higher order of cluster matches.

Conte: Yes, many thanks for this suggestion.

Krämer: Your inactivation cross sections versus LET showed only a very small part of the data base which is available. There are also data for inactivation for very high LET particles like uranium, etc., and all the very high LET-data showed these famous hooks. Can you explain them also? They are not so interesting for therapy, of course …

Conte: We were concentrated more on particles which are of interest in hadron therapy …

Krämer: It might be interesting to see what happens if you extend in the very high LET region because there the picture looks very much different.

Conte: The point is that we are missing the nanodosimetric measurements as well there. We have to move somewhere where high LET particles are accelerated to high energy.

Villagrasa: I am also aware of these results, and as Reinhardt says it is always exciting to see again their presentation. Can you comment about the volume in which you find this correlation. When you are looking at the radiosensitive cells, you find the correlation between F1 and the biological cross section in a volume of with a diameter of 0.3nm. This is the diameter of a single strand of the DNA molecule, and it corresponds perfectly. What I am a little bit more surprised is F2 and F3 with sizes that are less than the distances between the strands in the DNA molecule. Do you think, that this means that it is not the number of DSB's that is responsible for the correlation but just the number of ionizations?

Conte: My explanation using the DSB's was only intuitively. I am not a radiobiologist. The fitting of the volume diameter is fully phenomenological. I plotted the nanodosimetric quantity versus a biological quantity and I looked for the diameter which results the best linear fit. In the case of F2, it is roughly about 1nm and in the case of F3 it is 1.5nm.

Villagrasa: It sounds reasonable. How sensitive is this procedure, will it change completely, if you go from 1nm to 3nm?

Conte: Yes, definitely.

Schulte: Not every ionization causes a break. This is why you don't get the diameter of the DNA.

Conte: That is true. Not every ionization produces a damage. You only have a certain probability, and additionally the DNA is not oriented but somewhere around in the full solid angle.

Garty: I also wanted to comment on what Reinhardt said. When we did correlations between direct DNA damage and ionization cluster size we had a sensitive volume

that was probably 20-30 times larger than what you have, and we saw that if we assume that each ionization has a 10% chance of converting into a SSB, then we could fit the DSB-yields pretty well. So, this is a kind of modeling efficiency in chemistry at smaller sensitive volumes.

Conte: On this topic I agree. We can use this information for modeling purposes. We start from the physics and you can use this information to interpret what is happening in radiobiology. But that was not my intention. I was looking for a method to characterize the radiation field with an instrument measuring a physical quantity, which gives a picture of the physics within the time window of a therapeutic plan, without performing radiobiological measurement. The question is to what extend this method works. If it only works only for radio-resistant cells and nothing else, then it is losing interest. But if it works …

Garty: I agree, it works, and it looks great. Just if you are looking at it from the point of view of metrology and having a system for qualifying radiation you need to have consistency in your sensitive volume and basically use the same sensitive volume for all of the radiations fields and all of the …

Conte: For all radiation fields, I agree with that. Not for the biological endpoints …

Garty: I agree.

Conte: I can characterize the radiation fields in terms of the F's, and then it is a matter of the radiobiologist to know, which of the physical quantities is better related to the biological effect.

4.5.4 Alexander Dorn: Electron impact ionization of biomolecules as monomers and hydrated clusters

Video: Radiation Effects_day2_3 begin – 00:37:00

Essentials from talk:
Collaboration with PTB in Measurement of fully differential electron interaction cross sections with biomolecules
Outline: Demonstration of experimental technique
New processes on Electron atom interaction revealed by this technique
Transfer of technique to measure large biomolecules in relevant surrounding

Most of the damage caused by ionizing radiation by electron molecule interaction
Electrons are produced along the track of fast ions
Also very low energy electrons (< 10 eV) play a role, which are below direct ionization level

Goal and Questions:
Are data for track structure calculations correct

Do we need fully differential cross sections
What is the effect of the environment (condensed phase effects?)
Are there new interactions (ICD)

Technique allows also to look to fragmentation of residual ion

Relevant ionization processes:
ionization, excitation, dissociative attachment, ICD (Interatomic(molecular) Coulomb decay)
(e, 2e), MPIK introduced "imaging" technique (reaction microscope)
Helium is well understood and fits very well with theory.
It is therefore used to calibrate the instrument
Heavier noble gases (Ar...) experiments show more structured xsec-shapes, disagree with existing theories
water: fits reasonably with some theory
Tetrahydrofuran (THF) (biological relevant, part of DNA backbone)
Distinguished between different highest orbitals and looking different scattering angles

Discussion:

Zimbal: Impressive data, what is purpose behind?

Dorn: Simple targets: ab initio calculations possible
Complicated targets: theoretical models are not sufficiently good. Experimental data provide data for track structure calculations. Measurements provide experimental data base. Also provide benchmark for calculations and check if physical processes used are complete and good enough (example ICD)

Newhauser: Improving XSECS seem useful for different things. But track structure calculations are analytical calculations and use analytical models. How do they enter the analytical calculation, For MC it is clear, but in analytical models?

Dorn: I am not expert. But in analytical calculations you need to input good models. If experimental data are neglected these models miss important input.

Newhauser: Benchmarking?

Dorn: Yes

Krämer: I find this interesting, even if it is not aiming for track structure calculations (TSC). which most people here understand as MC calculation, indeed. But it has a value to benchmark quantum mechanical calculations. What is the most complex system you can calculate today, Helium was shown? Can theoreticians calculate reasonable exact beyond Helium?

Dorn: Be careful with the terminus "exact". "Exact" one can calculate hydrogen, 2-body. Helium is 3 Body. Very accurate results, but still a numerical calculation with

approximations. All more complex systems are less precise. The art is to find the most important ingredients.

Bug: Data for TSC will not only improve description of track with respect to energy transfer, the broken bonds. But with fragmentation data it will add valuable information of the damage of the DNA

Dorn: MC is a random generator, but you have to put in physics.

Newhauser: TSC usually consider lateral profile of ionization. Very simple models.

Krämer: Radial dose profile, averaged, not specific to orientation... (*the rest was not recorded)*

Villagrasa: Depends on how you simulate track. In MC details of all interaction XSECs are used.
In the MC I presented water XSECS are used. In GEANT4 DNA (Bioquart) the effects presented here are not included (double ionization). For some of the data we try to implement ….
Question: How important are these effects? THF…

Dorn: Which effect?

Villagrasa: Double ionization which leads to Coulomb explosion

Dorn: If water is initiation: not very importing (3-4 % or total xsec)
For THF its not yet known

4.5.5 Philip Tinnefeld: DNA in new roles: superresolution and fluorescence enhancement

DNA can be used to build structures of various shapes with sizes in the order of 100nm x 100nm

Starting point is a circular DNA strand from a phage with a known sequence, the approximate length is 8000bp (~ 3µm). Shaping is done by application of specified oligonucleotides having a specified sequence of bases. Due to the specific sequence of the bases, the oligonucleotides will connect to the DNA strand at those points which match to their specific sequence of bases. With this technique the DNA strand can be shaped almost arbitrarily. Additionally, the oligonucleotides can be equipped with some functionality like a fluorescent dye, so one knows exactly where the dye is located on the DNA strand.

Examples of functional devices

Energy transfer switch: excite one dye (e.g. blue), which has dyes of another wave length in its vicinity (e.g. red). The excitation energy of the blue dye is transferred to that red dye, which has a transfer dye between itself and the blue dye.

Molecular force balance: depending on the force of the balance it will go down on the respective side and can be read out by flourescence light

Nanoruler: twelve dyes each in two rows separated by 70nm to check resolution of STED-microscopy

Single molecule mirage: if a dye is close to a nanoparticle, the position where the dye is seen by the observer, may be shifted with respect to the true position of the dye, because the dye can excite a plasmon in the nanoparticle making the nanoparticle act like an antenna which "helps" emitting fluorescence photons

Fluorescence amplification system (for improving single molecule detection): binding of two nanoparticles close to a dye can enhance the intensity of the flourescence light by a factor of almost 100

Possible application in radiation physics:

DNA-dosimeter (slide 25): attach DNA nanostructure between two electrodes and measure the change in the electrical characteristics in dependence of the radiation field

Idea for optical detection of strand breaks (slide 26): put DNA nanostructure under tension such that it falls apart upon a single strand break and visualize this e.g. by a change of the fluorescence resonance energy transfer (FRET)

Discussion:

Schulte: Thank you, it looks like you kept the best for last. While you were talking I had exactly that idea with origami under tension as you said. I think you mentioned you have two fluorescent dyes that would excite each other and that would disappear if you have a break there. So you could do that even like a bulk measurement and then monitor the disappearance of fluorescence in the bulk, I would suggest.

Tinnefeld: These are some ideas I had. The problem is that you do not want to detect the DSB in a specific position. That would be easy. The problem is you have a relatively large DNA nanostructure, and wherever the break occurs you want to detect it. There I see a difficulty, because the fluorescence resonant energy transfer would only be sensitive for one specific position on your DNA nanostructure.

Schulte: You never get a track crossing through one of these structures, this will be a very rare event. You need a lot of these structures to see an appreciable number of breaks unless you give a kGy or so.

Tinnefeld: Well, if you have one break in one of these DNA origami structures, you have to create a signal from this one break in the whole big structure. One has to think about, how to amplify this signal by making a smart design, e.g. if you could put the origami under pressure, such that it would completely fall apart whenever something breaks. That will be much easier visualized than just a small conformational change, if you have only one break in a DNA origami.

Nicht erkannt: The interesting point from my point of view is that you have an enhancement system there, which is not only suitable for fluorescence effects. But if you have these exciting antennas, as you call them, close enough, you might also do other things such as surface enhanced Raman scattering, but I don't know whether this system is sensitive enough. But it still remains to be seen that in principle it should be able to detect single molecules and also

the DNA, and when you then use something like Ramen spectroscopy, you would have actually information which goes beyond that what you have with fluorescence. So this might be something to keep in mind that you might also see more detailed information with such kind of spectroscopy in combination with this kind of enhancement.

Tinnefeld: Yes of course. Meanwhile, Raman spectroscopy has also been shown to work with DNA origami structures. The problem I see is, that the volume you probe is so very small, if you are only restricted to the hot spot. And this is a problem of this dosimetry, where you want to probe a large volume of DNA, in which something happens. So, whenever something happens in a large volume, you must to be able to detect it, and I am not sure how to do this with Raman spectroscopy. It is the same problem as we have it with fluorescence.

4.6 Protocols Final Discussion:

Video: Radiation Effects_day2_4 12:55 – end

Schäffter's final remark:

Structure of the Discussion:

Demand

Societal (clinical, industrial, academic)

Legal -is there demand for new legislation

Nature of Demand: Research (Fundamental and Applied), hos can this be transferred to Service (e.g., calibrations)

Opportunities

-Leadership in New Areas of Metrology, is is new and innovative, can PTB, NPL take a leadership in this field

-Collaboration (PTB internal, Germany, Europe, Worldwide)

-Innovation

-Funding

How does it fit to PTBs research environment:

-Expertise

-Infrastructure

-Research Environment

Stenger: Guiding questions for PTB:

-Considering the mission of PTB and the general capabilities, which are to create traceability, provide accurate measurements, contribute to standardization, provide reference data open access,

- Also consider capabilities which we have, like beams, beam quality

- Also consider other NMI's like NPL and the combined access to a European research program

We need more guidance to prioritize, e.g. the nuclides or species which need to be considered
And how do it together under an European research program to address the most important issues

Essence of foil:

- In which areas are metrological issues of immediate importance;
- where demand is greatest for development of metrological approaches from the point of view of
  a) healthcare and protection of people and environment
  b) industry
  c) research?

Which are the most relevant partners for collaborations in Germany, Europe and worldwide?

Dörr: I put another field on the agenda which needs metrological support and was not addressed: i.e. Nuclear Medicine
All bio-kinetical methods are not sufficient

Schäffter:
Interesting topic, was already brought up and ranked high in earlier discussion in another department: Nuclear medicine, Pharma-kinetical modelling, internal dose calculations,

Schettino: there was an EMRP project and a follow up started this year called MetroMRT,
This looks into molecular issues of radiotherapy. PTB and NPL are involved in this.

Dörr: I am more thinking of imaging

Schettino: Imaging is part of it

Giesen: What is missing is HIGH LET, not Auger

Newhauser: PTB mission is relevant to different sectors, e.g. industry. Nanoparticles are becoming an issue and for this internal dosimetry is relevant. Is similar to nuclear medicine, synergistic.

Hornhard: I represent radiobilogy of BFS. We have dosimetry and there are a lot of uncertainties.
Biologist do not think so much about exact dose.
We need more interdisciplinary approaches:
In a new project we include microbeam and track stucture calculation in a new project. This will provide and represent the full picture. We (biologists) need to get more information of what can be provided by PTB and the physicists.

Newhauser: Lets abandom RBE and predict outcome. If we to do this what are the new quantities?

Hornhard: I cannot judge for clinics. In radiation protection we have weighting factors. For establishing other models it has to go through all committees. This may be possible.

Sauerbrey: Of what we have heard these days the tasks are only part in the realm of PTB and what they can do. For me it is not completely clear what has to be measured. But if there is anything to do it calls for on an European level of collaboration. Collaboration with institutions with capabilities which PTB does not have. Helmholtz centers may be a good partner and I can offer to start such a discussion.

Gargioni: comment form a former PTB member and now in applications of these methods in conventional radiotherapy with photons. Wo I know both areas.

I see following tasks for PTB:

1. Its strength is availability of different standardized irradiation beams and tools for standardization and harmonization.

2. Develop and derived data and correlation between measureable physical quantities and biological effects. Valeria Conte elaborated on this. Develop a primary standard for radiation quality, however we define it. This is a research issue not resolved till today.

Also provide a portable detector for people in the clinic to decide which (radiation) quality should be used for a certain patient and his disease. PTB can provide a primary standard for calibrating these detectors and for providing standard beams.

What I better see for the European level would be the data base. Cross sections for Monte Carlo. and in collaboration with Helmholtz, GSI or UKE also for biological data. Mission of PTB and NMI can be to provide tools for standardizing protocols like mentioned by Giuseppe Schettino.

Schäffter: As outsider I got feeling that on the physical level of radiation quality there was a consensus. It's clear that it is an energy deposition which can be measured. Complications started when we go to the chemical stage and even more when we go to biological reactions. There no consensus is reached. Cell experiments? With which cells? Which directions? Which cell lines? Shall we use cell kill phantoms? Shall PTB move in this direction and/or shall we move into collaborations. That's not clear for me.

Krämer: Comment on RBE (from E. Gargioni's comment) If RBE shall become a metrological standard you have to associate a unit to it … You want to provide a standard: Standardization for biological effects have large error bars. Part is due to biological system but other arise from the experimental system, procedures, materials etc. I don't know if this fits into realm of a PTB, probably better to a Biological (Bundes Anstalt)- which does not exist. Possibly PTB can move a bit into this direction with a physicists' background and with experience in reproducibility...

Schäffter: I agree. PTB should not do a definition of cells etc. But in the whole field this seems to be very important. A recent reference article stated that 50 % of all landmark papers (VD: in radiation biology?) cannot be reproduced because materials and setup were not properly described and there are no standards. Stimulating standardization can be organized by PTB on European and also community level

Schulte: We need to refocus. Why I am sitting here. I started career to develop proton therapy because we have a Bragg peak, expected to cure tumor without side effects etc. This dream was destroyed quite early. We saw that same physical dose, measured with traceable standards to PTB instruments had completely unexpected side effects which could not be explained.

This was with proton therapy, which we believed is marvelous. I was in a center which was the first clinical center in the field. People there did not like to admit that they see something that they can't explain. That made clear that dose is not a metrological quantity to

characterize the effects of what is seen in patients. But also biological effects are not useful as replacement for a metrological quantity which should be a physical quantity. Error bars (in biology) are huge – regardless of dosimetry. Is the nature of biology! There is strong need for new quantities which characterize radiation quality. RQ means a radiation of that quality causes a certain biological effect. This quality can be determined from e.g. particle type and spectra, flux and time scale of delivery, direction. We need something to replace dose. But I am shure that it is not just RBE times dose.

Güttler: In chemistry and biochemistry, to characterize status of health of an environment or a person we use markers or "analytes" which should represent a large environment of person. Markers need to be selected and prioritized. They cover a large range, e.g. for food, water air, health. etc. PTB's task is not to select and prioritize the applications nor the markers. This comes from the specific community. PTB needs the input from outside where to set priorities. E.G. data bases cover a huge field. We need input of what is required to put into data bases, selective with respect to its importance and generality. This should come from you as a community.

Newhauser: This is a good point and takes place in dosimetry since long. Example is ICRP and ICRU. They developed standardized dosimetry protocols where they call for NMI to provide service. In that way I would point out that proton therapy is now the fastest growing treatment technology and there is not a worldwide primary standard for proton absorbed dose. Sounds a bit shocking, e.g. to have a multi-billion blockbuster drug and have not absolute certainty about dosage of the drug. In case of protons the dosimetry is similar enough to photon therapy to use similar concepts and calculate correction or conversion factors. But the community would wish to send their dose meters to a calibration lab to calibrate them in a proton beam.

Schettino: Absolutely. That is priority of NPL to have proper calibration before the UK centers becomes operational. We will have a primary standard and code of practice for proton therapy. This is mandatory in the UK. They will not start any treatment before they tis is not available. Having e.g. a calorimeter for protons as primary standard.
(To Güttler:) I agree with you, input must come from the community what needs to be measured. But it's quite clear that the community does not know that themselves, what quantity should be measured. Question is whether NMI should wait passively on community to come up with something and then start measuring or rather actively engage and help to define the quantities. NPLs mission is to engage in collaborations to actively support this new therapy by biological optimization. So NPL takes an active position.

Schulte: Let me speak as representative of the "community".

Schettino: if you know what they want tell us...

Schulte: I know, but in that respect I am not representative of the community. The proton therapy centers are the end users. Three groups are interacting: First the group of end users (therapy centers). We cannot expect them to work on new standards, do metrology or do biological research. We hear also that the metrology centers will not do the biological research which is

outside their realm. The missing link is what Wolfgang (Dörr) represented: A national center for particle therapy research, connected to clinic, medical physics, doing biological research but has to collaborate with the NMI to make it most efficient. One of such institutes per country, e.g. Germany has GSI, Austria has MedAustron.

Giesen: In the past we came up with lot of new ideas, improvements and measurements. E.g GSI came up with LEM 4 but the clinics doesn't use it, instead still using LEM1. How to improve transfer of the ideas (research results) by the medical community?

Following shot discussion was not recorded.

Krämer: you have to talk to the doctors if you want innovative methods implemented. You need to find the most innovative doctors to get through with new methods. And there are also legal aspects: To use it in clinic you need to follow a medical product certification. Usually you cannot do this as a research institute or as PTB. You need commercial partners because it costs a lot of money and time.

They use still LEM 1 because they do not want to change the protocols too often. Even if they know they can do better they go for established protocols. Don't forget legal aspects – you cannot change a treatment protocol if you have a newer and better insight unless it is approved and legal. I guess in the US this is even more so the case.

Conte: I want to provide a recommendation. I understand that RQ can be obtained from particle type and energy. What if we do not know these parameters? Frequently this is the case in radiation protection but also in therapy.

My optimistic vision is that there is another measurable quantity which is included in the physical information which can predict the radiation quality. I see nanodosimetry as an approach to this. A capability to have a measurable quantity for radiation quality; which does of not include everything but provides relevant parameters to characterize the biological effect of ionizing radiation. My recommendation is to separate the physical characterization of the radiation form the biological effect.

Example: For hunting I need gun and bullets. Bullets are not specified by their capability to kill a certain animal but rather on their composition, caliber, penetration capability etc. The customer makes his selection on this parameters, measurable quantities of the gun and ammunition, and judges by his experience and knowledge on what is needed to yield a certain "biological" outcome.

The Discussion is here interrupted because some people start leaving and some concluding remarks have to be provided by Dangendorf and Stenger. After that the discussion was not resumed since several people had to leave.

4.7 Summary by Newhauser and Schäffter:

Video: Radiation Effects_day2_4 begin – 00:12:55

Newhauser:
Reminnding participants that this workshop is to give PTB input and vision and develop a strategic direction

Schäffter:
Slide 1: puts on list of questions send to experts

Conclusions drawn from different presentations:
Newhauser emphasizes secondary cancers to become major problem in radiation therapy
Metrological needs to assess secondary cancer and complication risk:

- Calculate dose, radiation quality (debated) and risk in treatment and diagnostics for all irradiated tissue
- Spectrometry for all kind of radiations
- Quote uncertainties, especially in simulation work

Participate in a long-term multi-disciplinary endeavor involving physics, epidemiology, oncology, informatics, biology. How can this be established?

Newhauser:
Schulte summary:

-Validation of treatment codes and models.
-Validation of microscopic and nanoscopic dose distributions.
-Radiobiological studies to validate e.g. nanodosimetric approaches to biological effects
-Develop new approaches to biological effectiveness than just the traditional

Schäffter:
Krämer summary:

- Choose pragmatic approach from physics to biology
- Interdisciplinary: physics, (radio)biology, chemistry, engineering, doctors
- Therapy at higher energy
- Microscopic damage (clustering)
- Therapy in combination with imaging

Newhauser:
Verhaegen: need for

- better cross sections, stopping powers, imaging
- verification imaging
- physics input (LET, DNA damage, dose rate neutron dose,..
- go beyond cell experiments: small animal radio therapy for protons
  (this was requested by many participants to overcome the present shortcomings in the radiation action concepts.

Schäffter:

Dörr emphasizes this latter point

Explains all the complexity of what is necessary

PTB as a metrology institute cannot do it themselves but requires collaboration

Rothkamm mention collaboration on European level:

- EU Concert / Melodi for low dose research
- DEGRO and ESTRO for oncology
- Universities and other large scale infrastructure (HHZ)

PTB key role here: Radiation sources, Modelling, Data analysis

Newhauser:

Summary of all sessions:

Applications: Research/standardization/calibration in support of radiotherapy (especially particles), with consideration of imaging (therapy and underlying mechanisms)

Quantities: Absorbed dose, radiation quality (lots of dispute about this concept), risk of detrimental radiation effects (traditional concepts in radiation protection are not adequate), ionization clustering, and uncertainties

Nuclear Data Needs: Stopping powers, W-values, and cross sections

Validation of Computational Codes, e.g., treatment planning, track structure, Monte Carlo, benchmark data …

Validation of Experimental Methods: Standardized bio-dosimeters (e.g., cell lines, methods), imaging, …) Comparability today is largely missing, therefore validation and standardization is apriority

Multidisciplinary Collaborations: medical physics, oncology, informatics, radiation biology, epidemiology, engineering, and others

Schäffter:

Structure of the Following General Discussion:

Demand

Societal (clinical, industrial, academic)

Legal -is there demand for new legislation

Nature of Demand: Research (Fundamental and Applied), hos can this be transferred to Service (e.g., calibrations)

Opportunities

-Leadership in New Areas of Metrology, is is new and innovative, can PTB, NPL take a leadership in this field

-Collaboration (PTB internal, Germany, Europe, Worldwide)

-Innovation

-Funding

How does it fit to PTBs research environment:

-Expertise

-Infrastructure

-Research Environment

4.7.1 Rabus: Forecast on future on Ionizing Radiation Metrology:

-Radiobiology will play a central role in future radiotherapy treatment planning

->requires development of metrology support for radiobiology

- Verification of the treatment by biologically relevant in-vivo dosimetry will become more important

-> requires development of suitable detectors

- Absorbed dose will continue to be used for QA of treatment delivery

->additional quantities needed to account for radiation quality

- Modelling for treatment planning will be more challenging

->Efficient simulation tools needed (including uncertainty assessment)

->Measurement of reaction parameters needed (e.g. DNA dosimeter)

5 Annex 2: List of participants

Invited Experts:

Dr. Valeria Conte	Istituto Nazionale di Fisica Nucleare (INFN), Legnaro National Laboratories (LNL) Legnaro, Padua, Italy valeria.conte@lnl.infn.it
Prof. Dr. Nils Cordes	OncoRay, National Center for Radiation Research in Oncology Dresden, Germany nils.cordes@oncoray.de
Dr. Alexander Dorn	Max-Planck-Institut für Kernphysik (MPIK) Heidelberg, Germany dornalex@mpi-hd.mpg.de
Prof. Dr. Wolfgang Dörr	Medizinische Universität Wien, Klinik Strahlentherapie Angewandte und Translationale Strahlenbiologie (ATRAP) Wien, Austria wolfgang.doerr@meduniwien.ac.at
Dr. Elisabetta Gargioni	Universitätsklinikum Hamburg-Eppendorf (UKE) Hamburg, Germany e.gargioni@uke.uni-hamburg.de
Dr. Guy Garty	Columbia University RARAF, Nevis Laboratory Irvington, New York, USA gyg2101@cumc.columbia.edu
Dr. Sabine Hornhardt	Bundesamt für Strahlenschutz (BfS) FB Strahlenschutz und Gesundheit Oberschleißheim, München, Germany shornhardt@bfs.de
Dr. Michael Krämer	GSI Helmholtzzentrum für Schwerionenforschung Darmstadt, Germany m.kraemer@gsi.de
Prof. Dr. Wayne Newhauser	Louisiana State University Baton Rouge, Louisiana, USA newhauser@lsu.edu
Prof. Dr. Kai Rothkamm	Universitätsklinikum Hamburg-Eppendorf (UKE) Hamburg, Germany k.rothkamm@uke.de

Prof. Dr. Roland Sauerbrey	Helmholtz-Zenrum Dresden-Rossendorf e. V. (HZDR) Dresden, Germany r.sauerbrey@hzdr.de
Dr. Giuseppe Schettino	National Physical Laboratory (NPL) Teddington, London, UK giuseppe.schettino@npl.co.uk
Prof. Dr. Uwe Schneider	University of Zürich, Science Faculty (UZH) Zürich, Switzerland uwe.schneider@uzh.ch
Prof. Dr. Reinhard Schulte	Loma Linda University (LLU) Loma Linda, California, USA rschulte@llu.edu
Prof. Dr. Philip Tinnefeld	Technische Universität Braunschweig Braunschweig, Germany p.tinnefeld@tu-braunschweig.de
Fabiano Vasi	University of Zürich, Science Faculty (UZH) Zürich, Switzerland fabiano.vasi@uzh.ch
Prof. Dr. Frank Verhaegen	Maastro Clinic Maastricht, Netherlands frank.verhaegen@maastro.nl
Dr. Carmen Villagrasa	Institut de Radioprotection et de Sûreté Nucléaire (IRSN) Fontenay-aux-Roses, Paris, France carmen.villagrasa@irsn.fr

Participants from PTB, Various Divisions

Dr. Bernd Güttler	PTB, Division 3, Chemical Physics and Explosion Protection Braunschweig, Germany bernd.guettler@ptb.de
Dr. Andre Henrion	PTB, Working Group 3.12, Bio-organic Analysis Braunschweig, Germany andre.henrion@ptb.de
Prof. Dr. Rainer Macdonald	PTB, Department 8.3, Biomedical Optics Berlin, Germany rainer.macdonald@ptb.de

Prof. Dr. Tobias Schäffter
PTB, Division 8, Medical Physics and Metrological Information Technology Berlin, Germany
tobias.schaeffter@ptb.de

Participants from PTB, Division 6 "Ionizing Radiation"

Dr. Ulrike Ankerhold — Department 6.2, Dosimetry for Radiation Therapy and Diagnostic Radiology
ulrike.ankerhold@ptb.de

Dr. Woon Yong Baek — Working Group 6.51, Phase Effects in Radiation Action
woonyong.baek@ptb.de

Dr. Marion Bug — Working Group 6.53, Track Structure Simulation
marion.bug@ptb.de

Dr. Volker Dangendorf — Working Group 6.52, Nanodosimetry and Detector Development
volker.dangendorf@ptb.de

Dr. Ulrich Giesen — Working Group 6.54, Biological Radiation Effects
ulrich.giesen@ptb.de

Dr. Gerhard Hilgers — Working Group 6.52, Nanodosimetry and Detector Development
gerhard.hilgers@ptb.de

Dr. Hans Rabus — Department 6.5, Radiation Effects
hans.rabus@ptb.de

Dr. Annette Röttger — Department 6.3, Radiation Protection Dosimetry
annette.roettger@ptb.de

Dr. Thorsten Schneider — Working Group 6.34, Dosimetry for Brachytherapy and Beta Radiation Protection
thorsten.schneider@ptb.de

Dr. Jörn Stenger — Division 6, Ionizing Radiation
joern.stenger@ptb.de

Dr. Andreas Zimbal — Department 6.4, Neutron Radiation
andreas.zimbal@ptb.de

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Physikalisch-Technische Bundesanstalt
Braunschweig und Berlin
Nationales Metrologieinstitut

Bundesallee 100
38116 Braunschweig

Presse- und Öffentlichkeitsarbeit

Telefon: (0531) 592-93 21
Fax: (0531) 592-30 08
E-Mail: presse@ptb.de
www.ptb.de

Vertrieb:
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