High-dose femtosecond-scale gamma-ray beams for radiobiological applications

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Abstract

Objective. In the irradiation of living tissue, the fundamental physical processes involved in radical production typically occur on a timescale of a few femtoseconds. A detailed understanding of these phenomena has thus far been limited by the relatively long duration of the radiation sources employed, extending well beyond the timescales for radical generation and evolution. Approach. Here, we propose a femtosecond-scale photon source, based on inverse Compton scattering of laser-plasma accelerated electron beams in the field of a second scattering laser pulse. Main results. Detailed numerical modelling indicates that existing laser facilities can provide ultra-short and high-flux MeV-scale photon beams, able to deposit doses tunable from a fraction of Gy up to a few Gy per pulse, resulting in dose rates exceeding $10^{13}$ Gy/s. Significance. We envisage that such a source will represent a unique tool for time-resolved radiobiological experiments, with the prospect of further advancing radio-therapeutic techniques.

1. Introduction

The complex response of a cell to ionising radiation can be broadly divided into three main stages: physical, chemical and biological (Adams and Jameson 1980). In the physical stage, approximately lasting for a few up to tens of femtoseconds, the primary ionising particle generates a shower of secondary particles and radicals around its track. It is then during the chemical stage, i.e. picoseconds to seconds after irradiation, that the free radicals produce a wide and complex range of damage to the DNA of the cells. Finally, in the biological stage, seconds to years after irradiation, the macroscopic effects of irradiation are observed (Feuerhahn and Egly 2008, Vozenin et al 2019).

Traditionally, radiobiological research is carried out with irradiation times ranging from microseconds up to minutes, inducing significant dose deposition during the DNA damage and repair processes. This is known to impact on the cellular response to radiation, for instance via influencing the efficiency of signalling channels and repair processes in protracted exposures (Feuerhahn and Egly 2008, Rigaud et al 2010, Harrington 2019). Recent results have also shown that high dose-rate ($\sim 10$–100 Gy/s) effects might cause significantly different responses between cancerous and healthy cells. The effect, generally referred to as the FLASH effect (Brown and Wilson 2004), is attributed to radiation-induced oxygen depletion in the cell environment, although recent experimental results have put this assumption into question (Jansen et al 2021). To the best of our knowledge, only a limited number of experimental studies of FLASH effects have been performed using synchrotron sources, highlighting the need to further investigate FLASH effects with photons (Montay-Gruel et al 2021). As recently highlighted by the research community (Freeman 2021), the technological advancements in dose delivery and control have not yet been matched by the same level of biological understanding of their effects. This is further exacerbated at ultra-high dose rates where doses are delivered on microsecond down to femtosecond timescales, corresponding to the chemical and physical stages of radiation exposure. There is thus a wide recognition that experimental studies of ultra-short, high dose-rate irradiation of biological samples will
represent a disruptive approach in radiobiology, towards a deeper understanding of a wide range of outstanding fundamental questions.

Ideally, one would thus require single-shot Gy-scale dose depositions on a femtosecond timescale but, ultimately, experimental work in this direction has been significantly hampered by the lack of high-flux and ultra-short MeV-scale photon sources. Typical techniques for generation of photon beams of interest for medical applications include synchrotron emission (Wu 2013), bremsstrahlung (Koch and Motz 1959) and Compton scattering (Phuoc et al 2012, Chen et al 2013, Sarri et al 2014, Yan et al 2017). Synchrotron emission generally requires expensive, large-scale facilities and are limited to relatively low energies, in the keV range. While of great importance for imaging (Olbinado et al 2017) and studies of the structure of matter, their low energy prevents their use in treatment of deep-seated tumours. Bremsstrahlung sources can easily reach multi-MeV photon energies and are the main sources currently used in radiotherapy, exploiting electron beams from linear accelerators (LINAC). However, they suffer from a broadband energy spectrum and a high divergence; the photons must be energy-filtered and collimated, reducing the final useful flux. Typically, bremsstrahlung sources require irradiation over several minutes to build up sufficient dose for radiobiology studies (Faddegon et al 2008, Ling et al 2010).

Finally, Inverse Compton Scattering (ICS) requires ultra-relativistic (≥100 MeV) electrons to obtain MeV photon energies with optical or near-IR lasers. This, combined with the relatively low scattering cross-section, has resulted in ICS based radiobiology being limited to a few experimental facilities, which also typically require long exposures to obtain Gy-scale doses. However, advances in laser plasma acceleration have resulted in high-brightness electron sources becoming available at high-power laser facilities, enabling high-brightness MeV photon sources in highly compact setups (see, for instance, (Phuoc et al 2012, Chen et al 2013, Sarri et al 2014, Yan et al 2017)). These laser-based ICS sources (see figure 1 for a typical experimental setup) can present a high degree of energy tunability, narrow divergence, and high-flux of photons per pulse (see, for example, (Sarri et al 2014)), which have the potential to provide experimental platforms for the study of ultra-high dose rate effects.

Here, we numerically demonstrate that existing high-intensity laser facilities can already provide ICS photon sources with unique and appealing characteristics for novel radiobiological studies. In a nutshell, the electron beam is accelerated exploiting the laser wakefield acceleration mechanism (LWFA) (Tajima and Dawson 1979), which can now routinely produce femtosecond-scale electron beams with ≈mrad divergence, total charges in the range of 10s of pC up to a nC, and a maximum energy of the order of a GeV (Faure et al 2004, Osterhoff et al 2008, Lundh et al 2011, Guillaume et al 2015, Mirzaie et al 2015, Gonsalves et al 2019, Götzfried et al 2020) in cm-scale plasmas. The interaction of electron beams of these characteristics with a moderately intense laser (from few times 1018 to 1020 Wcm−2 corresponding to dimensionless laser intensities I0 ≈ 1 – 5) can generate high-flux photon beams with a peak energy of the order of a few MeV and relatively narrow divergence in the mrad range. Crucially, the duration of the photon pulse is approximately equal to that of the electron beam, which can be as short as a few to tens of femtoseconds (Hartemann et al 2007, Lundh et al 2011). Monte-Carlo simulations using TOPAS (add-on radiobiological toolkit in Geant4) (Perl et al 2012) show that multi-Gy dose depositions in biological tissue can be achieved in a single shot with a high degree of dose uniformity.

![Figure 1. Typical experimental configuration: The drive laser is focused using a long off-axis parabolic mirror (OAP) onto a gas jet producing a relativistic electron beam via LWFA. A second laser is focused at the exit of the plasma to scatter off the LWFA electron beam. The second OAP has a hole in the centre to allow for the unperturbed extraction of the electron and photon beam (Sarri et al 2014). A magnetic dipole deflects the electron beam off-axis and provides diagnosis of the post-interaction electron spectrum. The photon beam irradiates a cell culture positioned inside lead housing. The photon beam is characterised after cell irradiation to reconstruct the dose for each individual shot. The photon energy spectra can be measured using a compact gamma-ray spectrometer, such as the one described in (Corvan et al 2014). Reprinted (figure) with permission from Sarri et al 2014, Copyright (2014) by the American Physical Society.](image-url)
The article is organised as follows. Section 2 introduces the main theoretical aspects of inverse Compton scattering and provides estimates of the expected photon source parameters. Section 3 shows detailed calculations of the angularly resolved photon spectra for a range of laser parameters. Section 4 then shows the main results of numerical simulations of dose deposition from the calculated photon yields. Section 5 discusses the potential of using a novel laser focussing technique, the so-called flying focus (Froula et al 2018), to increase the photon yield when compared to diffraction limited focussing. Finally section 6 describes the dependence of the delivered dose on the spectrum of the electron beam. Concluding remarks are then given in section 7.

2. Inverse Compton scattering in the field of a laser

We will consider here the interaction of an ultra-relativistic electron beam (Lorentz factor $\gamma_0 \gg 1$) with a counter-propagating high-intensity focussed laser (peak dimensionless laser amplitude $a_0 = cE_0/\omega_0m_e$ $\gtrsim 1$, where $E_0$ and $\omega_0$ are the laser peak electric field and central frequency, respectively), in conditions where quantum effects in the electron dynamics can be neglected and the electron loses a negligible fraction of its energy during the propagation through the laser field. Quantum effects, such as pair production in the laser field, are important only if the ratio between the electric field experienced by the electron in its rest frame and the QED critical field approaches, or overcomes, unity (Di Piazza et al 2012). For an electron beam with a maximum energy of 1GeV and a laser with a maximum dimensionless intensity of 5 (typical maximum parameters used hereafter), this ratio is of the order of 6%, justifying a fully classical treatment of the electron dynamics (Thomas et al 2012). For these electron and laser parameters, the energy lost by the electron during propagation in the laser field can then be estimated by using the Landau–Lifshitz equation (Di Piazza et al 2010), which predicts a maximum energy loss of $\approx 7\%$, thus justifying the assumption of constant electron energy during the propagation in the laser field. In this regime, the main process taking place is Inverse Compton scattering (ICS), whereby the electron emits high-energy photons as a result of the energy up-shift of the laser photons. The motion of an electron in the electromagnetic field of the laser can then be described by the Lorentz force:

$$\frac{dp'}{dt} = \frac{\partial a}{\partial t} - v \times (\nabla \times a),$$

where $p' = p/m_e c$ is the normalised electron momentum, $v$ is the electron instantaneous velocity, and $a$ is the vector potential of the scattering laser. We assume here the laser field to be circularly polarised and propagating along the $z$ direction, i.e. $a = a_0 \hat{z} + a_\phi \hat{\phi} = a \cos \phi \hat{x} + a \sin \phi \hat{y}$ where $a$ is the field envelope with a maximum of $a_0$ and $\phi = \omega_0(t-z/c) + \phi_0$ is the phase. For a focused Gaussian laser pulse, the on-axis normalised vector potential envelope is given by,

$$a(z, t) = a_0 \frac{w_0}{w_z} \exp \left[-\left(\frac{z-ct}{c\tau}\right)^2\right]$$

where $\tau$ is the laser pulse length, and $w_z = w_0 \sqrt{1 + (z/z_r)^2}$ is the laser beam waist for a Rayleigh length $z_r = \pi w_0^2 / \lambda$. One particular advantage of using a circularly polarised laser is that it will produce a radially symmetric ICS photon beam, ideal for dose uniformity on the sample.

The four-momentum components for an electron with initial values of $p_\gamma' = (\gamma_0, P_{x\gamma'}, P_{y\gamma'}, P_{z\gamma'})$ are given by,

$$p_{x\gamma'} = a_x + P_{x\gamma'}$$
$$p_{y\gamma'} = a_y + P_{y\gamma'}$$
$$p_{z\gamma'} = \frac{P_{x\gamma'}^2 + P_{y\gamma'}^2 - \alpha^2}{2\alpha}$$
$$\gamma = \frac{1 + P_{z\gamma'}^2 + \alpha^2 + \alpha^2}{2\alpha}$$

where $\alpha = (\gamma_0 - P_{z\gamma'})$. For a counter-propagating laser pulse with an electron travelling in the $-z$ direction, the initial normalised four-momentum is $p_\gamma' = (\gamma_0, 0, 0, -[1 - (1 - \gamma_0^{-2})^{-1/2})$. One can numerically integrate the electron velocity to get $x(t) = [x_0, y_0, z_0]$ and consequently calculate the unit vector from the particle to the observer, $n = (x_{obs} - x(t)) / \|x_{obs} - x(t)\|$. The Liénard–Wiechert potential can then be used to calculate the radiated energy per unit frequency and solid angle:

$$S = \frac{d^3 W}{d\omega d\Omega} = \frac{e^2}{16\pi^3 \epsilon_0 c^4} \left| \int \frac{n \times (n - \beta) \times \beta}{(1 - n \cdot \beta)^2} \exp \left[i\omega \left(t - \frac{n \cdot x}{c}\right)\right] dt \right|^2,$$
where $\mathbf{p} = \mathbf{p}'/\gamma$, $\mathbf{x}$ is the electron position, $\mathbf{n}$ is the unit vector from the electron to the observation position and $\hat{\mathbf{p}} = \partial \mathbf{p}/\partial t$. The integral $\int_0^{2\pi} \int_0^{\theta_0} S \sin(\theta) d\theta d\phi, \gamma$ gives the spectral distribution of the radiation emitted within an annulus between angles $\theta_1$ and $\theta_2$. For circular polarisation equation (7) is independent of the azimuthal angle $\phi$. Numerical solutions of equation (7), for given laser and electron beam parameters will be used throughout the remainder of the article to calculate the angularly resolved spectra of the scattered radiation.

Before presenting detailed numerical results, it is useful to consider simple heuristic estimates of the photon beam parameters to identify the scattering laser properties of interest. An ultra-relativistic electron oscillating in the electromagnetic field of a laser emits dipole radiation that is Doppler shifted when observed in the laboratory frame. Furthermore, any structure with a periodicity $\lambda_0$ in the laboratory frame used to create the transverse oscillations is relativistically Doppler shifted in the electron rest frame. In the counter-propagating regime, the frequency of the forward-emitted radiation is given by $\omega_f = 4\gamma_0^2 \omega_0$ for an electron energy of $\gamma_0 m_e c^2$ and scattering laser $a_0 \lesssim 1$, where $\omega_0 = 2\pi c/\lambda_0$ (Yan et al. 2017). As $a_0$ increases above 1, the transverse motion of the electron becomes relativistic and one has to consider several non-linear effects such as the relativistic increase in electron mass, which leads to a red-shift of the emitted radiation by a factor $1 + (a_0/\eta)^2$, with $\eta = 1$ or $\sqrt{2}$ for circular or linear polarisation of the laser, respectively.

The number of emitted photons can be estimated by first estimating the mean photon energy after integration over the angular distribution. From this, the number of scattered photons, per electron per optical period, can be estimated as $N_{\text{scat}} = (2\pi/3)\alpha_0 (a_0/\eta)^2$ in the low-intensity ($a_0 \ll 1$) regime and $N_{\text{scat}} = (5\sqrt{3}\pi/6)\alpha_0 (a_0/\eta)$ in the high-intensity regime ($a_0 \gg 1$), where $\alpha_0$ is the fine structure constant. In practical units, the number of emitted photons per electron and their critical frequency can be estimated as (Di Piazza et al. 2012, Corde et al. 2013):

$$a_0 < 1 \left\{ \begin{array}{ll}
\omega_0 \approx 4\gamma_0^2 \omega_0 N_{\text{abs}} \\
N_{\text{scat}} \approx 3.1 \times 10^{-2} N_{\text{opt}} (a_0/\eta)^2
\end{array} \right. \quad (8)
$$

$$a_0 > 1 \left\{ \begin{array}{ll}
\omega_0 \approx 4\gamma_0^2 \omega_0 N_{\text{abs}} / [1 + (a_0/\eta)^2] \\
N_{\text{scat}} \approx 4.7 \times 10^{-2} N_{\text{opt}} (a_0/\eta)
\end{array} \right. \quad (9)
$$

where $N_{\text{abs}}$ is the number of laser photons absorbed by the electron and $N_{\text{opt}}$ is the number of optical periods in the laser field (1 optical period $\approx 2.7$ fs for $\lambda_0 = 800$ nm). The number of photons absorbed by a single electron can be approximated as $N_{\text{abs}} \sim 1$ for $a_0 < 1$ and up to $N_{\text{abs}} \sim a_0^2$ for $a_0 \gg 1$ (Di Piazza et al. 2012).

For the applications sought in this article, one would then require a high charge, GeV-scale and micro-meter size electron beam. Moreover, it would be ideal to have an electron source that is inherently synchronised with the scattering laser, and can provide femtosecond-scale electron beams. While these electron beams are in principle achievable with a radio-frequency accelerator, they are more readily obtainable with a laser-driven plasma accelerator, exploiting the laser-wavefield acceleration mechanism (LWFA).

LWFA implements the large accelerating electric fields that can be sustained by a laser-generated wakefield to accelerate particles to GeV energies over millimeter scale distances (Faure et al. 2004, Lundh et al. 2011). Careful selection of the laser parameters can generate electron beams with micrometer scale size (Cole et al. 2018, Wood et al. 2018) and mrad divergence (Osterhoff et al. 2008, Poder et al. 2018, Kettle et al. 2019). Through ionisation injection (Pak et al. 2010, Mürzai et al. 2015), nC-scale electron beams (Guillaume et al. 2015, Götzfried et al. 2020) with a large energy spread and a maximum energy in the GeV range can be produced (Kneip et al. 2009, Kettle et al. 2019). For the detailed calculations in the following section, we will then consider an ultra-relativistic electron beam with an overall charge of 1 nC and a flat spectrum extending from 0.4 to 1 GeV. The results reported hereafter can then be easily scaled for different total charges of the primary electron beam, thanks to the linear relation between dose deposited and electron beam charge. From equations (8) and (9), one can thus predict ICS photon energies on the order of 4–20 MeV, comparable to that produced from medical linacs for radiotherapy (Verhaegen and Seuntjens 2003).

The duration of LWFA electron bunches can be approximated by considering the radius of the plasma bubble (Thomas 2010). To achieve a high charge electron beam, one can assume that the acceleration portion of the plasma bubble is completely filled. Thus, an upper limit for the duration of the electron bunch can be obtained as:

$$\tau_s = \tau_b/c$$
$$\tau_b = 2\sqrt{a_0} c/\omega_p$$

where $\omega_p$ is the plasma frequency. For example, considering a drive laser with $a_0 = 1.5$ generating a plasma with $n_e = 10^{19}(10^{20})$ cm$^{-3}$, results in a bunch duration $\approx \tau_b(13)$ fs. For highly relativistic electrons, i.e. $\gamma_0 \gg 1$, the electron drift relative to the photons is negligible, scaling as $\Delta t \approx L/2\gamma^2 c$, and so the photon pulse duration is almost identical to that of the electron beam for interaction lengths $L \lesssim 1$ cm.
From equations (8) and (9), it can be seen that the photon yield can be increased by increasing \( a_0 \) (tight focusing, short pulse) or increasing \( N_{opt} \) (stretched pulse). However, increasing \( a_0 \) leads to several undesired effects, including an increase of gamma-ray photon divergence (scaling as \( \propto a_0/\gamma \) for \( a_0 > 1 \)). It is thus preferable to increase the laser duration, while keeping \( a_0 \approx 1 \), until the duration matches the Rayleigh range of the chosen focusing optics. As an example of the expected properties of the ICS photon beam, one can consider a laser with intensity \( a_0 = 2 \), duration \( \tau_L = 1 \) ps, and wavelength \( \lambda_0 = 800 \) nm interacting with a 1 GeV electron beam containing 1 nC of charge (\( 6 \times 10^9 \) electrons). In this case, one would expect approximately \( 10^{11} \) photons with an energy of the order of 7 MeV contained in a cone with an opening angle of the order of 1 mrad. As shown in detail in the next section, these parameters are of direct relevance for multi-Gy and ultra-high dose rate radiobiological experiments.

3. Calculated parameters of the Compton-scattered photon beam for Gaussian focussing

As an example of the ICS photon properties attainable, results of numerically integrating equation (7) are shown in figure 2. The calculations assume a 10 J, 2 ps, circularly polarised laser focused with either an f/6 or f/14 optic (\( a_0 \sim 2.6 \) and \( a_0 \sim 1.1 \), respectively) interacting with a single electron with an energy of 1 GeV (\( \gamma = 1957 \)) or an electron bunch with a flat spectrum from 0.4 to 1 GeV and a divergence of 1 mrad.

As expected, the decrease of \( a_0 \) from \( \sim 2.6 \) to \( \sim 1.1 \) slightly reduces the divergence of the ICS photons, while maintaining a similar spectrum. From this example, it is thus already apparent that, while higher laser intensities would generate more Compton photons (as shown in equations (8) and (9)), they would also result in a broader divergence and a smaller peak energy, suggesting that an optimum intensity must be identified in order to maximise the dose deposited on a sample placed downstream of the interaction. For example, in figure 2, the modal photon energy is shifted from 3.4 to 2.8 MeV and the divergence is increased from 1.5 to 1.6 mrad when \( a_0 \) is increased from 1.1 to 2.6. Moreover, the bandwidth of the scattered photons is also increased from 5.1 to 5.8 MeV when \( a_0 \) is increased. To determine the optimal focusing geometry and pulse length, we then present numerical calculations of the expected properties of the Compton-scattered photon beam, varying the scattering laser f/ number from f/6 to f/14 and the pulse length over \( \tau \approx 0.1 - 10 \) ps, while keeping a constant laser energy of 10 J.

It is important to select a central angular region of the ICS photon beam to irradiate the sample, bearing in mind that, for radiobiological experiments, it is fundamental to ensure a high level of dose uniformity across the irradiated region. For ICS sources, this region has to be carefully selected, due to the well-known angular dependence on the photon spectrum (as also visible in figure 2). We will thus only consider the dose deposited from photons contained within 40% of the standard deviation of the photon angular distribution, which contains, in the case of a 2D Gaussian distribution, 8% of the whole photon population. This leaves the source to phantom distance as a free parameter, ultimately governed by the divergence of the scattered photon beam and the transverse region of the sample to be irradiated. Within this angular region, the variation in photon spectrum is negligible (see figures 2 (c) and (g)). As shown later, this results in a high degree of dose uniformity.

The photon yield and modal photon energy calculated in these conditions are shown in figure 3. As expected, the peak energy of the ICS photons increases when longer pulses and looser focusing is used. Using tighter focusing increases the total photon yield, due to the higher amplitude oscillations experienced by the electron, at the cost of a reduced modal energy. For each f/ number, there is an optimal pulse length \( \tau_{opt} \) which maximises...
the photon yield. For shorter pulses ($\tau < \tau_{\text{opt}}$), increasing $\tau$ reduces the peak intensity but this is compensated by increasing the interaction length. As ICS is more efficient at lower intensities, this results in an increased total photon yield. Increasing the pulse length beyond $\tau = \tau_{\text{opt}}$ reduces the peak intensity without further increasing the interaction length, due to the limitation of the Rayleigh range $z_r = 4LN^2/\pi$, where $N$ is the $f$/ number, thereby reducing the photon yield. The optimal pulse length, $\tau_{\text{opt}}$, increases with increasing $N$ due to the corresponding increase in $z_r$.

The above calculation neglects the finite spatial extent of the electron beam which reduces the overall scattering efficiency when $w_0 < \sigma_r$, where $\sigma_r$ is the electron beam waist. More realistic electron beam properties will be considered in the next section.

### 4. Simulations of deposited dose

To calculate the dose deposited by the ICS photon beams described above, Monte Carlo simulations were performed using the TOPAS code (Geant4 based) (Agostinelli and Allison 2003, Perel et al 2012, Allison et al 2016). As shown above, numerical solution of equation 7 yields the photon number, energy spectrum and divergence of the ICS photon beam (see figures 2, 3). The source size of the photon beam will be of the order of the electron beam size at the point of interaction with the scattering laser. Electron bunches produced via LWFA typically have micron scale sizes upon leaving the plasma (Cole et al 2018, Wood et al 2018), with a divergence of the order of 1 mrad (Poder et al 2018). If the interaction with the scattering laser occurs 1 cm from the exit of the plasma, the electron beam size will thus be of the order of 10 $\mu$m, which can in turn be taken as the source size of the ICS photon beam. As a target for the ICS photon beam, a water phantom is assumed. The phantom is a 0.5 $\times$ 0.5 $\times$ 10 cm water box, with the dose recorded in the central 0.3 $\times$ 0.3 cm region. This irradiation area is of interest for in vitro studies, such as investigation of DNA double stand break kinetics (Rigaud et al 2010), Avenues to increase the irradiated area up to cm-scale, while maintaining Gy-scale doses per irradiation, will be discussed in section 7. The phantom is placed downstream of the photon source at a specific distance to capture the central part of the photon beam, i.e., within 0.4 standard deviations of its angular distribution. This has been chosen in order to ensure percent-level uniformity of irradiation as shown in more detail later. Within this cone, 8% of the photon beam is captured, with an energy spectrum averaged over this angular acceptance. This is shown in figures 2(c), (g), highlighting the validity of this angular selection.

In figure 4, we show the number of photons per primary electron [frame (a)] and the resulting dose in the phantom [frame (b)], as a function of $f$/ number of the focussing optic and the pulse duration ($\tau$) of the scattering laser. For each simulation, we report the maximum dose within the phantom, which typically ranges within 1 to 5 cm deep in the phantom, depending on the specific spectrum of the ICS photon beam. The primary electron beam is assumed to have a transverse diameter $\sigma_r = 10 \mu$m. For $f$/ numbers producing a laser focal spot $w_0 < \sigma_r$, the reduction in the number of electrons effectively interacting with the laser is taken into account by rescaling the number of emitted photons by a factor $\zeta = (w_0/\sigma_r)^2$.

As expected, the maximum number of emitted photons and, therefore, the maximum dose, are obtained in proximity to the condition where the waist of the scattering laser matches the transverse size of the electrons. For a 800 nm laser, this corresponds to a focussing optic with an $f$/ number of approximately 10. It has to be pointed out that we are assuming diffraction-limited quality of the focussing. Any deviation from this ideal scenario should be taken into account for each specific laser system to be used.

The dose deposited is strongly linked to the number of photons produced. This can be seen when comparing figure 4(a) and (b). A maximum dose of the order of 2.2 Gy is obtained for an $f$/10 focussing optic [4(c)] and a pulse duration of approximately 1 ps of the scattering laser, resulting in a dimensionless intensity of the laser of $a_0 \approx 2$.  

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**Figure 3.** Simulated (a) total number of emitted photons per electron within an angular cone of $\pm 0.4\sigma$ and (b) modal on-axis photon energy of the ICS photon beam. The photon beam parameters are shown as a function of $f$/ number and $\tau$ for a collision with a 1 GeV, 1 mrad divergence electron beam. Contours for the peak $a_0$, of the scattering laser are overlaid on each plot as white lines.
For irradiation studies, it is not only important to ensure Gy-scale delivered doses, but also a high level of uniformity across the irradiated area. This is not obviously obtainable with an ICS photon source, mainly due to the strong angular dependence of the spectrum of the generated photons. In order to ascertain the level of uniformity attainable by an ICS source of this kind, additional simulations have been carried out. The simulation set-up is the same as before, with the only difference that now the dose is also measured in 200 μm thick, X-Y slices across the phantom.

Again, only the central 0.3 × 0.3 cm region of the phantom was considered, which is sufficient for irradiating a large number of cells. To measure the uniformity, the coefficient of variance (CoV) was extracted (standard deviation divided by the mean) to provide a relative variation in dose across the region of interest. The results are shown in figure 5 as a function of f/ number and laser pulse duration.

The uniformity is observed to remain relatively constant, in the range of 3%–7%, across all investigated parameters. Figure 5(b) shows an example of the transverse dose profile for the maximum dose attainable (f/10, τ = 1 ps), with the dose profile strongly reflecting the Gaussian profile of the incident beam. In this case, the average value of the CoV was found to be 6%. Figure 5(c) shows an example of the longitudinal dose profile, again shown for the maximum dose attainable, with the dose peaking at a depth of approximately 3 cm into the phantom. These values are in line with other laser driven radiobiological studies (see, for instance, (Oppelt et al 2015, Brack et al 2020)) and lower than typical values achievable with an unfiltered bremsstrahlung source (Mesbahi and Nejad 2008).

5. Enhanced dose deposition using a flying focus

In the previous section, we have shown that electron and laser parameters readily available at existing laser facilities can provide single-shot Gy-scale irradiations with a high level of uniformity. For specific high-dose and high dose-rate studies, such as in a FLASH regime, it would be desirable to increase the dose per shot into the multi-Gy regime. Although several techniques have been proposed to reduce the effects on bandwidth by tailoring the chirp of the laser pulse to counteract non-linear effects (Rykovanov et al 2016, Seipt et al 2019), this can be more readily done by increasing the interaction length of the electrons in the laser field. However, diffraction of the scattering laser pulse limits the maximum interaction length and, as previously mentioned, there exists and optimal pulse length, τ$_{opt}$ ≈ 4L/c, to maximise the photon yield.
One possibility to extend the interaction length is to exploit the spectral spatial coupling of the ‘flying focus’ technique (Froula et al 2018). By tuning the velocity of the laser focus to match that of the electrons, it is possible to increase the interaction time experienced by the electron beam, and significantly reduce the influence of diffraction on the generated photon yield.

The basic principle of the technique is that a chirped laser pulse can be combined with chromatic focusing to allow a focused laser pulse to travel a distance much greater than the Rayleigh length, before defocussing (see figure 6, for an illustration of the effect). The focus can move at a velocity controlled by the laser properties, allowing for the intensity to be coupled to the counter-propagating electron beam. The velocity of the flying focus is given by (Froula et al 2018),

$$\beta(z) = \left[ 1 + \left( \frac{d \lambda}{df} \right)^{-1} \left( \frac{dz}{d \lambda} \right)^{-1} \right]^{-1}$$

(11)

where $d \lambda/df$ and $dz/d \lambda$ are the chirp and chromatic focusing respectively. Setting $\beta(z) = -1$, one obtains the relation for the required laser chirp and chromatic focusing,

$$\frac{d \lambda}{df} = -c \sqrt{2} \left( \frac{dz}{d \lambda} \right)^{-1}$$

(12)

For a refractive plano-concave focusing lens, the focal length is given by $f = R/(n - 1)$, where $R$ is the lens radius of curvature and $n = n(\lambda)$ is the refractive index as a function of wavelength. Therefore,

$$\frac{df}{d \lambda} = -\frac{R}{(n - 1)^2} \frac{dn}{d \lambda}$$

(13)

As an example, for fused silica (a typical high power laser lens glass) and for $\lambda_0 = 800 \text{ nm}$, $n = 1.45$ and $dn/d \lambda = -1.7 \times 10^{-3} \text{ nm}^{-1}$. Therefore, $df/d \lambda(\text{nm}) \approx 4 \times 10^{-5}f$. For a laser spectral bandwidth of 35 nm, typical of short high-power Ti:Sa laser systems (Hooker et al 2006), the flying focus can therefore be sustained for an interaction length of $L = 1.4 \times 10^{-3}f$.

If we assume an $f/5$ focusing optic with a unfocused beam diameter of 150 mm, this would give an interaction length of $L = 1 \text{ mm}$ and require a pulse length $t = 2L/c = 6.5 \text{ ps}$. For a 10 J laser, this would result in a maximum dimensionless laser intensity of $a_0 \approx 1.1$. These values must be compared with an interaction length of about $90 \mu \text{m}$ and an intensity $a_0 \approx 8$ in the case of Gaussian focussing with a fully compressed laser.

Figure 7(a) shows a direct comparison between photon yield from a diffraction limited laser pulse and a laser pulse focussed with the flying focus technique. Figure 7(b) shows a comparison between the dose deposited using a flying focus and a Gaussian diffraction-limited focussing, keeping all the other parameters the same as in the simulations shown in the previous section. Note that for the enhanced yields achieved with the flying geometry electron energy loss becomes more significant and would result in a softer spectrum that was calculated here. However, the final result would not be significantly changed as the dose deposition is relatively insensitive to photon energy in this range.

As shown in figure 7, the maximum dose deposited in a flying focus configuration is of the order of 10 Gy per shot, well within the requirements for studies of FLASH-like effects. When compared to a diffraction-limited focussing technique, the dose is increased by a factor of the order of 5 to 10. When flying focus is compared to
Gaussian focusing for the same pulse length, the number of photons and dose is increased by a factor of the order of 15.

6. Dependence on the spectrum of the electron beam

The calculated yields outlined above show the scattered photon beams and resulting dose considering a 1nC 0.4–1 GeV electron beam with a 1 mrad divergence as an example. While an electron beam with such characteristics is currently achievable, it is important to show how the proposed scheme is dependent upon different electron energies. Intuitively, a lower electron energy is expected to result in a lower peak energy and a broader divergence of the ICS photon beam, thus potentially resulting in a lower dose deposited in the phantom.

We have thus carried out a series of additional simulations for the best condition of the scattering laser (f/number of 10 and duration of 1 ps) but now varying the electron beam spectrum, which is still assumed to be flat, but in three different energy ranges: 0.1–0.3, 0.2–0.5 and 0.2–0.8 GeV, covering a large portion of realistic LWFA energies achievable today. The results are shown in figure 8. As expected, lower electron energies result in lower energies of the ICS photons, which fall below 1 MeV for electron energies less than approximately 400 MeV.

For these electron spectra, the average depth of maximum dose deposition was found to be 0.6, 1.2 and 2.2 cm from the surface of the phantom, for electron spectra of 0.1–0.3, 0.2–0.5 and 0.2–0.8 GeV, respectively.

Lower electron energies do result in a lower dose deposited, mainly due to the lower energy of the photons produced. Furthermore, one can see that the divergence of the beam rapidly increases as electron energy decreases, resulting is source to phantom distances as small as 0.6 m to capture the central 8% of the photon beam. A reduction in central electron energy below 0.2 GeV results in the dose decreasing to < 1 Gy per shot. Therefore, to maintain a dose of 1 Gy per shot, the central electron energy should be maintained above ≳0.2 GeV.

7. Discussion and conclusions

Using laser and electron beam properties now readily available in high-power laser facilities, we have numerically demonstrated the possibility of generating inverse Compton scattering photon sources with high flux and energy per photon exceeding the MeV. These sources are found to be able to deliver Gy-scale doses in a single shot, thus being of interest for fundamental radiobiological studies. Moreover, the dose is delivered with an intrinsically high degree of spatial uniformity, greatly exceeding that of other sources without the insertion of...
further filtering or collimation (Mesbahi and Nejad 2008). As an example of the performance of this photon source, a maximum dose per irradiation of 2.2 Gy over an area of 3x3 mm² and with a percent-level spatial uniformity is reported, assuming a flat spectrum 1 nC primary electron beam from the wakefield accelerator. These irradiation conditions are readily applicable for in vitro studies of double strand DNA damage. Adopting a flying-focus technique for the scattering laser, this dose can be increased up to 10 Gy, while keeping the same electron and laser beam parameters. Given the linear relationship between deposited dose and charge of the primary electron beam, the maximum attainable dose can be further increased by using higher-charge electron beams, with recent work demonstrating the possibility of producing multi-nC electron beams (Guillaume et al 2015, Götzfried et al 2020). A multi-Gy dose per irradiation will allow for detailed clonogenic studies to be performed. Moreover, thanks to an inherent divergence of the photon beam in the mrad range, increasing the source-to-sample distance will allow for wider irradiation areas, with Gy-scale irradiations attainable over regions with cm-scale diameter, of direct applicability to in vivo studies (see, e.g., (Oppelt et al 2015)).

Complementing existing photon sources used for radiotherapeutic and research applications, this laser-driven inverse Compton scattering source has the additional advantage of delivering the required dose in an ultra-short time scale, of the order of tens of femtoseconds. To the best of our knowledge this is the first photon source able to deliver a significant amount of dose on timescales comparable to the physical stage of cell response (see figure 9). It is worth noting that all the aforementioned properties are still preserved over a relatively broad range of laser and electron parameters, demonstrating the robustness of the proposed method.

A femtosecond-scale irradiation time is expected to open new avenues of research in the experimental study of cell response to radiation. For instance, even in FLASH irradiations incident particles are separated in time by periods that are long compared to the timescales physical and early chemical interactions. This greatly reduces the possibility of any cumulative inter-track effects impacting on initial damage and subsequent radiobiology. This is an effect that it was not possible to isolate with existing radiation sources and that could have a strong influence in the effects of radiation on cells (Feuerhahn and Egly 2008, Rigaud et al 2010, Harrington 2019).

Moreover, a Gy-scale dose delivered in a femtosecond timescale will result in unprecedented dose rates of the order of, if not exceeding, $10^{14}$ Gy/s (see figure 9). Recent simulation work has already hinted at significant effects when having multiple ionising radiation tracks within a close spatial and temporal proximity, such as what would be achieved with ultra-high dose-rate studies (Kreipl et al 2009, Ramos-Méndez et al 2020). These works have mostly focused on the effect of radical-radical reactions on the total radical yield. This is of particular interest as it is mainly these free radicals that cause the indirect damage to the DNA. As an example, it has already been shown for 100MeV protons (see (Ramos-Méndez et al 2020)) that the radical yield is dependent not only on the dose deposited but also on the duration of the proton beam. Our proposed source will allow for the first time investigating high dose-rate effects of this kind in biological environments.

Finally, it has been shown that adopting a novel laser-focussing technique, the flying focus (Froula et al 2018) allows for an approximately ten-fold dose increase when compared to a standard Gaussian focalising system, using the same laser system. In this case, the delivered dose is expected to reach up to 10 Gy within a single shot, in a regime of direct relevance to the study of FLASH-like effects (Hendry 2020, Wilson et al 2020), at unprecedented short irradiation times and ultra-high dose rates.
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