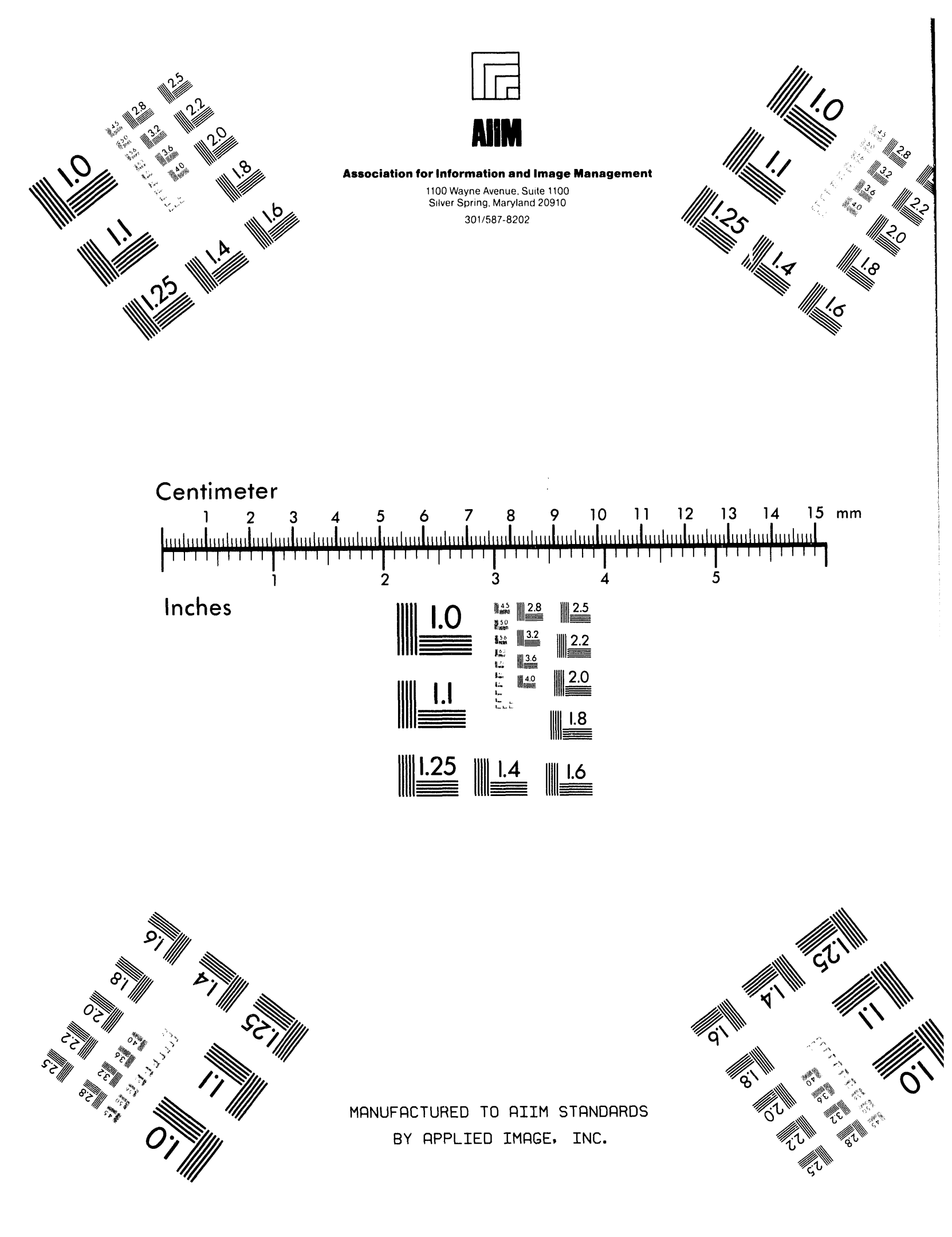
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BIOMEDICAL USER FACILITY AT THE 400-MeV LINAC AT FERMILAB

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Biomedical User Facility at the 400-MeV Linac at Fermilab

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In this paper, general requirements are discussed on a biomedical user facility at the Fermilab's 400-MeV Linac, which meets the needs of biology and biophysics experiments, and a conceptual design and typical operations requirements of the facility is presented. It is assumed that no human patient treatment will take place in this facility. If human patients were treated, much greater attention would have to be paid to safeguarding the patients.

General requirements for biology user facility

First, let's consider the differences between biomedical experiments and physics experiments that are conducted at an accelerator facility. Physics experiments generally take a long time to set up, and take an extended period, over days, weeks, and even years at a stretch, to accumulate data. During an experiment, changes in beam characteristics, such as the particle energy or beam intensity, are requested only occasionally, unless these variables are specifically designed parameters of the experiment. On the other hand, biology experiments have to be set up quickly, in minutes to hours at most, and the irradiations of biological samples are accomplished quickly, again in minutes or hours. Therefore, in a typical biology running time of an 8-hour shift, several biology experiments are scheduled requiring frequent switching of beam parameters, such as the beam energies impinging upon the biological samples, dose rates, beam sizes, and extents of modulation of stopping range within the samples. This implies that a biomedical facility must be designed to accommodate varied requirements of biology experiments quickly and reproducibly. As the same irradiation room as well as the preparation rooms will be successively used by several different experimenters, they must be designed as a multi-user facility.

Next, the extracted beam characteristics are discussed to meet varied biomedical experimental requirements. Many cell experiments need uniform radiation fields of moderate size, e.g., 10 cm diameter with a dose uniformity within ±2.5% of the norm. Then, there are experiments in which large mammals or groups of animals are

irradiated, requiring 30 cm x 30 cm fields, and sometimes even up to 1 m x 1m radiation field. The biology experiments also use varied thicknesses of the targets in which the protons are brought to rest; therefore, requiring different widths of the spread-out Bragg peak. Typical cell colonies grown on the flat surfaces of incubation flasks measure less than 100 μm, and usually pristine (*i.e.*, unmodified) Bragg peaks are used to irradiate them. When tumors or organs in animals, or entire animals are irradiated, the width of the spread-out Bragg peaks must be enough to cover the thick targets, up to the entire range of the beam in the target (≈30 cm or more). Certain experiments, such as for irradiating yeast or spores, call for high dose, e.g., $>10^6$ cGy, in ≈1 minute of irradiation time. There are occasions when the experimenters vary dose rates, in which very high dose rate may be requested, *e.g.*, an instantaneous rate of $>10^6$ cGy/sec. On the other hand, in a low-dose chronic irradiation experiment, such as simulating the galactic cosmic-ray environment, experimenters may request the beam of 10^4 protons/cm^2/sec administered in 1-second exposure per animal per day, 5-7 days per week, for 6 months. All these varied experiments must be accommodated in a sequence in quick succession; the Linac must provide extracted beams of varied beam characteristics, with their change-over accomplished quickly and reliably.

Next, general requirements are considered of accelerator and the beam delivery reliabilities. Most experiments with living organisms are time-sensitive, in the sense that delays in irradiation schedule due to breakdowns in accelerator operation, beam delivery, or dosimetric system painfully, and sometimes irrevocably, affect the biology experiments. In the case when the sensitive time-window of the living organisms is missed, the experiment must be postponed as the biological samples must discarded and new samples re-prepared. Such preparation may take weeks for cells and months for animals. Another important aspect of biology runs is delivering repeated irradiations on schedule. In most biology experiments, many samples are irradiated to account for variations in biological systems (statistics), or samples are sometimes irradiated many times (fractionation). Some samples are irradiated over extended periods, weeks, months, and even years. It implies that the accelerator performance, dosimetry, beam quality, and experimental setups must be accurately and reliably reproducible. In a certain fractionation experiment using cells, for example, 12 samples are to be irradiated 10 times in succession, every 4 hours, with allowed 10 minutes of slips in irradiation schedule. Such an experiment requires that the 120 irradiations must be delivered in approximately 40 hours without missing a single irradiation schedule by more than 10 minutes. Otherwise the whole experiment must be repeated from scratch. In simulating radiation treatments, two-dozen animals may be irradiated three times

per week (Mondays, Wednesdays, and Fridays) for four weeks. Any miss in the irradiation schedules will result in obtaining new (non-irradiated) animals and start the experiment all over — an expensive affair for the experimenters. If the miss occurs at the latter stage of the experiment, it is more costly as the loss of the experimenters' labor must be accounted for. Typically a biology research group consists of a scientist (the principal investigator), a post-doc, and a technician. The group's annual budget for experiments may include two trips to the accelerator facility. It is easy to appreciate the devastation the group suffers of an accelerator failure that ruins one of their experimental runs. (Because of the accelerator failure, an assistant professor may lose the chance of obtaining her tenure.) Physics experiments can be usually repeated at a later time; biology experiments often do not have the luxury of next time or later time. Because any unrecoverable malfunctioning during the irradiation process can ruin biological samples, it is important that the irradiation procedure must be reliable. The facility, including the accelerator, beam delivery, and dosimetry systems, should be, within reason, ready when needed by the experimenters. The availability of the proton beams with appropriate beam parameters must be better than 99.9% within minutes of demands. The beam delivery and dosimetry system should be designed "fail-safe"; and when the malfunctions do occur, the irradiation data must be recoverable so that the interrupted irradiation procedure can be resumed without wasting the biological samples.

Typical biomedical facility

A typical biomedical irradiation facility may consist of a shielded irradiation room, two experimental preparation rooms, a biomedical control room, and an irradiation control station.

The irradiation room should be able to bring protons of all interested energies into the shielded irradiation room. The beam line should probably be split into two independent and fully-equipped beam lines to facilitate setting up two different experiments at the same time, because the beam-line setups are different for different experiments. As soon as one experiment is over, the beam can be switched to the other beam line, possibly at a different beam energy, to start the second experiment.

The experimental preparation rooms should be located in an immediate vicinity of the irradiation room. It is necessary to protect the biological samples from natural elements during transportation from the preparation room to the irradiation area. One of the experimental preparation rooms is for cell experiments and the other for animal

experiments. The former is equipped with laminar air flow hoods to prevent contamination of an experiments, and one experiment contaminating the other. The latter has two segregated areas to store two kinds of animals at the same time. (For details, see below.)

The beam delivery and dosimetry are controlled from the biomedical control room, which should be distinguished from the main Linac control room, which controls the accelerator and the beam transport up to the irradiation room. An irradiation control station is located immediately outside of the irradiation room to facilitate biology experiments. Many biology experiments irradiate multiple samples requiring many sample changes and short exposures (opening the radiation door breaking the radiation chain, entering the irradiation room by experimenters for sample exchanges, exiting the room, resetting the radiation chain, and resuming irradiations). For these experimenters, controlling the exposure procedures from the irradiation control station greatly facilitate the running of the experiments. Availability of robotic sample changers will greatly facilitate the multi-sample biology runs.

Dosimetry control system

The protons are accelerated in the Linac, extracted at a certain specified energy, and transported into the irradiation room by a series of bending and focusing magnets. As the proton beam enters the irradiation room, it is modified according to the requirements of the biology experiments. Various beam parameters are manipulated and monitored by the dosimetry control system to ensure the delivery of the desired radiation.

Here, the impact on biology experiments is discussed of the emittance of the proton beam from the Fermilab Linac, which is taken to be: the transverse emittance (unnormalized 90%) of $<1\pi$ mm-mrad (minimum) and 7π mm-mrad (maximum). When a proton beam impinges a biological sample, taken to be of uniform water density, the multiple scattering broadens the beam. An order-of-magnitude analysis will be performed to see whether the Linac emittance will be the limiting factor in the biomedical beam delivery. The first analysis is for a proton beam irradiating a field of r = 10-cm radius into z = 20-cm range. For such protons the multiple scattering will produce a Gaussian-like spread with $\sigma_y \approx 0.43\,\text{cm}$. A comparable divergence is given by: $\varepsilon \approx r \cdot \theta \approx r\frac{\sigma_y}{z} \approx 10^{\text{cm}}\frac{0.43^{\text{cm}}}{20^{\text{cm}}} \approx 2.2\times10^{3}\,\text{mm}-\text{mrad}$, which is two orders of magnitude larger than the Linac emittance. The second analysis is for a proton beam irradiating a field of r = 0.5-cm radius into z = 10-cm range. For such protons the

multiple scattering $\sigma_y \approx 0.23\,\text{cm}$. A comparable divergence is given by: $\varepsilon \approx r \cdot \theta \approx r\frac{\sigma_y}{z} \approx 0.5^{\text{cm}}\frac{0.23^{\text{cm}}}{10^{\text{cm}}} \approx 1.2\times10^{2}\ \text{mm}-\text{mrad}$, which is again much larger than the Linac emittance. In either case, the Linac emittance is not the limiting factor for biomedical beam delivery. Practical limitations originate from not only the multiple scattering in the target, but also in beam path, as well as the angular confusion and effective "source-to-target" distance. All these considerations strengthen the above conclusion: the Linac emittance is quite acceptable for most of contemplated biomedical experiments.

A beam line may be built over optical rails, which facilitate the alignment and positioning of various monitors and beam modifying devices. Since the beam transported into the irradiation room has a small spot size, <1 cm in diameter, and since the desired target size is larger than the beam spot, the beam is scattered and/or defocused to broaden its profile laterally. The profile of the scattered beam is approximately Gaussian, and, for radiation fields of <5 cm diameter, the scattered beam is collimated to utilize the portion of the beam around the central ray before it irradiates the biological sample. The attainable field size depends on the proton beam energy, and the required field uniformity within the useful field (usually biologists insist on getting better than ±2.5%). The lateral beam broadening is determined by the beam energy, the beam emittance, the scattering material and its thickness, and the drift space between the scatterer and the target. Larger fields necessitate thicker scatterers, which produce more fragmentations of the target nuclei and much background neutrons, and consequently compromise the beam quality of the radiation received by the biological samples. For larger radiation fields up to ≈20 cm diameter can be produced either using double scattering system with occluding post-and-ring assembly[1, 2] or the contoured scatterer.[3] Even larger fields may be obtained using a beam scanning system.[4-6]

The sample is positioned at the end of the beam line, usually at the distal location on the optical rail. For multiple sample experiments, the samples are mounted on a sample translator which sequentially place the samples in the beam line for irradiation. The sample translator eliminates the tedious sample exchange by the experimenters that necessarily break the radiation chain, entering and exiting the irradiation room by the human experimenters, and resetting the radiation chain. In irradiating large animals, a computer-controllable precision target alignment table, with 6 degrees of freedom (3 space and 3 angles) will be very useful. The alignment of a sample on the beam line is facilitated by laser localizers, and verified by two orthogonally-positioned x rays.

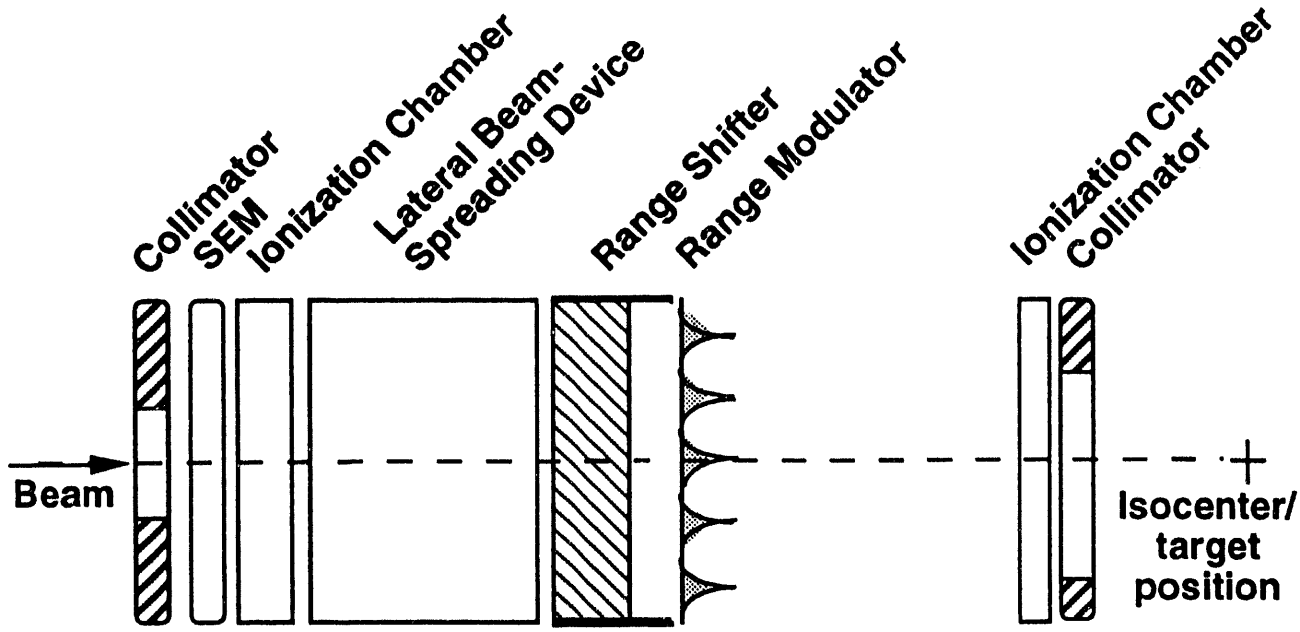


Fig. 1. A typical beam line for biology experiments.

A typical beam-line set up for a biology experiment is shown in Fig. 1. The proton beams are tuned using wire chambers, which measure x and y positions and dimensions of the beam spot. (Here, the beam axis is taken as +z direction, and the lateral directions x and y.) Most of the instruments discussed below are described in a recent review article,[7] and their descriptions are kept to minimum here. Parallel-plane, segmented-element ionization chambers are used as dose detectors. Each ionization chamber has two charge collecting planes, one of them is divided in four quadrants to detect the position of the center of the beam, and the other is divided into several concentric circles which measure the size of the beam spot if the Gaussian distribution of the beam profile is assumed and the beam is centered accurately.[8] In each biology experiment, the ionization chambers are calibrated against a standard thimble ionization chamber, which is positioned at the center of the target, and whose calibration is traceable to a National Institute of Standards and Technology (NIST, formerly the NBS) source. A secondary emission monitor (SEM) is used as a backup to the ionization chambers. It has a lower dose sensitivity than the ionization chambers, but it serves well when the ionization chambers saturate because of a high dose rate.

The beam range is varied using a variable water column, which automatically places specified thickness of water in the beam path. A Bragg curve of a proton beam may be

measured by placing one ionization chamber upstream of the water column, and the second ionization chamber downstream of it and immediately upstream of the target. If a series of measurements at various water thickness settings is made, the dose measured by the second chamber (relative ionization at a given depth of water) normalized to the readings of the first chamber (the total number of the incident protons) produces the Bragg curve of the ion beam inside a water absorber. Either plastic or metal range shifters (called "binary filters") may be used in place of the variable water column.

The width of the Bragg peak can be spread out by modulating the range using a ridge filter. The profiles of the plastic or metallic ridge absorbers are machined in such a way that a constant biological dose is imparted across the entire width of the spread-out Bragg peak. A monoenergetic beam so modulated would have particles of different energies with different divergences. The shorter-range particles would suffered higher scattering by going through the thicker material, and consequently larger divergence. Therefore, a ridge filter must be designed for each energy of the incident beam, and for a given drift space. Low-Z materials, such as plastic or aluminum, are preferred for making ridge filters as they scatter the beam particles less than the higher-Z materials, such as copper or steel. As mentioned above, thin samples, such as cells grown on flat plates, do not need range modulation and are irradiated using pristine Bragg peaks.

The dosimetry control system performs irradiation procedures according to the parameters specified by the experimenters. It should also perform various irradiation procedures, such as beam monitoring, Bragg curve taking, calibration of the dosimetry system, irradiation procedures for single sample and multiple samples, and data collection and bookkeeping of all the irradiation procedures performed by the system. It also controls the position of the beam plug, the thickness of the variable water column, the placement of the target by the sample translator, etc. Recently a very extensive dose delivery control system, that was developed for human treatments at LBL, was described,[9] and specifications of a patient treatment control system were published.[10]

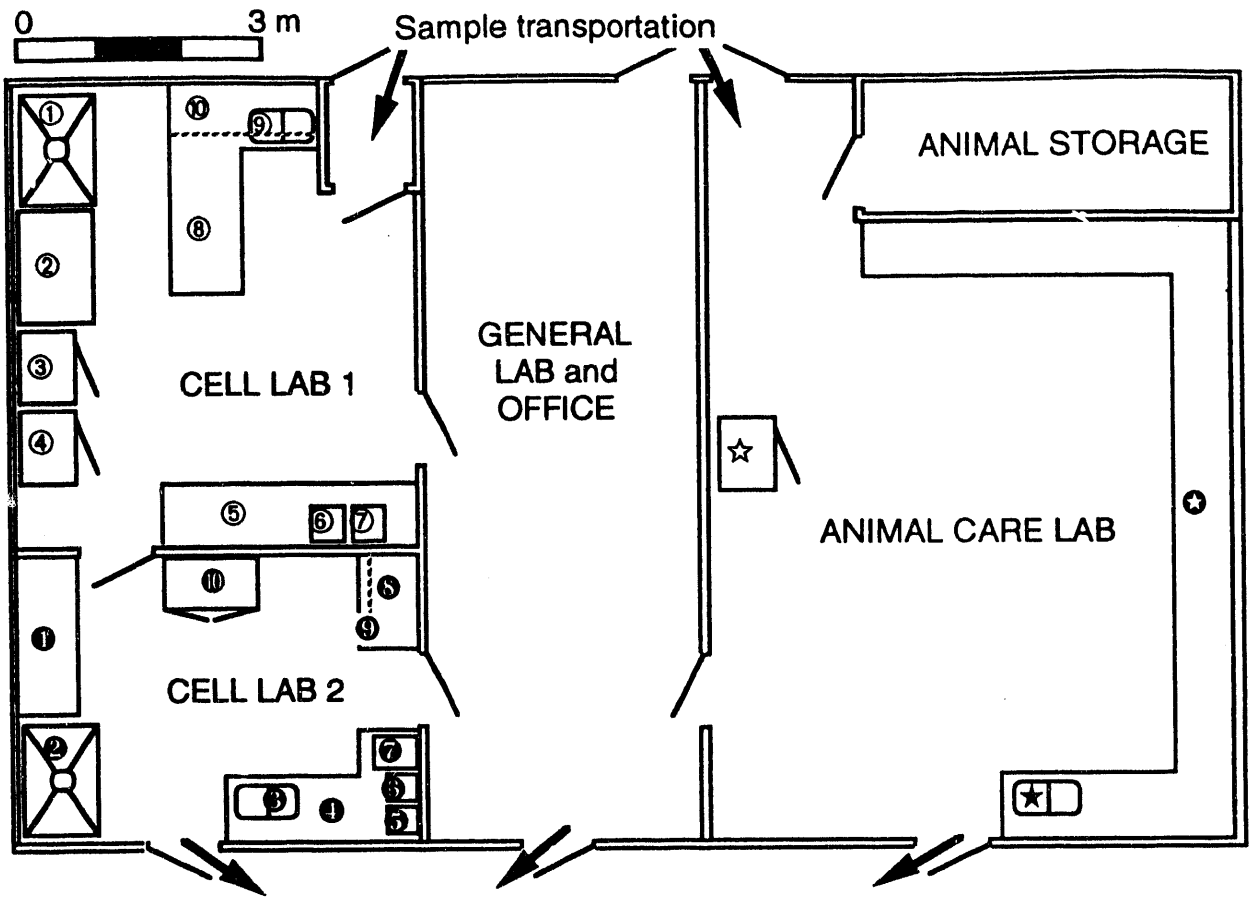
Description of a biomedical irradiation facility

A sketch is made to equip a biomedical user facility as described above. The items are grouped in the following categories:

- Biomedical control room: The operator must have visual access to all computer functions and monitors, and immediate access to the controls of critical devices to terminate irradiations in case of malfunctions. It includes a control room structure, electronics racks, CCTV systems to monitor the experiments, and an

operator's console. Dosimetry control computer system — Computers, peripheral devices, graphics display terminals, as well as the software implementation and documentation.

- Irradiation room equipment includes the beam-line modifiers and monitors for two beam lines, laser localizers, x-ray units to align animals, automatic sample positioner for multi-sample experiments, overhead hoist, CCTV, and intercom system. The beam-line monitors include optical rails, wire chamber for beam tuning, ionization chambers for dose measurements, secondary emission monitor, associated power supplies, dosimetry control electronics, including VME or CAMAC and appropriate electronic crates and patch panels, and fast beam chop system to terminate the irradiation. Also included is testing equipment such as a standard current source for calibrating charge integrators for ionization chambers, an electrometer for calibration verification, an oscilloscope, and a Geiger counter for monitoring items removed from radiation area. Beam-modifying devices include degrader foil system to scatter the beam for broadening of the beam profile, set of ridge filters to modulate the proton ranges, and a variable water column to modulate the range of the beam. Also, collimators to define the port shape or to protect the detectors must be provided. If on-line imaging system is not available, and films are used for alignment aids, x-ray film developer should be provided.
- Biology experimental preparation rooms: To perform biology experiments, experimental preparation facilities must be located in the immediate vicinity of this irradiation room. A sketch of a biomedical experiment preparation room is shown in Fig. 2. Constructing a cell preparation room equipped with cell handling equipment, and a animal holding room which has two segregated areas to hold two different experiments are proposed. To perform biology experiments using large uniform-dose fields to irradiate large animals, such as monkeys and dogs, a large radiation field must be prepared without resorting to the scattering method which provides a limited field size while degrading the beam quality of proton beams. A large uniform-dose field of radiation may be provided by using a wobbler[4] or a raster scanner.[5] It is also highly advisable to provide an alignment couch if large animals experiments are planned. It will provide an efficient way to align the target accurately to the beam. Such a setup may include: alignment couch and its control electronics (required for accurate alignment in 3-dimension



① Laminar flow hood, vented
② Laminar flow hood
③ CO_2 incubator
④ Flammable material storage refrigerator
⑤ Workbench, with drawers under
⑥ Coulter Counter
⑦ Coulter Channelyzer
⑧ Workbench, with drawers under
⑨ Double sink
⑩ Wall-hung storage cabinet

❶ Workbench, with drawers under
❷ Chemical fume hood, vented
❸ Double sink
❹ Workbench, with drawers under
❺ Milli-Pore Purifier
❻ Milli-Que Purifier
❼ Sterilematic Autoclave
❽ Wall-hung storage cabinet
❾ Workbench, with drawers under
❿ Flammable material storage cabinet

☆ Flammable material storage refrigerator
★ Double sink
✪ Workbench

Fig. 2. A sketch of a biomedical experimental preparation room

with respect to the beam), a raster scanner (2 magnets, their power supplies, and the scan control system), and a large-area (30 cm x 30 cm), high resolution (3600 elements) ionization chamber and associated electronics.

Operating a biomedical facility

For physics experiments, the accelerator operations group produces a desired beam, transports it to the experimental area, and tune it into a desired target. The experimenters set the experiment up, check the workings of detectors, calibrate them, and finally take data. What you do with the beam is almost entirely left to the experimenters. On the contrary, the biologists walk in the accelerator facility with biological samples, and expect the accelerator operations group provide not only the beam with appropriate parameters, but also the controls and monitoring of the beam so that the biological samples would obtain right doses on planned schedules. One may consider automating the beam-line setup procedures, beam calibration procedures, and irradiation procedures, so that the biology experimenters go about their ways by themselves with little help from the accelerator operations group. Such a process is hard to implement for various reasons: computer illiteracy of experimenters (even they are dying breeds) and physics inexperience of experimenters (biologists do not feel comfortable unless a physicist tell them what dose their samples got).

To make the biomedical experiments work well at the planned Linac facility, an biomedical operator must be present whenever there is a biology user group performing an accelerator experiment. The operator must be knowledgeable to change the beam-line setups, calibrate the beams, and perform reliable dosimetry for the experimenters. Once the beam and the beam line are set up, the experimenters can run the experiment by turning the beam on and off from the irradiation control station with little supervision by the operator. During the irradiation time, however, the operator must be on call to resolve problems or uncertainties the experimenters may experience.

The accelerator operations group should also provide sufficient physics support. Whenever a new biology experiment is planned, the biology users must confer with the physicists to discuss for any peculiar requirements of the planned experiments, so that the solutions may be proposed and implemented. The physics staff should be responsible for setting up the beam line, and accurate execution of the experiment. The physicists will be responsible for running the biomedical facility and training the operators.

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