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Free-Electron Lasers and their Application to Biomedicine

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The application of free-electron lasers (FELs) to biology and medicine has recently become an area of intensive activity. Because of this interest, there is a need for a discussion of FELs in the context of applications. In this paper, the operating characteristics of FELs which are relevant to biomedical application are reviewed. Assuming present-day FEL technology, the trade-offs in FEL operating parameters for different types of biomedical applications are discussed. The long term technical advances in FEL physics and technology which may have an important impact on the applications are described.

I. Introduction

Lasers have been used with success in medicine for almost two and a half decades, and biomedicine has clearly benefited greatly from the ongoing evolution of laser physics and technology. It is therefore compelling to attempt to identify new medical applications for new laser technologies as they are developed. The free-electron laser (FEL) [1] is a prime example of an exciting new laser technology which has been developed and refined over the past decade. Consequently, the application of free-electron lasers to biomedicine is worthy of consideration.

The identification of the most appropriate and useful applications of any new laser technology to medicine will be facilitated by interdisciplinary discourse. The medical researcher must develop a good idea of the capabilities and the limitations of the new laser technology in order to better identify potential applications in his discipline. Similarly, in order to maximize the possible utility of a new technology to another disipline, the laser scientist must develop an understanding of those particular laser characteristics which are desired for the different applications.

The purpose of this paper is to better acquaint the medical researcher with the properties and capabilities of the free-electron laser vis-á-vis biomedical applications. It does not purport to be a detailed tutorial of the intricacies of free-electron laser physics but rather an overview of those salient features of FELs which should be understood by any researcher using FELs. Nevertheless, this task necessarily involves a presentation and discussion of some of the technological issues associated with FEL operation.

The need for an analysis of the issues associated with the application of FELs is motivated by recent increased interest in their application to medicine, biology, and material science. The identification and development of FEL applications has been stimulated in part by a specific government program [2].

This paper is organized as follows. In Section II, an introduction to free-electron lasers and an overview of the current status of FEL technology is provided. The characteristics of FEL radiation which are of particular importance to the biomedical community are identified. A brief survey of free-electron lasers which are presently operating or are planned is presented in Section III. The operating characteristics of these FELs which are

of particular importance to biomedicine are highlighted. Section IV contains a discussion of some of the different areas of medical research and the FEL operational requirements particular to each of these research areas. This section also contains a discussion of the FEL specifications which must be determined in defining a system which is applicable to biomedical research. In Section V a discussion of long term FEL technological advances and their relevance to photobiology and photomedicine is presented. The conclusions of this paper are contained in Section VI.

II. OVERVIEW OF FEL PHYSICS AND TECHNOLOGY

A. Introduction

The free-electron laser (FEL) is a versatile source of high-power, frequency-tunable, coherent radiation which has many potential applications. The basic principle of operation of this device was first outlined by Motz in the early 1950's [3], and a device operating in the microwave region of the spectrum, termed the ubitron, was built by R. Phillips [4]. Today, devices which rely on this basic interaction and operate in the microwave region of the spectrum are still usually called ubitrons. The first generation of coherent optical radiation from a high energy electron beam was the result of work by J. M. J. Madey and coworkers at Stanford University during the 1970's [1]; this device is known as a free-electron laser. Since the mid-1970's, many research groups worldwide have studied and built free-electron lasers.

The free-electron laser uses a high-quality, high-energy (relativistic) electron beam passing through a periodic transverse magnetic field to amplify an electromagnetic (optical) wave (Fig. 1). As the electrons pass through the transverse magnetic field, they first radiate spontaneously and then by the process of stimulated emission as the optical field amplitude grows. The electron beam is produced in an accelerator, and, in general, several different accelerator technologies can be used to produce this electron beam. The periodic transverse magnetic field through which the electron beam passes is produced by a magnetic structure known as a wiggler or undulator. The optical laser beam which is produced and amplified by the electron beam inside the wiggler is contained in a laser resonator, which consists of sets of mirrors and other optical elements to allow the optical power to build up on

successive passes in the resonator. The three main components of the FEL are thus the accelerator, the wiggler, and the optical resonator or cavity. Different types of accelerators, wigglers, and resonators can be combined to produce FEL output power with different characteristics. Consequently, there are a wide variety of FEL configurations corresponding to different combinations of these three main components; only some combinations are appropriate for biomedical applications. There is a large body of literature on the FEL, including both primary [5–7] and secondary sources [8]. This section is not meant to be a detailed tutorial on either FEL physics or technology, but rather an overview of those salient features of FELs which are relevant to biomedical applications.

The basic FEL resonance condition which determines the output laser wavelength λ_s can be written

$$\lambda_s = \lambda_w (1 + a_w^2) / 2\gamma^2. \tag{1}$$

In this equation, λ_w is the period of the transverse magnetic field (typically $\lambda_w = 2-5 \,\mathrm{cm}$), and a_w is a dimensionless measure of the strength of the transverse magnetic or wiggler field ($a_w = 0.0934 \,\lambda_w \,\mathrm{[cm]}\,\mathrm{B_w}\,\mathrm{[kG]}/\sqrt{2}$). Typical values of a_w are $a_w = 0.2-2$. The factor γ in the resonance condition is proportional to the energy of the electron beam and is given by

$$\gamma = \frac{E\left[\text{MeV}\right]}{0.511} + 1. \tag{2}$$

For laser output at $\lambda_s = 3 \,\mu\text{m}$, for example, with $\lambda_w = 3 \,\text{cm}$ and $a_w = 1$, an electron beam with $\gamma = 100$ or $E = 50.6 \,\text{MeV}$ is required.

As is apparent from the resonance condition, variation of λ_w , a_w , or γ will vary the output wavelength of the FEL. It is usually impractical to vary λ_w once a wiggler is constructed, so that in practice the output frequency of FELs is varied by either changing the energy (γ) of the electron beam, or by changing the strength of the magnetic wiggler field (a_w) , or both. It is this capability of frequency tunability of the FEL which sets it apart from all but a few of the conventional lasers. Such frequency tunability is of potentially great importance for the biomedical applications considered here. Tunability over two octaves has already been achieved [9].

The free-electron laser can operate in an oscillator, amplifier, or amplified spontaneous emission (ASE) configuration. The FEL oscillator is the only configuration which will be discussed in this paper. Future operation of FELs in the uv or x-ray region of the spectrum

may require other configurations (such as ASE) due to the absence of adequate mirrors in this region. In addition, there are actually many different gain regimes in which the FEL can operate. The gain of the laser is a measure of the amount by which a signal is increased on passing through the laser. Different gain regimes correspond to different FEL operating parameters, including the beam current density (amperes per cm² of the electron beam), the wiggler field strength (a_w) , the length of the wiggler (L), and the amount of transverse temperature and energy spread in the electron beam. FEL oscillators operating in the visible to far-infrared regions of the spectrum which are appropriate for medical applications are expected operate in what is termed the Low-Gain Cold-Beam Compton Regime. In this regime, the gain per pass for the optical field is small, [P(L)-P(0)]/P(0) < 1, where P(z) is the optical power at axial position z. That the interaction occurs in the Compton regime implies that the Coulomb repulsion between electrons in the beam is negligible.

In the Compton regime, the optimization of the single-pass FEL gain depends on many parameters. Accelerator parameters such as the peak current in the electron beam, I, and the transverse temperature of the electron beam, which is characterized by a normalized emittance, ϵ_n , are both important for optimization of the gain. Similarly, other design parameters such as λ_w , a_w , and the desired operating wavelength, λ_s , influence optimization of the gain. For very small emittance, the gain is optimized by increasing the beam current. At short wavelengths, the gain is more often limited by the emittance, and the single pass FEL gain, $G \equiv [P(L) - P(0)]/P(0)$, then scales as [10]

$$G \propto \lambda_s^{3/2} \, \lambda_w^{1/2} \, N^2 \, \frac{a_w^2}{(1 + a_w^2)^{3/2}} \, B_n,$$
 (3)

where N is the number of wiggler periods $(N = L/\lambda_w)$, and B_n is the electron beam brightness. The beam brightness is a property of the accelerator used for producing the electron beam, and it is related to current, I, and emittance, ϵ_n , by $B_n \propto I/\epsilon_n^2$.

Several observations can be made upon examination of this gain expression. The FEL gain is seen to decrease as the operating (optical) wavelength decreases. Both larger wiggler wavelengths λ_w and number of wiggler periods N will increase the gain. The optimum value of a_w , the wiggler field strength, is approximately unity; for $a_w \ll 1$, the gain scales as a_w^2 . Finally, low gain can be overcome by the use of a high brightness (i.e.

high-quality) electron beam. In the FEL oscillator, as with any laser oscillator, when the small-signal gain is greater than the resonator losses, the optical field will grow in time until the interaction is saturated and the gain equals the losses.

The efficiency of an FEL oscillator, namely, the fraction of the electron beam power that can be converted into radiation, can be shown [11] to be given by $\eta \equiv P_{opt}/P_{e-beam} = 1/2N$ for the case of a perfect, untapered wiggler. Real wigglers are never perfect, and the imperfections tend to reduce both the gain and the efficiency. Increasing the number of wiggler periods will increase the gain but decrease the efficiency. The FEL wiggler periodicity and/or field strength can be tapered along the beam propagation direction in order to maintain resonance between the optical wave and the electron beam as the electron beam loses energy. The basic principle can be understood by reference to Eq. (1). As the electron beam gives up energy to the optical wave, γ decreases, and the optical wave of wavelength λ_s will no longer satisfy Eq. (1). By tapering (reducing) the wiggler periodicity λ_w or reducing the wiggler strength a_w along the beam direction, the resonance can be maintained. This technique of wiggler tapering can increase the efficiency over 1/2N [11], but the gain is also reduced. Thus the FEL designer must choose carefully between two competing requirements. A small value of N insures high efficiency and thus a higher power output. However, a low N reduces the single pass gain with the result that very high quality optics is needed. A typical FEL for biomedical applications is expected to have N in the range of 30 - 100.

The generation of light in the infrared, visible and ultra-violet regions of the spectrum from free-electron lasers demands long high-field wigglers and very high brightness electron beams. The ability of accelerators to produce the high-quality electron beams required for FEL operation at short wavelengths is one of the factors governing the extension of FEL operation into the visible, ultra-violet, and even x-ray regions of the spectrum. Although the FEL interaction itself should be operative in these regions, some improvement of accelerator technology is required to realize these shorter wavelengths. Storage rings [12] and linear accelerators with photocathode injectors [13] appear promising for the extension of FEL operation into the uv. The availability of mirrors at short wavelengths is a significant technological problem. The further development of wiggler technology is also of importance for the successful extension of FEL operation to shorter wavelength operation.

The successful operation of an FEL at any frequency depends on the operation of three different components: the accelerator, the wiggler, and the optical resonator. Moreover, the operating characteristics of the FEL such as its output frequency, power, temporal pulse structure, frequency bandwidth, and frequency tunability, all depend on the choices made for these three components. It is thus useful to discuss the present technological capabilities and their impact on FEL operation for each of these three components.

B. Accelerator Technology

There are many different accelerator technologies capable of producing the electron beam for the FEL. Different accelerator technologies are appropriate for FELs of different output wavelength (Fig. 2), because different accelerators produce electron beams of different energy. Pulse-lines are relatively low energy (< 5 MeV) accelerators which are used with FELs (or Ubitrons) operating in the microwave, millimeter, and submillimeter bands. Conventional microtrons operate at energies below about 20 MeV and at low current; they are therefore appropriate for the far infrared to the millimeter band. The extension of emission into the IR using a Cerenkov FEL and microtron accelerators has been suggested [14] and recently demonstrated.

FELs based on electrostatic and induction accelerators have, until now, been used for operation in the range $10\,\mu\mathrm{m}$ to $> 1\,\mathrm{mm}$. Most induction linacs have pulse lengths too short for use with FEL oscillators; they are used in FEL amplifier systems. Electrostatic accelerators can produce long pulse electron beams. However, a potentially serious problem with electrostatic accelerators is the variation of beam energy during the pulse; if not corrected, this can result in variation of both the output power and the frequency during the optical pulse. For operation in the visible, near and mid-infrared, the radio frequency (rf) linear accelerator (linac) with energy between 20 and 100 MeV is appropriate, while for operation at wavelengths in the visible or ultraviolet to x-ray regions of the spectrum, the electron storage ring is a relevant electron beam source. The racetrack microtron has also received attention recently as an accelerator technology which is relevant to IR - uv FEL operation [15]. Of course, for any given operating wavelength, the appropriate accelerator technology also depends on the wiggler wavelength. Furthermore, different accelerator technologies can be used to produce the same energy electron beams, and, consequently,

FEL systems with similar operating wavelengths can have different types of accelerators. The dashed vertical lines in Fig. 2 are meant as a reminder that as accelerator technology improves, some accelerators may be useful for FELs operating at shorter wavelengths.

Other important factors which also enter into the choice of the accelerator technology for a given wavelength FEL are cost, size, the electron beam current and brightness produced, and the electron beam temporal structure. For the optical powers and wavelength range of interest here, the most relevant accelerator technology is the rf linac (either conventional or superconducting). The electrostatic accelerator may also be useful if far-infrared wavelengths are of interest or if the two-stage FEL concept described below is successful. FELs based on induction accelerators are much larger, more costly, and produce much higher power than that needed for biomedical applications. Electron storage rings are useful for the production of visible and uv radiation at power levels appropriate to biomedicine and material science. They are considerably more expensive than rf linacs and electrostatic accelerators, and as a result their development will probably occur at only a small number of user facilities.

Both conventional, room-temperature linacs and superconducting linacs are appropriate for infrared and visible wavelength FELs. Conventional linacs employ room-temperature cavities for storage of the rf fields used to accelerate the electrons. In superconducting linacs, these cavities are manufactured from superconducting materials; the operation of superconducting linacs requires that the cavities be maintained at temperatures close to absolute zero (typically 2 - 4 K). The relative performance of room-temperature versus superconducting linacs is a complicated subject and will not be discussed here.

RF linacs, electrostatic accelerators, and racetrack microtrons may all be applicable and useful for biomedical FEL systems. At the present time only FELs with rf linear accelerators (or storage rings) have operated in the visible to near-infrared wavelength range. This is the spectral region for which there is the largest interest by biomedical researchers. In systems employing conventional wigglers, the wiggler wavelength is typically 2-5 cm, and only rf linacs are capable of accelerating electrons to sufficient energy that radiation in the near-ir region of the spectrum can be produced.

For FEL operation in the far-infrared (> $10 \,\mu\mathrm{m}$) spectral region, the electrostatic accelerator is a useful accelerator technology because lower energy electron beams are required.

For operation in the near-IR and visible spectral region, the electrostatic accelerator may prove to be a viable and, for some applications, an advantageous long-pulse alternative to the rf linac as an accelerator technology, provided novel short-period wiggler concepts or two-stage devices [16–19] are successful. However, at the present time, FELs based on the rf linac technology appear to be the only option for a near-ir biomedical FEL which is available at the present time. Any significant advance in the area of novel short-period wigglers could allow the construction of IR or visible FELs with electrostatic accelerators, and such an advance would necessitate a reevaluation of which accelerator technology is best suited to the different biomedical FEL applications in this spectral region.

An important difference between electrostatic and rf linear accelerators, apart from their different energy capabilities, is in the electron beam temporal structure produced. The electron beam temporal structure determines the temporal structure of the optical pulse produced by the FEL. The rf linac produces an electron pulse (macropulse) which consists of a large number of short (1-100 picosecond) micropulses. The electrostatic accelerator produces an electron pulse which is constant over the duration of the pulse. The different shape optical pulses produced by FELs employing these different accelerators are discussed more fully in a later section.

The major issue in accelerator technology is the improvement in beam brightness B_n . For example, a hundred-fold increase in B_n would result in a major leap in FEL performance. The resulting increase in gain (see Eq. 3) could push the FEL performance into the High-Gain Compton Regime where an exponential growth of radiation intensity takes place. Alternatively, keeping the gain constant, one could reduce the number of wiggler periods N and thereby decrease the system length and increase the system efficiency.

Several approaches are being persued at the present with the aim of increasing the beam brightness. One approach is to eliminate the emittance growth in various sections of the accelerator. Another approach is to increase the current and decrease the emittance of the beam in the electron gun itself. Typical guns employ thermionic cathodes that provide current densities $< 10 \,\mathrm{A/cm^2}$, and the electrons are accelerated by a d.c. voltage applied between cathode and anode. Recent experiments using photocathodes yield current densities in excess of $100 \,\mathrm{A/cm^2}$ [13]. In addition, high frequency rf rather than d.c. acceleration in the gun region shows promise.

Being able to access the high gain Compton regime carries with it an additional bonus. In the high gain regime the phenomenon of optical guiding may take place, in which the electromagnetic wave is refracted radially inwards (guided) by the electron beam in a manner somewhat akin to the guiding properties of an optical fiber. Optical guiding mitigates the effect of diffraction and hence allows the length of the FEL wigglers to exceed the optical Rayleigh range. Such long wigglers are needed if FELs are to operate either in the vacuum ultraviolet (vuv) or at high efficiencies (with tapered wigglers) in the ir and visible regions.

C. Wiggler Technology

Conventional wigglers for free electron lasers most often employ permanent magnetic material such as samarium cobalt or neodymium-boron-iron. The magnetic material, in the form of bar magnets, is usually arranged in a linear array as illustrated in Fig. 1. The ensuing radiation is then linearly polarized. Helical wiggler arrangements have also been used, but they are not very common. The radiation leaving a helical wiggler is elliptically polarized. Wiggler magnetic fields can also be produced by electromagnets. All of these types of wigglers produce static, time-independent magnetic fields, and we shall refer to them as magnetostatic wigglers. Typical wiggler wavelengths which are practical using conventional wiggler designs are in the range of 2 cm or greater. Fabrication of wigglers of shorter period becomes difficult due to the machining tolerances required and the requirement for a reduced separation between the two opposing magnet faces. This separation, or wiggler gap, must be reduced in order to keep the wiggler field strength high as the periodicity decreases. This in turn results in little clearance for the electron and optical beams. Shorter period wigglers are generally not capable of producing magnetic fields as strong as those produced by longer period wigglers. Conventional wiggler technology is fairly advanced at this time; short-period wigglers are beginning to receive considerable attention.

Several FEL groups are presently working on novel short-period wiggler concepts. Short-period magnetostatic wigglers are being investigated at the University of Maryland [17], and at the University of California at Santa Barbara [18]. Their success would allow the generation of near-IR radiation with lower voltage electron beams. Lower voltage

electron beams would be desirable in the medical environment because of the reduction in radiation hazard, shielding required, and overall system size.

Another wiggler concept presently being studied by several groups is that of the electromagnetic wiggler, in which monochromatic electromagnetic radiation from a separate source acts as the wiggler field for the FEL. In one concept, known as the two-stage FEL [16], an FEL interaction produces a high-power short-period electromagnetic wave. This wave then serves as the wiggler for the same electron beam and an even shorter period optical radiation is generated in the second stage. Such a concept is attractive because of the reduced requirement on the electron beam energy. However, ultra-high-quality electron beams are required, and this concept has yet to be demonstrated in a regime of interest for biomedical applications. In an alternate concept developed at MIT, a millimeter band electromagnetic wave generated in a high-power cyclotron resonance device such as the gyrotron is used as the wiggler [19,20]. If successful, such a device would reduce significantly the electron beam energy required to reach the near- and mid-IR. For example, as Eq. (1) indicates, a ten-fold reduction in the wiggler period allows a reduction in the beam voltage be approximately a factor of three.

The success of any of these novel short-period wiggler concepts could result in substantially more compact FEL systems in the long run. In the near term, FELs relying on the proven performance of conventional wiggler technologies may be more appropriate for medical research or as a medical facility.

D. Optical Cavities and Optical Pulse Characteristics

The optical cavities employed in free electron lasers are similar to those employed with conventional lasers. For FELs based on rf linacs, the optical pulse format produced by the FEL has the same temporal characteristics as the electron beam pulse format (Fig. 3) (provided one is not cavity dumping the resonator). The output of the FEL consists of a pulse train of micropulses of width τ_{μ} and separation τ_{s} . This micropulse train constitutes a larger pulse, the macropulse, which has duration τ_{M} . The macropulses are then also repeated at a frequency f_{REP} which is generally in the neighborhood of 10 to 100 Hz. Typical micropulse durations, τ_{μ} , are 3 – 30 ps, and typical micropulse separations, τ_{s} , are 0.3 ns to 100 ns. Too short a micropulse length, less than about 3 ps, is undesirable because of

"slippage". Slippage is a phenomenon in which the electron pulse lags behind the optical pulse because the electron speed is less than the speed of light. When $N\lambda_s/c = \tau_\mu$, an originally coincident electron micropulse and optical pulse have become spatially separated by the end of the wiggler, and the single-pass gain is thus substantially reduced. The minimum value of τ_s is the reciprocal of the rf accelerator frequency, f_{rf}^{-1} . The maximum value of τ_s depends on details of the accelerator injector. The allowed values of τ_s are n/f_{rf} , where n is an integer. The case with n=1 is sometimes referred to as "filling every rf bucket", whereas the case n>1 is usually termed subharmonic injection. The macropulse length is determined by the duration of the rf power pulse supplied by the klystron to the accelerator. Typical macropulse lengths vary from $3-100\,\mu\text{s}$. The macropulse length may be fixed or variable depending on the klystron and its power supply. Superconducting accelerators and some room-temperature accelerators [15] are capable of longer macropulses $(100\,\mu\text{s}-\text{cw})$. A variety of pulse formats corresponding to different combinations of the parameters τ_μ , τ_s , and τ_M are available from different FEL systems. Several combinations of these parameters may also be available from a single versatile system.

Operation of the optical cavity in a cavity dumping configuration may be possible for FELs. This would allow the generation of higher peak power optical pulses than in a non-cavity-dumped resonator. With cavity dumping, an active optical element is switched between a highly reflecting state and a transmissive state. The element is initially highly reflecting and the optical power in the cavity reaches saturation. At this point the optical element is electronically switched to have relatively high transmission and a single high-peak-power pulse is emitted from the cavity. For some applications, this may be a desirable mode of operation, provided optical materials can be found which will survive the intense optical pulses.

The optical power produced by the FEL can be specified in different ways. The micropulse peak power, P_{μ} , is the peak power within a single micropulse. The macropulse average power is related to the energy contained in the macropulse, E_M , by $P_M = E_M/\tau_M$. P_M and P_{μ} are related by $P_M = (\tau_{\mu}/\tau_s) P_{\mu}$ if the energy per micropulse is constant. The true average power of the FEL is given by $\bar{P} = P_M \tau_M f_{REP}$, where f_{REP} is the macropulse repetition rate. For rf linac FELs, $\bar{P} \leq P_M < P_{\mu}$; for FELs based on electrostatic accelerators, there is no micropulse structure and only \bar{P} , P_M , τ_M , and f_{REP} are relevant (that is,

 $\tau_s \to 0$, $\tau_{\mu} \to \tau_M$). FEL output power is often quoted in terms of the macropulse average power. The peak P_{μ} is then inferred from the known macropulse temporal shape.

The optical cavity length, L, is constrained by the condition that the electron micropulse separation be equal to 2L/mc, where m is an integer and c is the speed of light. When m=1, the cavity length is such that the optical pulse makes one round trip in the time between micropulses, and there is one optical pulse in the cavity at any time. For m>1, the cavity length is such that an optical pulse in the cavity makes a complete round trip every m micropulses, and there are m separate optical micropulses in the resonator at any time. In order to provide overlap between the successive optical micropulses and new incoming electron micropulses, the cavity length must be carefully maintained. Failure to maintain the regularity of the micropulse arrival or the cavity length can lead to the poor overlap of electron and optical micropulses, resulting in fluctuations in the optical micropulse power.

The use of several optical techniques which are well developed for conventional lasers will be of significance if they can be applied to FELs. The technique of cavity dumping, discussed above, may allow the generation of the very-high-peak-power single pulses useful for some applications. Similarly, the techniques of harmonic generation by external nonlinear crystals are well suited for use with the FEL pulse structure. High conversion efficiencies can be obtained and tunable radiation produced by the FEL can be converted to tunable radiation in other spectral regions [21]. FELs also emit incoherent light with moderate power at odd harmonics of the fundamental frequency in normal operation; this radiation may be useful for some applications. Direct lasing of the FEL oscillator on harmonics has been proposed, but results are inconclusive at present.

III. SURVEY OF FREE-ELECTRON LASERS

There is a wide variety of free-electron lasers already in operation around the world. In this section, a brief review of FEL facilities which produce output radiation in the visible to the far-infrared spectral region is presented. Most of these facilities are operated primarily for the purpose of research on free-electron laser physics. However, recently several FEL user facilities have either begun operation or have been planned or proposed. This review will focus only on FELs which are compatible with biomedical applications. It includes

those presently dedicated exclusively to FEL physics as well as those which are at least partially operated as a user facility. The properties of some of the free-electron lasers which are of interest for biomedical applications have been tabulated in Table I. FEL facilities which intend to support outside users are noted.

In general, free-electron laser systems tend to be considerably larger than most conventional laser systems, requiring anywhere from 50 m² to considerably larger areas for their installation. Furthermore, because of the radiation hazard from the high-energy electron beams which are required for FEL operation in the near-IR and visible spectral regions, the FEL system components must be located in a radiation shielded vault with concrete or earthen walls several feet thick. This vault can significantly increase the total system size and cost. The cost of complete FEL systems is generally on the order of several million dollars or more, depending on the details of the system design. FEL reliability is also an issue for users; although FELs are becoming more reliable as the physics community becomes more skilled at their design and operation, they remain considerably less reliable than most conventional lasers.

There are several free-electron lasers presently operating which employ rf linear accelerators as the electron beam source. The MARK III IR FEL at Stanford University is a relatively compact FEL operating in the near-IR [22]. Its operating parameters are listed in Table I. A notable feature of this FEL is the novel microwave electron gun. The electron beam micropulse separation in this accelerator is ~ 350 ps; every rf bucket is filled. As a result, the macropulse average power can be very high compared with that from FEL accelerators which use subharmonic bunching. Future plans include installation of a cavity dumping resonator and the use of optical harmonic generation with nonlinear crystals in order to reach the visible and perhaps the UV [21].

The FEL at the Los Alamos National Laboratory (LANL) has operated in the 9-35 μ m spectral region and produced average and peak output powers of $P_M = 6 \,\mathrm{kW}$ and $P_\mu = 10 \,\mathrm{MW}$ respectively [9]. This accelerator employs a subharmonic buncher at the 60^{th} subharmonic of the fundamental 1300 MHz frequency of the accelerator; consequently, the electron micropulses are separated by $46.2 \,\mathrm{ns}$. Other typical parameters are listed in Table I.

A separate group at Stanford University is operating a free-electron laser based on

a superconducting rf linac [23]. This FEL operates in the near-IR to visible spectral region and has the notable feature of very long (> 10 ms) macropulses. Such very long macropulses are possible because the high Q of the superconducting cavities reduces the rf power requirements. In contrast to the MARK III FEL, only every 110^{th} period of the RF is filled with electrons for acceleration; consequently, the optical micropulses are separated by ~ 85 ns. Future plans with this experiment include the generation of visible light both from a third harmonic FEL interaction and from the fundamental interaction with a higher energy electron beam.

The FEL at the University of California at Santa Barbara is based on an electrostatic accelerator. This FEL is designed to have output in the far-infrared region of the spectrum (typically $100-500\,\mu\mathrm{m}$) with peak output powers in the tens of kilowatts for pulse lengths of $1-50\,\mu\mathrm{s}$ [24,25]. A notable feature of this FEL is the use of beam recirculation with the electrostatic accelerator; this allows output pulse lengths of the order of tens of microseconds. Furthermore, the output pulses have no micro-structure as do those from an rf-linac. This FEL is now operating as a user facility.

A large high average power, high efficiency FEL experiment in the visible is underway at the Boeing Corporation in collaboration with Spectra Technologies, Inc. and several other companies [26]. FELs based on rf linacs are also planned or under construction in the U.K. and in Japan.

An FEL based on an electron storage ring is being operated at the University of Paris, Orsay [27], and a group at Stanford University is also building a storage ring for use with an FEL [12]. This storage ring will maintain electrons at an energy of 1 GeV; generation of coherent laser light from the FEL interaction in the UV appears feasible.

A far-infrared FEL based on a microtron is presently being built at AT&T Bell laboratories [28]. Several other FEL facilities which will support users have recently been planned or proposed, including a facility at the National Bureau of Standards employing a cw racetrack microtron [15] and a facility at FELCORP, Inc. employing an rf linac [29].

IV. BIOMEDICAL/MATERIAL SCIENCE FEL SPECIFICATIONS

A. Introduction

The application of lasers to medicine is a well-studied discipline, and there exists a large volume of literature in the field [30-34]. However, the application of free-electron lasers to medicine has only recently been considered [35,36]. Different medical applications will require different sets of FEL operating parameters. A few of the possible FEL applications are outlined here.

The FEL output wavelength range of primary interest for many biomedical researchers is in the $0.7-3.0\,\mu\mathrm{m}$ range. The lower end of this range is often referred to as the theraputic window [30]; light in this near-ir range suffers little attenuation in propagation through tissue. This in turn allows straightforward targeting of exogenous or endogenous chromophores in vivo. Wavelengths shorter than $0.7\,\mu\mathrm{m}$ are used widely in medicine, but the availability of conventional laser sources, such as the tunable dye laser, in this spectral region makes it less imperative that a biomedical FEL operate in the visible. Of course, operation in the ultraviolet is attractive if feasible, provided the mutagenic effects of the radiation are not of concern. With several stages of harmonic generation or direct FEL operation at odd harmonics, an FEL designed for operation in the $0.7-3\,\mu\mathrm{m}$ region could possibly reach the UV spectral region although this has not yet been demonstrated. The upper limit on wavelength for many biomedical applications is in the neighborhood of $3\,\mu\mathrm{m}$.

Laser tissue ablation with $3\,\mu\mathrm{m}$ radiation is one of the primary medical applications envisioned for the FEL. CO₂, Nd:YAG, Ho:YAG, Er:YAG, excimer, and HF lasers have been used for tissue removal [31,14,37]. More recently, there has been considerable interest in using pulsed IR lasers, especially those emitting near $3\,\mu\mathrm{m}$, for tissue ablation. The advantage of laser operation near $3\,\mu\mathrm{m}$ results from a water absorption peak near $3\,\mu\mathrm{m}$ that has sufficiently strong absorption that cleaner surgical cuts can be made with less thermal damage to adjacent tissue [38]. For tissue ablation, the macropulse length, τ_M , must be relatively short compared with the thermal relaxation time of the tissue volume being ablated in order to avoid damage to adjacent tissue. A high macropulse power (P_M) is required to obtain a satisfactory tissue removal rate. For some clinical applications,

high average power ($\bar{P} \sim 10-50\,\mathrm{W}$) will be required in order to maintain reasonable treatment times. As with many medical applications the micropulse power (P_{μ}) must be kept low enough to allow fiber transmission without damage. The biomedical effects of the microstructure of the macropulse must be investigated.

In selective photothermolysis, pulses of selectively absorbed optical radiation are used to cause selective damage to pigmented structures, cells, and organelles in vivo [33]. Nonspecific thermal damage is caused when the laser pulse lengths are long and the tissue around the target is heated uniformly, causing thermal necrosis. Very short exposure durations, on the other hand, can cause vaporization and shock wave formation. Variation of the laser pulse duration between these two limits can lead to varying degrees of confinement of the thermal injury. For laser pulse durations less than or approximately equal to the thermal relaxation time of a given volume of tissue, the thermal damage in contained within that volume. It is therefore desirable to have variable laser pulse lengths (τ_M) in order to target different size structures in tissue. Typical pulse lengths corresponding to thermal diffusion over distances of $1 \mu m$ and $100 \mu m$ are approximately $1 \mu s$ and 10 ms. Variable macropulse lengths are readily obtained with an FEL, with macropulse durations out to some maximum determined ultimately by the pulse length capability of the klystrons powering the FEL accelerator. The capability of the FEL to deliver continuously variable macropulse lengths of tens to hundreds of microseconds at high power is unmatched by most conventional laser sources. The ability to deliver variable τ_M may be important for clinical studies concerning the optimization of pulse length for treatments of various conditions, such as port-wine stain.

The ophthalmological applications of lasers include uses for both short and long pulses of visible and IR radiation [32,39]. Very short (tens of picosecond) optical pulses are used to produce surgical disruption of transparent or pigmented ocular tissues [32]. For these applications, the capability of switching out a single micropulse from the macropulse is clearly desired. Long pulses of optical radiation have been employed to cause retinal photocoagulation [39]. An FEL with both single micropulse capability and a variable macropulse capability would be applicable in both cases.

A fourth application of interest is in the area of high-peak-power photochemistry. A tunable high-peak-power (P_{μ}) FEL optical pulse could be used to initiate sequential two-

photon absorption in dye molecules for the enhanced production of singlet oxygen [40]. High peak powers are difficult to obtain from other laser sources in the spectral region of interest for these dyes, approximately $0.6 - 0.9 \,\mu\text{m}$.

B. Development of FEL Specifications

As one element of the biomedical FEL program at the Massachusetts General Hospital (MGH), a set of specifications for an FEL relevant to biomedical applications was compiled by the authors and researchers at MGH. Some of these specifications are presented in this section. General guidelines regarding the use of FELs for material science applications were also considered, and these considerations are included here. These specifications do not represent a final set of desirable parameters; rather they should be considered a guide to the issues which must be addressed by the researcher in determining the FEL system appropriate to his specific application. As FELs evolve, the range of possible operating parameters will likely change. This discussion assumes only presently demonstrated capabilities, and any significant development in FEL technology may alter these guidelines.

In designing an FEL system appropriate for medical applications, the FEL parameters which have the most significant impact on the biomedical researcher are the parameters describing the temporal format of the optical pulse and the macropulse and micropulse energy required. In many cases, an FEL system which is applicable to medical research is also applicable to material science research. Therefore, to some extent, such applications are also considered in defining the system applications. The four temporal parameters that define the optical pulse format are the micropulse length, τ_{μ} , the separation between successive micropulses, τ_s , the macropulse length, τ_M , and the macropulse repetition rate, f_{REP} . The micropulse durations (τ_{μ}) are typically in the range of 3-20 ps. Shorter micropulses are desirable for probing the dynamics of systems having rapid relaxation times (e.g. liquids), and for vibrational photochemistry, while longer micropulses result in lower peak powers for a given energy and may be desirable for biomedical applications requiring fiber transmission of the optical power. As the micropulse length is not easily varied for a given accelerator, choice of this parameter will require tradeoffs.

The separation of successive micropulses should be variable in a discrete sense; the availability of several modes of operation with different micropulse spacing is perhaps

the most crucial requirement to insure overall system versatility. The material science applications typically require $\tau_s > 50 \, \mathrm{ns}$; important biomedical applications fall into two groups requiring both long (> 50 \, \mathbb{ns}) and short pulse separations. The lower limit on τ_s is the reciprocal of the rf accelerator frequency, f_{rf} , typically 0.3 - 1 ns. The maximum separation is determined by the maximum desirable cavity length or the availability of nonlinear optical components necessary for cavity dumping of the FEL laser resonator. Three modes of operation are probably desirable: one with $\tau_s = 1/f_{rf}$, a second with $\tau_s \sim 50 \, \mathrm{ns}$, and a third allowing single pulse selection. Single pulse selection may be possible with cavity dumping techniques, or with optical modulators external to the laser cavity. Although these are standard techniques with conventional lasers, nonlinear optical materials suitable for the broad wavelength range produced by the FEL may be difficult to obtain or incapable of handling the optical power density produced by the FEL.

The choice of the macropulse length, τ_M , will have significant implications for the applications and for the accelerator and klystron components, and for the system size. Some material science applications may involve the use of single micropulses and are therefore concerned with events occurring on time scales shorter than the micropulse spacing. Consequently, the macropulse length is relatively unimportant. However, many applications involving laser tissue interaction depend in a detailed way on the rate of energy deposition into the tissue. Thus, the macropulse length, the energy contained in a macropulse, and the variability of macropulse length are crucial issues.

The choice of macropulse length is an equally crucial issue for the accelerator part of the FEL system. In the rf linac, the electrons are accelerated by the rf power produced by a high power pulsed klystron. The maximum macropulse length is determined by the pulse length available from the klystron powering the accelerator. Only certain combinations of power, pulse length, and rf frequency are available from currently available klystrons. Klystrons can be grouped roughly into three categories: short pulse (typically $3-10\,\mu s$), long pulse ($10-250\,\mu s$), and continuous (CW). Consequently, there are, in this sense, three different rf accelerator technologies associated with different maximum macropulse lengths, short pulse ($\tau_M < 10\,\mu s$), long pulse ($10\,\mu s < \tau_M < 250\,\mu s$), and cw ($\tau_M > 250\,\mu s$). The last option corresponds to the superconducting linear accelerator, which can operate cw, i.e. $\tau_M \to \infty$, and utilizes lower power cw klystrons. There are many tradeoffs in accelerator

technology between L-band (1.3 GHz) and S-band (2.4 - 3 GHz) frequency accelerators and between room temperature and superconducting structures; these tradeoffs will not be discussed here. RF accelerators are also available in other bands, such as X-band $(8-12\,\mathrm{GHz})$, but are far less common.

The final temporal parameter describing the optical pulse format is the macropulse repetition rate, f_{REP} . This parameter, which determines the average power of the FEL, can determine the rate of scientific data generation for scientific experiments or the treatment time for clinical applications. The average power available from the FEL will depend primarily on the average power available from the klystrons powering the accelerator as well as on other factors.

The energy required in the micropulse and macropulse will also depend on the application. For material science applications, micropulse energies of $> 20 \,\mu\text{J}$ are very attractive. If significantly higher peak energies can be obtained by cavity dumping techniques, there may well be very great interst in FEL user facilities. Ophthalmological applications, which generally rely on photodisruption and other single pulse, picosecond phenomena, require similar micropulse energies. The multiphoton excitation of exogenous chromophores for singlet oxygen production will also require high peak powers. For many biomedical applications the macropulse energy is the more significant variable; micropulse energies must be kept low enough to allow fiber transmission without fiber damage.

The bandwidth of micropulses generated by the FEL is typically of the order $\delta\omega/\omega > \lambda_s/l_{ep}$, where λ_s is the optical wavelength and l_{ep} is the length of the electron micropulse. Typical bandwidths of one part in 10^3 are adequate for many biomedical applications. Operation of the FEL at high power can result in broadening of the emission linewidth due to synchrotron instabilities; this effect is an ongoing area of research. A more crucial parameter is the shot-to-shot (micropulse-to- micropulse and macropulse-to-macropulse) center frequency jitter. Although bandwidths of $2\,\mathrm{cm}^{-1}$ are typical and adequate, the jitter of the center laser wavenumber must be $<\pm0.3\,\mathrm{cm}^{-1}$ for vibrational spectroscopy and other material science applications. Such stringent requirements are not required for biomedicine because condensed phase linewidths are quite broad.

A related specification is the tolerable fluctuation of the optical micropulse power. Fluctuations of less than $\pm 2 - 5\%$ are desirable and may require active feedback con-

trol of the klystrons or the use of isochronous beam lines in order to minimize the optical power instability resulting from electron micropulse arrival-time jitter (the so-called "Rocky Mountain Effect"). Stabilization of the optical micropulse power fluctuations will probably bring about some stabilization of the micropulse center frequency jitter. Stabilization of the center laser frequency from macropulse to macropulse will also be desirable, but may be more difficult.

The ability to synchronize the FEL micropulses with external electronics and external lasers will be an important requirement of FEL systems designed for most applications. This capacity for synchronization is most crucial for pump-probe experiments in biomedicine and photochemistry. This may be possible by driving both an active mode-locker on the probe laser and the FEL klystrons with the same master oscillator. An alternative technique is attractive for accelerators employing photocathodes as the electron source. The laser producing the electron emission from the photocathode could also be used to pump a dye laser system for the production of a synchronized probe pulse.

V. DISCUSSION

For most of the spectral region of interest here, there has been and most likely will continue to be developments in conventional laser technology which may successfully challenge the FEL as a source for any given application. Notable examples include the continuously-tunable optically-pumped Raman lasers in the far-infrared [41–43], and the diode lasers and doped-crystal lasers in the near-IR [44,45]. The availability of other novel laser technologies may or may not alter the utility of free-electron lasers in the long run; only by comparison of the different systems by the users will the most desirable sources be selected. Neither conventional laser technology nor FEL technology is stagnant; advances in one source technology must ultimately be judged in comparison with the advances in others.

There are several areas of current FEL research which may have a significant further impact on the application of FELs to biomedicine. Of primary importance is the further progress on presently funded FEL systems and their application to biomedicine and material science. More experience with the application of existing FELs to all scientific disciplines will help in the characterization of which FEL specifications are best suited to

which application.

A major area of FEL research relevant to biomedical FELs is the development of short-period wigglers, either electromagnetic or magnetostatic. Significant progress in this area would have two important results. FELs based on rf linacs could be made significantly more compact, cheaper, and less hazardous with respect to x-ray radiation. The reduction in size of FEL systems will be a major factor facilitating the wider use of FELs in medicine and other disciplines. Size reduction would involve both a reduced accelerator length, resulting in reduced cost and complexity, and also a dramatic reduction in the required x-ray and neutron shielding. Consequently, further research on novel short-period wiggler concepts as described in [17–19] is likely to be of long term significance for the application of FELs to biomedicine.

The continued improvement of accelerator beam brightness will have a profound impact on the capabilities of free-electron lasers. Extension of FEL operation into the hard uv and possibly the x-ray regions may eventually become feasible with improvement of accelerator performance. FEL systems operating in the visible and near-ir may become substantially more compact by using low-energy high brightness accelerators and novel short period wigglers. The application of high brightness accelerators to conventional FEL designs in the visible and ir will also improve FEL performance.

The multiplication of the micropulse repetition frequency from that obtained with the usual FEL pulse format shown in Fig. 3 may be possible using a spatial time-division repetition rate multiplier (RRM) [46]. Such a repetition rate multiplier uses successive stages of pulse splicing and optical delay to produce a factor 2^N increase in the micropulse repetition rate and a factor 2^{-N} decrease in the micropulse peak power for N stages (Fig. 4). Such a system may be particularly useful for applications requiring a reduction of the micropulse peak power to levels appropriate for fiber transmission. Applications that require high macropulse average power but that cannot tolerate high peak powers could also benefit from this technique. A detailed analysis of the losses and power handling capability of such an optical device remains to be carried out.

VI. CONCLUSIONS

The application of free-electron lasers to biomedicine is in a very early stage. Nevertheless, the versatility of the FEL in terms of its pulse format and frequency tunability make it a new tool of potentially great importance for the medical researcher. The purpose of this paper has been to familiarize the biomedical researcher with those salient features of free-electron lasers which may directly affect their applications.

The FEL system concepts described in this paper are based on present-day technology. The evolution of FEL technology is itself a multifaceted process which includes competition between different accelerator technologies, such as rf linac, superconducting rf linac, and electrostatic accelerators. These technologies result in widely different temporal characteristics with important consequences for applications. Different temporal structures are useful for different applications. There is also a competition between different wiggler concepts, including magnetostatic wigglers, electromagnetic wigglers, and other approaches (e.g. Cerenkov FELs). These have important consequences for the size, cost, and reliability of an FEL system.

Although the FEL has been demonstrated in the physics research laboratory, its use has not resulted in any reported advances in the field of biomedicine at this time. The ability of the FEL to contribute to this field is still an open question. The free-electron laser is a very exciting new source which has many novel capablilities. In this early stage of its application to other disciplines, there are reasons for being optimistic, although the question of whether the FEL will ultimately be the technology of choice for different biomedical applications cannot be addressed at this time. Ultimately, the contribution of the FEL will depend heavily on the development of a reliable, compact FEL system. Research on such systems is very important to the future of FEL research and to the application of the FEL to other disciplines. Finally, it is important to understand that conventional laser technology is both impressive today and likely to show progress in the years to come. The degree to which FELs will ultimately be suitable for routine use in biomedicine requires consideration of both FEL and conventional laser technologies and their future development.

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Figures

- Fig. 1. Schematic of a free-electron laser showing the electron beam, wiggler, optical resonator, and optical beam.
- Fig. 2. Relationship between accelerator technology and FEL operating wavelength.
- Fig. 3. RF linear accelerator based FEL optical (or electron beam) temporal pulse shape.
- Fig. 4. Optical pulse repetition rate multiplier, reprinted from [46].

TABLE I.

MAJOR FEL RESEARCH RESULTS

	Institution			
PARAMETER	UCSB ^{1,2}	LANL ¹	STANFORD	STANFORD
			MARK III ^{1,2}	$SCA/FEL^{1,2}$
Accelerator	E.S.	R.F.	R.F.	R.F.
$\lambda_s \left[\mu \mathrm{m} ight]$	120 - 800	9 - 35	2.5 - 4.3	$1.4 - 3.1, \sim 0.5$
			$\sim 0.5 - 2.6^{3,4}$	$\sim 0.5 - 1.4^{3}$
$ au_{\mu}$	-	35 ps	3 ps	4 ps
$ au_s$	-	46.2 ns	$0.35 \mathrm{ns}$	84.6 ns
			S.P. ³	S.P. ³
$ au_{M}$	$1-50\mu\mathrm{s}$	$90\mu\mathrm{s}$	$3\mu\mathrm{s}$	10 - 60 ms
	$> 50\mu\mathrm{s}^{-3}$		$10\mu\mathrm{s}^{-3}$	
f_{REP}	1 Hz	1 Hz	15 Hz	10 Hz
	100 Hz ³			
P_{μ}	-	10 MW	400 kW	$\sim 1\mathrm{MW}$
			1 MW ³	
P_{M}	$10-40\mathrm{kW}$	6 kW	2 kW	70 W
P	$\sim 0.5\mathrm{W}$	0.54 W	60 mW	10 W
Reference	[24,25]	[9]	[22,47]	[23,48]

¹ FEL physics research facility.

² User facility.

³ Anticipated future performance (design goal).

⁴ Obtain with extra-cavity harmonic generation.

FREE - ELECTRON LASER

FEL PULSE SHAPE

Fig. 3

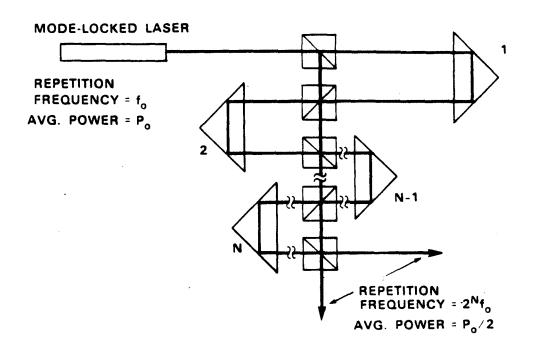


Fig. 4