Suitability of noble gas-filled ionization chambers for dosimetry of electron FLASH radiotherapy

by

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Outline

- Introduction to Ultra-high dose rate (or FLASH) radiotherapy
- Dosimetry challenges in electron FLASH (eFLASH)
- Ultra thin parallel plate ion chambers
- Noble gas-filled parallel-plate ionization chambers
    - Recombination model
    - Relevant parameters
    - Collection efficiency results
- Conclusions

Pre-clinical evidence for the FLASH effect

- Ultra-high dose rate (or FLASH) radiotherapy widens the therapeutic index by preserving normal tissue for the same tumor control

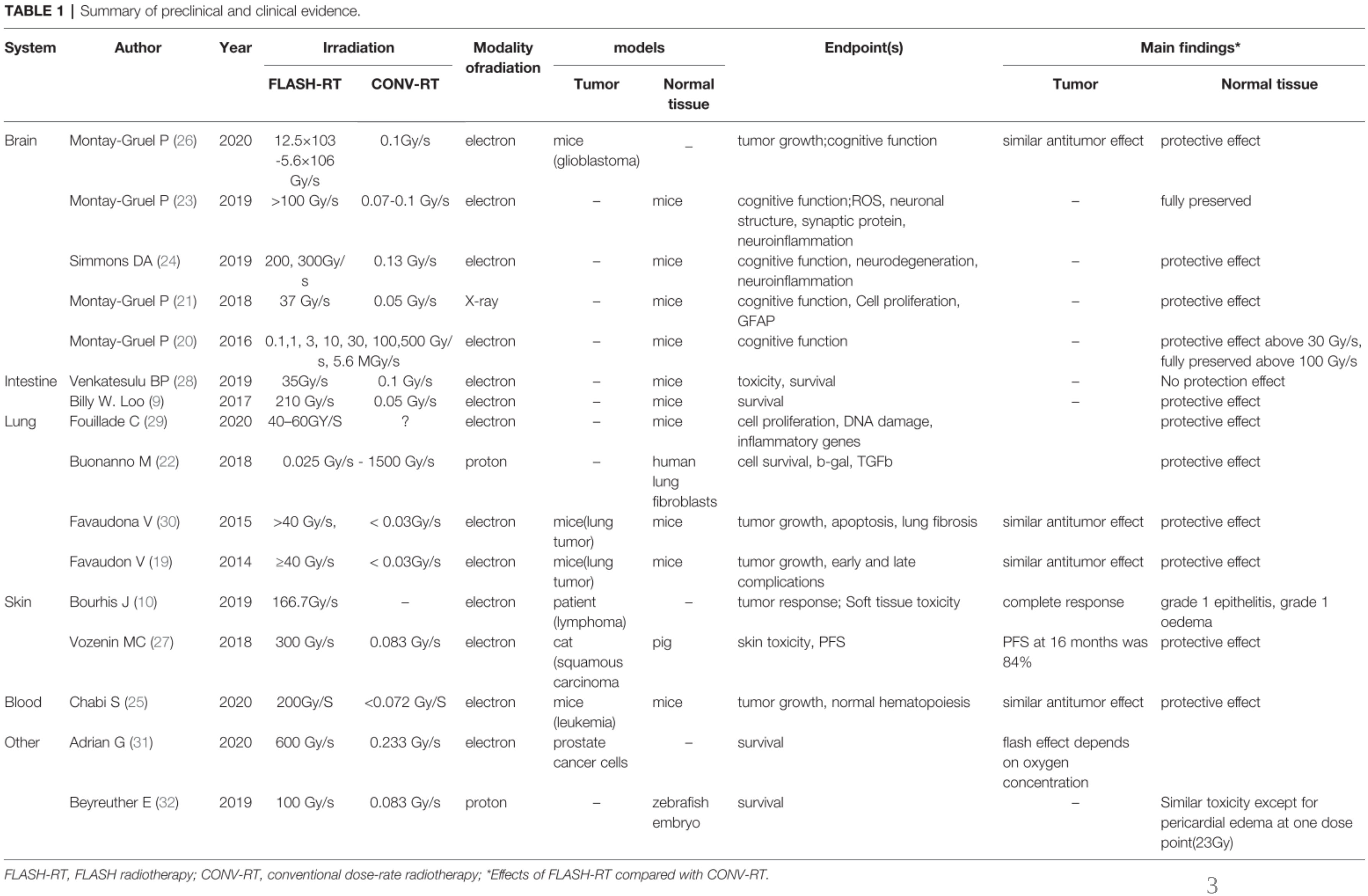


TABLE 1 | Summary of preclinical and clinical evidence.

System	Author	Year	Irradiation		Modality ofradiation	models		Endpoint(s)	Main findings*	
			FLASH-RT	CONV-RT		Tumor	Normal tissue		Tumor	Normal tissue
Brain	Montay-Gruel P (26)	2020	12.5×103 -5.6×106 Gy/s	0.1Gy/s	electron	mice (glioblastoma)	–	tumor growth;cognitive function	similar antitumor effect	protective effect
	Montay-Gruel P (23)	2019	>100 Gy/s	0.07-0.1 Gy/s	electron	–	mice	cognitive function;ROS, neuronal structure, synaptic protein, neuroinflammation	–	fully preserved
	Simmons DA (24)	2019	200, 300Gy/s	0.13 Gy/s	electron	–	mice	cognitive function, neurodegeneration, neuroinflammation	–	protective effect
	Montay-Gruel P (21)	2018	37 Gy/s	0.05 Gy/s	X-ray	–	mice	cognitive function, Cell proliferation, GFAP	–	protective effect
	Montay-Gruel P (20)	2016	0.1,1, 3, 10, 30, 100,500 Gy/s, 5.6 MGy/s		electron	–	mice	cognitive function	–	protective effect above 30 Gy/s, fully preserved above 100 Gy/s
Intestine	Venkatesulu BP (28)	2019	35Gy/s	0.1 Gy/s	electron	–	mice	toxicity, survival	–	No protection effect
	Billy W. Loo (9)	2017	210 Gy/s	0.05 Gy/s	electron	–	mice	survival	–	protective effect
Lung	Fouillade C (29)	2020	40–60GY/S	?	electron	–	mice	cell proliferation, DNA damage, inflammatory genes		protective effect
	Buonanno M (22)	2018	0.025 Gy/s - 1500 Gy/s		proton	–	human lung fibroblasts	cell survival, b-gal, TGFb		protective effect
	Favaudona V (30)	2015	>40 Gy/s,	< 0.03Gy/s	electron	mice(lung tumor)	mice	tumor growth, apoptosis, lung fibrosis	similar antitumor effect	protective effect
	Favaudon V (19)	2014	≥40 Gy/s	< 0.03Gy/s	electron	mice(lung tumor)	mice	tumor growth, early and late complications	similar antitumor effect	protective effect
Skin	Bourhis J (10)	2019	166.7Gy/s	–	electron	patient (lymphoma)	–	tumor response; Soft tissue toxicity	complete response	grade 1 epithelitis, grade 1 oedema
	Vozenin MC (27)	2018	300 Gy/s	0.083 Gy/s	electron	cat (squamous carcinoma	pig	skin toxicity, PFS	PFS at 16 months was 84%	protective effect
Blood	Chabi S (25)	2020	200Gy/S	<0.072 Gy/S	electron	mice (leukemia)	mice	tumor growth, normal hematopoiesis	similar antitumor effect	protective effect
Other	Adrian G (31)	2020	600 Gy/s	0.233 Gy/s	electron	prostate cancer cells	–	survival	flash effect depends on oxygen concentration	
	Beyreuther E (32)	2019	100 Gy/s	0.083 Gy/s	proton	–	zebrafish embryo	survival	–	Similar toxicity except for pericardial edema at one dose point(23Gy)

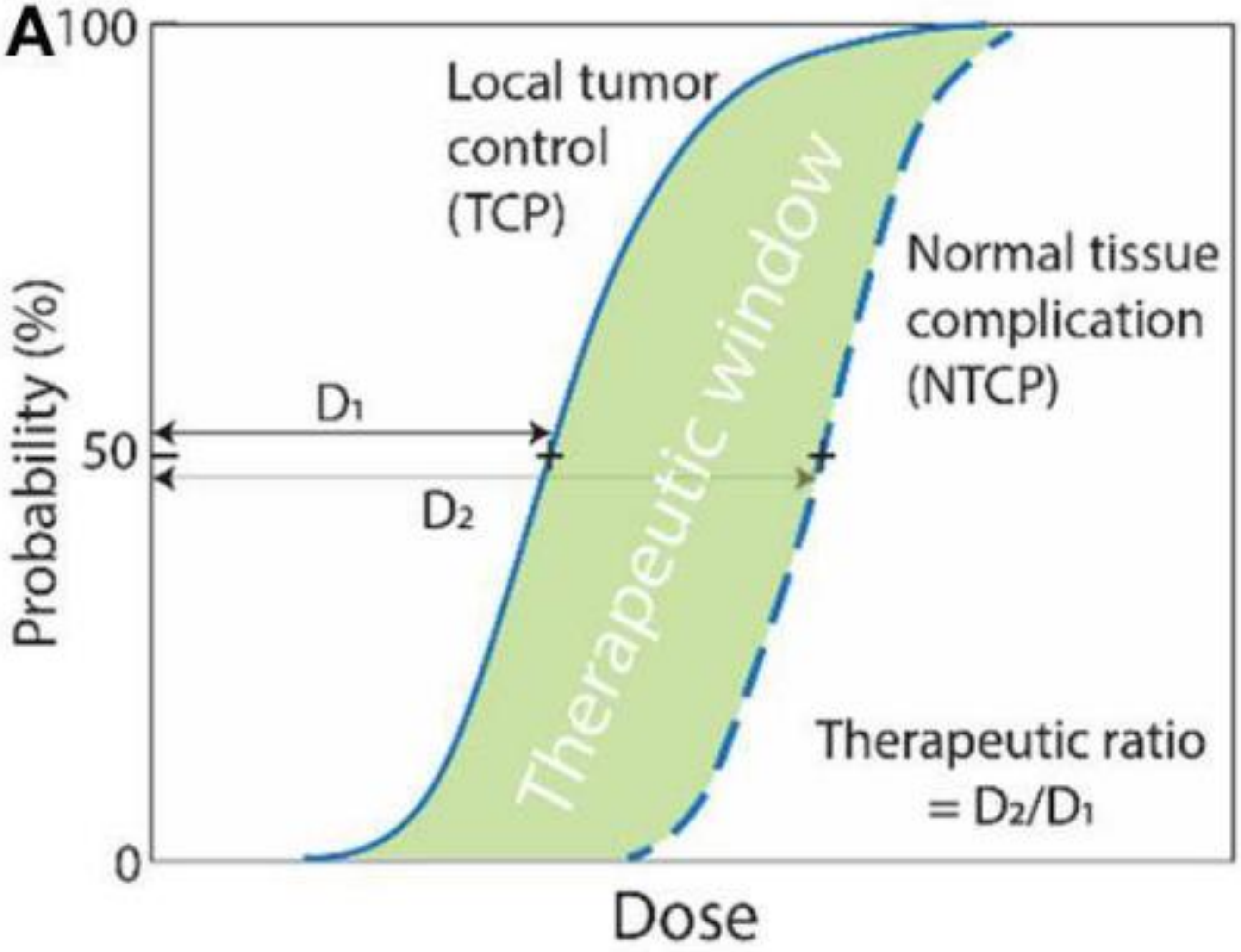
*FLASH-RT, FLASH radiotherapy; CONV-RT, conventional dose-rate radiotherapy; *Effects of FLASH-RT compared with CONV-RT.*

References:

Lin et al. - Frontiers in Oncology - 2021

Benefits of FLASH radiotherapy

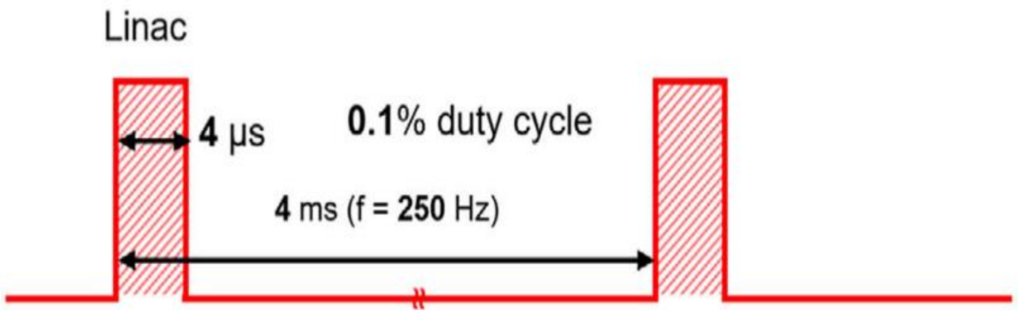
- Lower side effects and complications
- Possible new treatments that were previously limited by radiosensitive organs



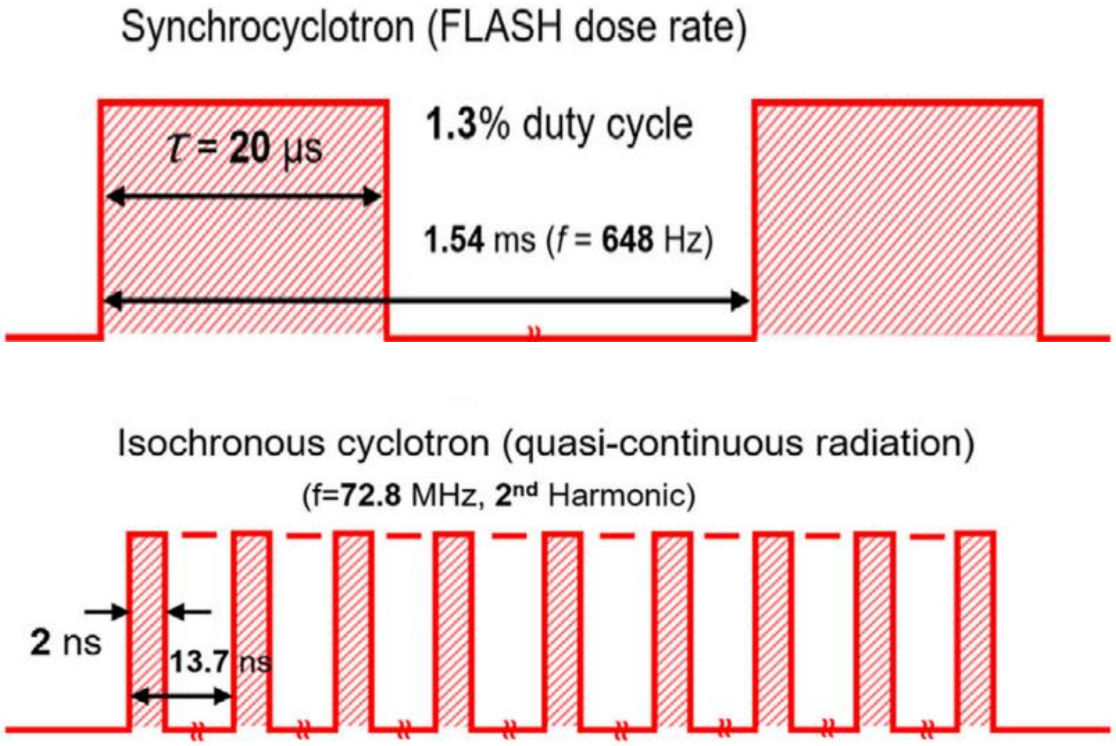
References:
Ashraf et al. - Frontiers in Physics - 2020

Beam pulse structure

- Radiobiological reasonings behind the FLASH effect are still under investigation
- Physical parameters play a key role in inducing the FLASH effect
  - Time-averaged dose rate (>40 Gy/s)
  - Cumulative dose



Electron/photon therapy

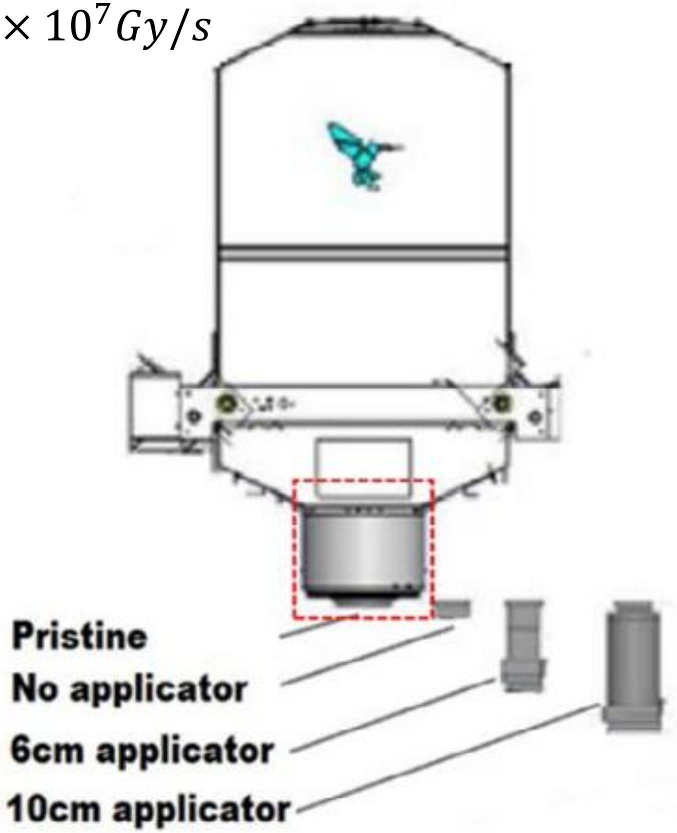


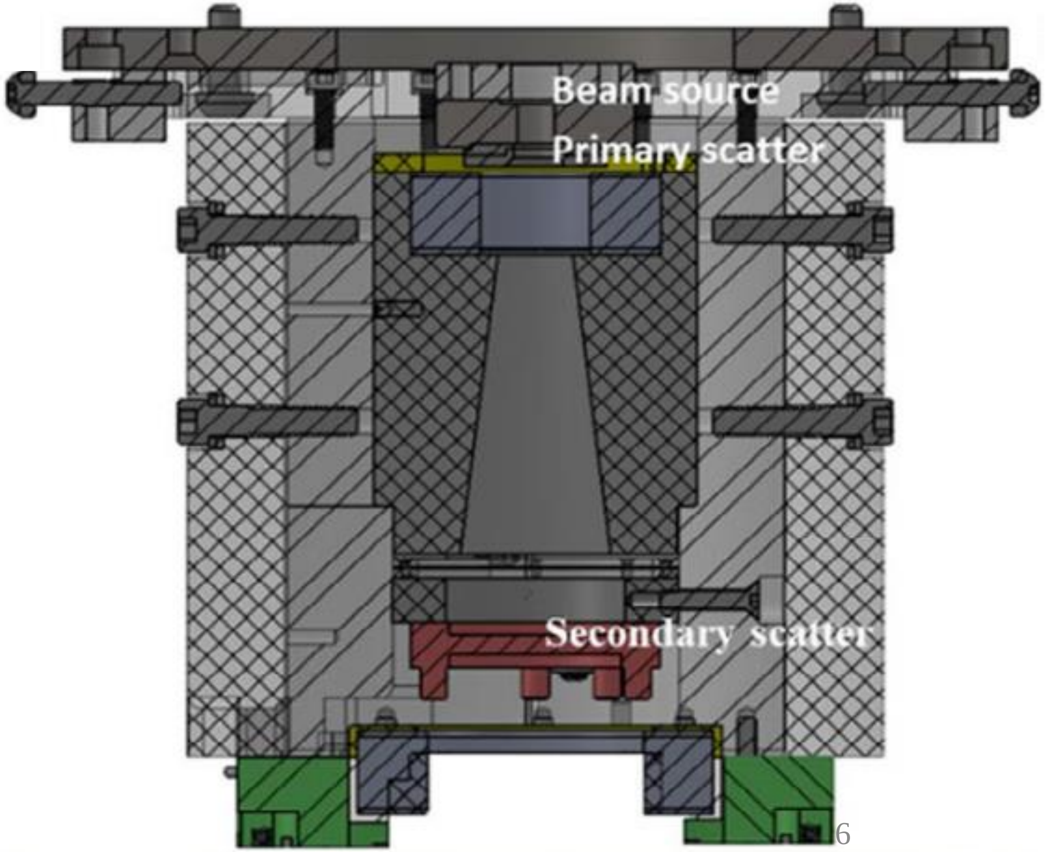
Proton therapy

References:
Modified from Diffenderfer et al. - Medical Physics - 2021

Electron FLASH (eFLASH)

- Mobetron intra-operative linac capable of delivering electron beams with FLASH dose rates
  - Pulse widths of 0.5-4 µs
  - Pulse repetition frequency of 5-120 Hz
  - Dose per pulse of up to 10 Gy
  - Instantaneous dose rates of up to $2 \times 10^{7} Gy/s$

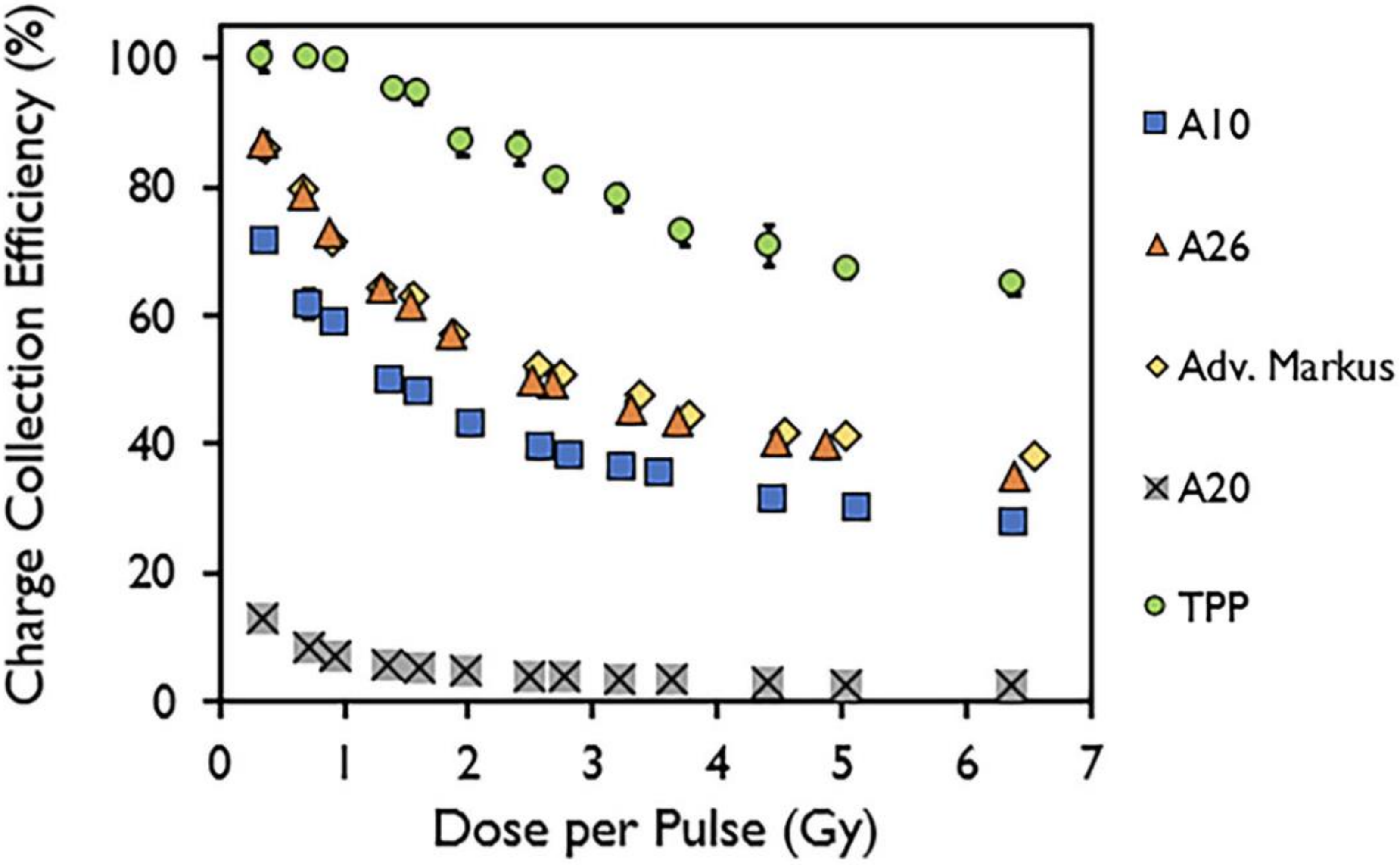




References:
Dai et al. - Medical Physics - 2024

Significant recombination effects in eFLASH

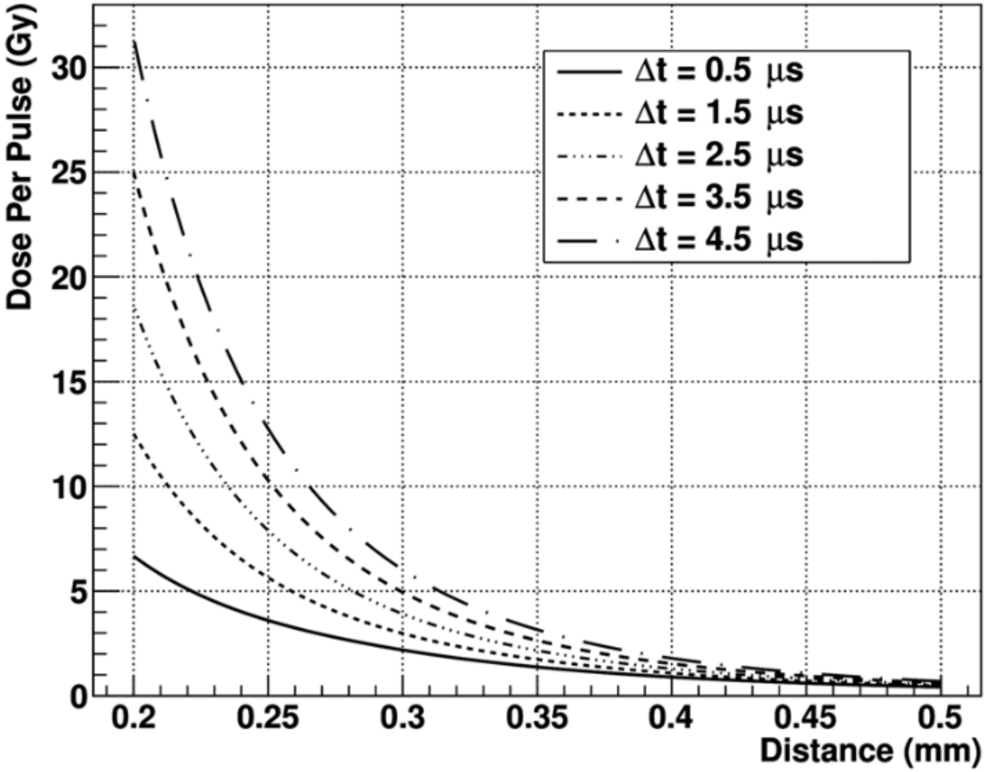
- Charge collection efficiency is inversely proportional to dose-per-pulse and directly proportional to pulse width



References:
Liu et al. – Medical Physics - 2024

Ultra thin parallel-plate ion chambers

- Smaller plate separations lead to higher charge collection efficiency (CCE)
  - Higher electric field strengths inside the air cavity despite utilizing voltages in the 100-300 V range
  - Different charge carriers experience each other for a shorter amount of time for smaller electrode separation
  - Electrons travel shorter distances inside the air cavity before reaching the anode



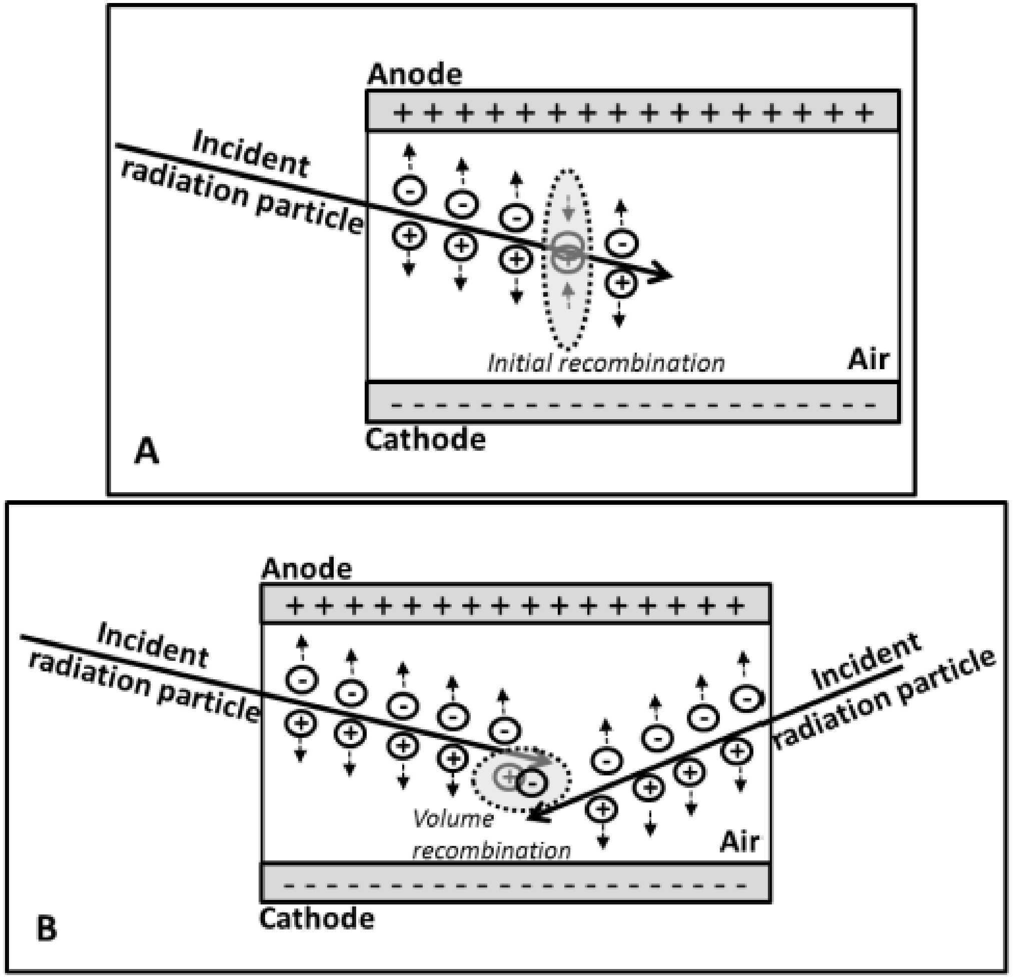
References:
Modified from Gómez et al. - Medical Physics - 2022

Alternative solutions

- Need for a dosimeter with a large dynamic range
  - Relevant for hypofractionated treatments with one or a few pulses
- Adaptable to other ion chamber geometries such as cylindrical ion chambers

Reasons for high recombination

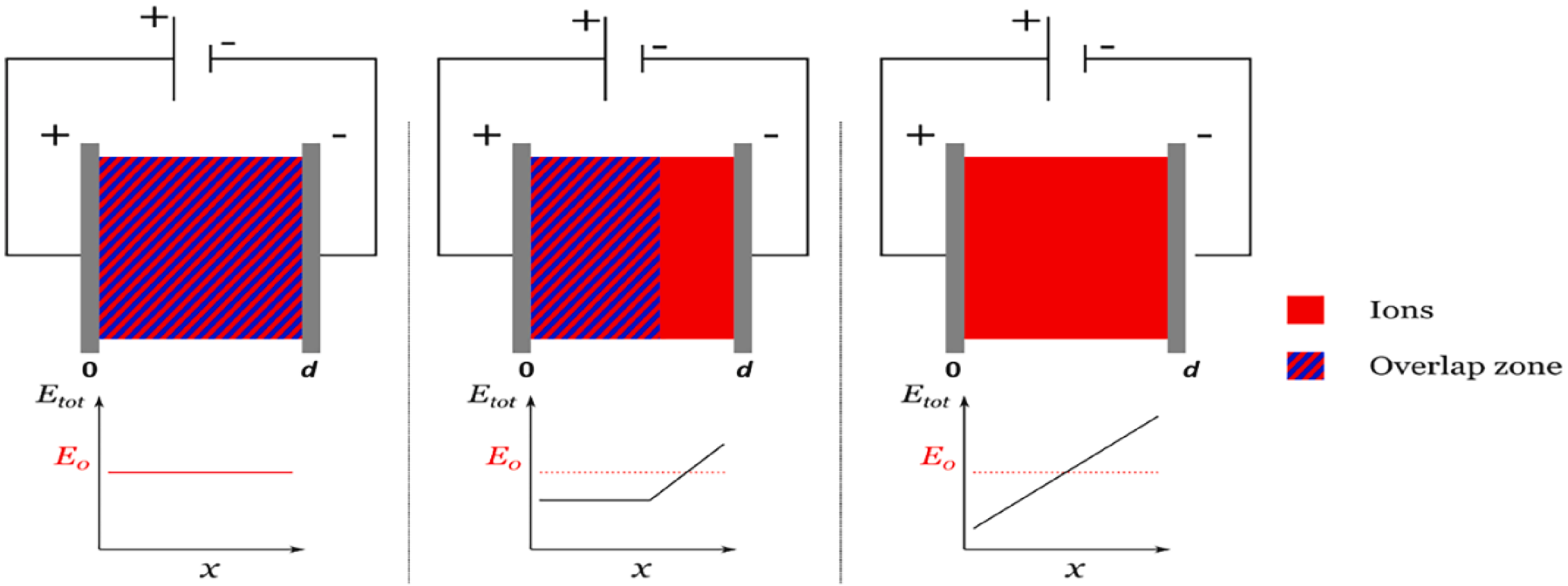
- Recombination due to
  - Cation-electron recombination
  - Electron attachment to atoms with high electron affinity
  - Ion-ion recombination



References:
Modified from Rossomme et al. - Medical Physics - 2016

Usage of noble gas eliminates anions

- Recombination due to
  - Cation-electron recombination
  - ~~Electron attachment to atoms with high electron affinity~~
  - ~~Ion-ion recombination~~



References:
Di Martino et al. - Physica Medica - 2022

ALLS Chamber

- Operates at 0.1 kPa
  - Possible limitations imposed by low signal (<0.5 nC for 20 Gy DPP)
- The impact of the perturbation of the electric field on the charge collection efficiency was not investigated

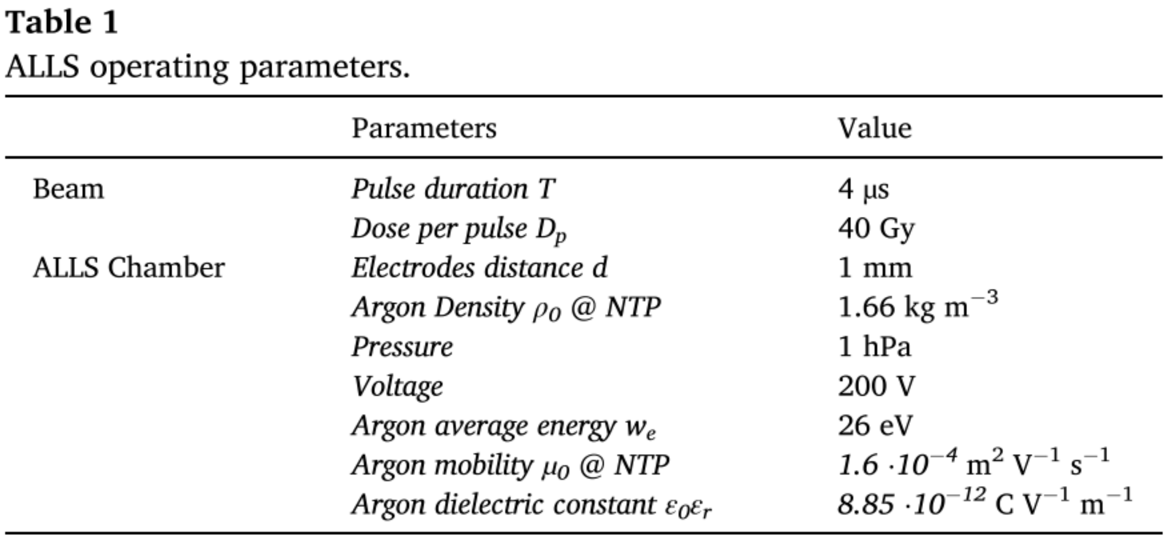
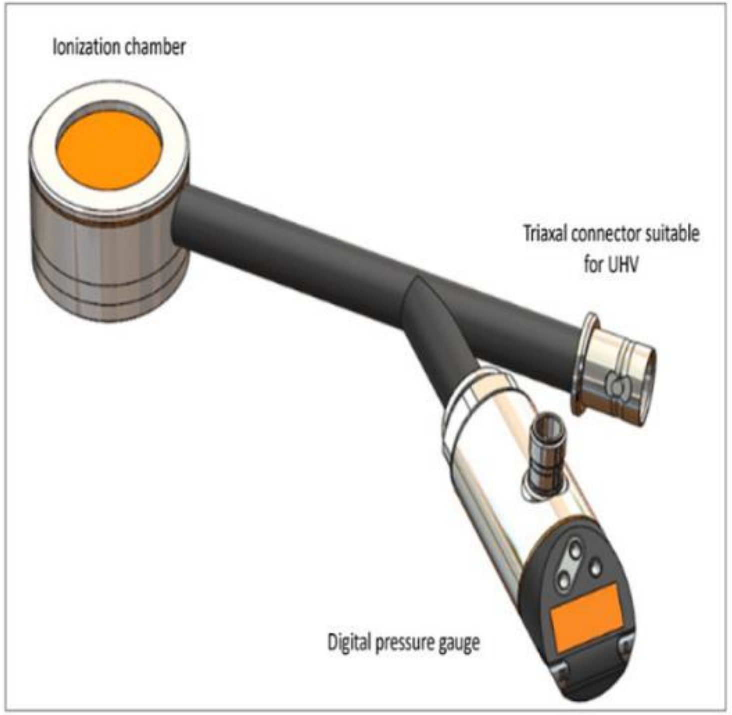


Table 1
ALLS operating parameters.

	Parameters	Value
Beam	*Pulse duration T*	4 µs
	Dose per pulse D_p	40 Gy
ALLS Chamber	*Electrodes distance d*	1 mm
	Argon Density ρ_0 *@ NTP*	1.66 kg m^{-3}
	Pressure	1 hPa
	Voltage	200 V
	Argon average energy w_e	26 eV
	Argon mobility μ_0 *@ NTP*	$1.6 \cdot 10^{-4}$ m^2 V^{-1} s^{-1}
	Argon dielectric constant $\varepsilon_0\varepsilon_r$	$8.85 \cdot 10^{-12}$ C V^{-1} m^{-1}



References:
Di Martino et al. - Physica Medica - 2022

Innovation

- Create a 1D charge collection efficiency (CCE) model to explore the suitability of noble gas-filled ionization chambers without operating at low pressures
    - Helium, neon, and argon

Recombination model

- Previously proposed by Gotz et al. for parallel-plate ionization chambers

Assumptions:

- Uniform electric field along the lateral axes
- Drift only considered along the direction of the electric field (1D case)
- Homogeneous dose distribution inside the air cavity
- Pulse separation >> Pulse duration
- Charge multiplication effects are not modeled

References:
Gotz et al. - Physics in Medicine & Biology – 2017
Gómez et al. - Medical Physics – 2022

Recombination model

- Task: solve for collected n_e and n_+

$$\frac{\partial n_+(x,t)}{\partial t} + \overbrace{\alpha n_+(x,t)n_-(x,t)}^{\text{Recombination}} + \overbrace{\mu_p \frac{\partial}{\partial x}[E(x,t)n_+(x,t)]}^{\text{Ion drift}} = \overbrace{I(x,t)}^{\text{Ionization}}$$

$$\frac{\partial n_e(x,t)}{\partial t} \underbrace{- \frac{\partial}{\partial x}[\mu_e(E)n_e(x,t)]}_{\text{Electron drift}} = I(x,t)$$

References:
Gotz et al. - Physics in Medicine & Biology – 2017
Gómez et al. - Medical Physics – 2022

Recombination model

- Local electric field changes:

$$\frac{\partial E(x,t)}{\partial x} = \frac{e}{\epsilon}\left[n_+(x,t) - n_e(x,t)\right]$$

$$\int E\,(x,t)dx = V$$

- Generated electron/positive ion pairs:

$$I(x,t) = \frac{DPP \times \rho}{t_{pulse} e \left(\frac{W}{e}\right)}$$

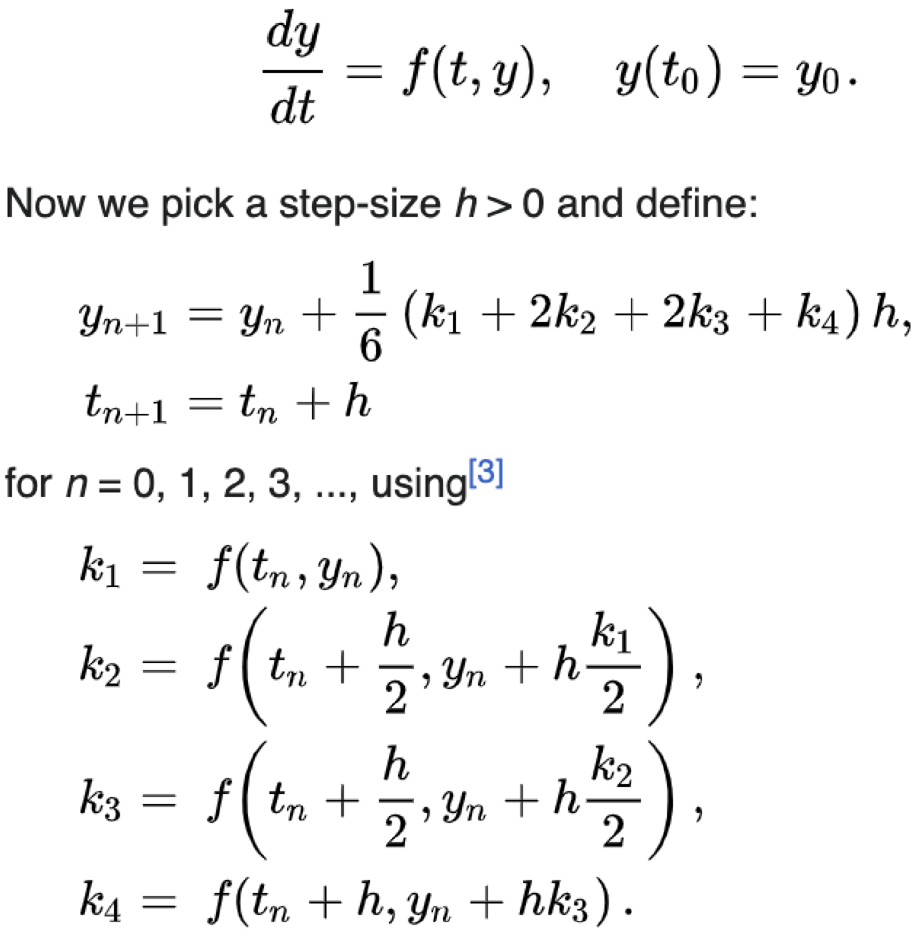
- Collected free electrons:

$$n_e^{collected} = \frac{\partial}{\partial x}\left[v_e(E) n_e(x=0,t)\right]$$

References:
Gotz et al. - Physics in Medicine & Biology – 2017
Gómez et al. - Medical Physics – 2022

Numerical methods

- The 4th order Runge-Kutta method:



$$\frac{dy}{dt} = f(t, y), \quad y(t_0) = y_0.$$

Now we pick a step-size $h > 0$ and define:

$$y_{n+1} = y_n + \frac{1}{6}\left(k_1 + 2k_2 + 2k_3 + k_4\right)h,$$
$$t_{n+1} = t_n + h$$

for $n = 0, 1, 2, 3, \ldots,$ using[3]

$$k_1 = f(t_n, y_n),$$
$$k_2 = f\left(t_n + \frac{h}{2}, y_n + h\frac{k_1}{2}\right),$$
$$k_3 = f\left(t_n + \frac{h}{2}, y_n + h\frac{k_2}{2}\right),$$
$$k_4 = f(t_n + h, y_n + hk_3).$$

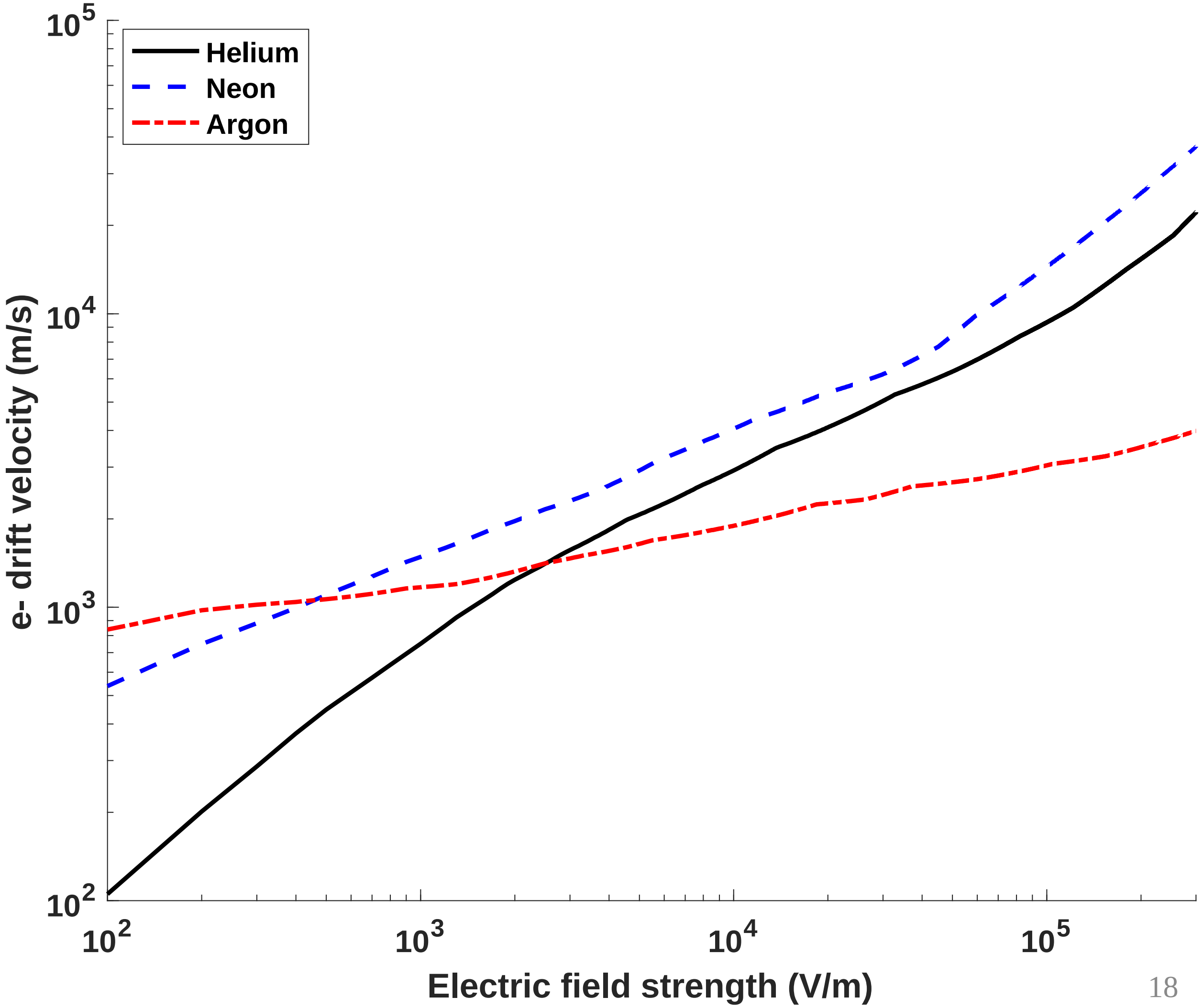
- Adaptive step size to reduce computational time (to within 1 hour)

$$h_{\text{new}} = 0.9 \cdot h \cdot \left(\frac{\epsilon}{TE}\right)^{1/5}$$

References:
Press – Computers in Physics - 1992

Input parameters

- Drift velocity, ion mobility, and recombination coefficients extracted from literature
  - Electron-ion recombination coefficients:
    - Helium: $1.7 \times 10^{-14} m^3/s$
    - Neon: $2.03 \times 10^{-14} m^3/s$
    - Argon: $3.0 \times 10^{-14} m^3/s$
  - Ion mobility:
    - Helium: $0.01\ m^2V^{-1}s^{-1}$
    - Neon: $0.004\ m^2V^{-1}s^{-1}$
    - Argon: $0.002\ m^2V^{-1}s^{-1}$



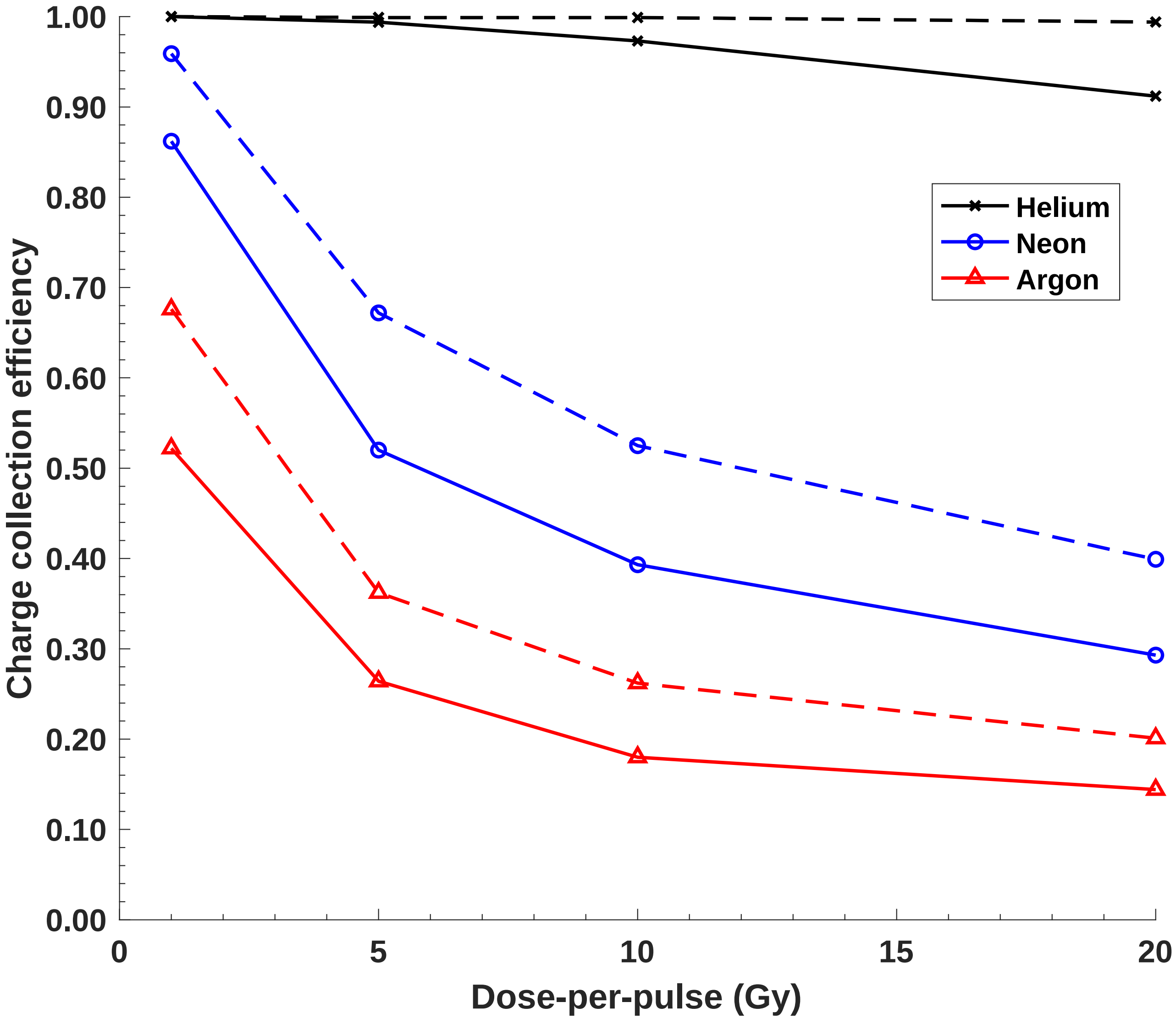
References:
Biondi & Brown - Physical Review – 1949
Oskam & Mittelstadt - Physical Review – 1963
Peisert & Sauli – CERN - 1984

Recombination model

- Charge collection efficiency for
    - Bias voltages of 150 V and 300 V
    - Plate separation of 1 mm
    - Pulse duration of 0.5 µs
    - Dose-per-pulse of 1-20 Gy
    - Instantaneous dose rates of $2 \times 10^6 - 4 \times 10^7\ Gy/s$

Main results

- Argon suffers from low CCE due to high electron-ion recombination and low ion mobility effects
- For 300 V, CCE >0.99 for helium



Limitations

- Need to investigate the magnitude of helium leakage from the sealed chamber
- Availability of helium

Conclusions

- Helium-filled ionization chambers with 1 mm plate separation are suitable for dose rates of up to $4 \times 10^7\ Gy/s$ with 300 V bias voltage
- Experimental results are needed to validate the suitability of noble gas-filled ion chambers for dosimetry of eFLASH

Acknowledgments

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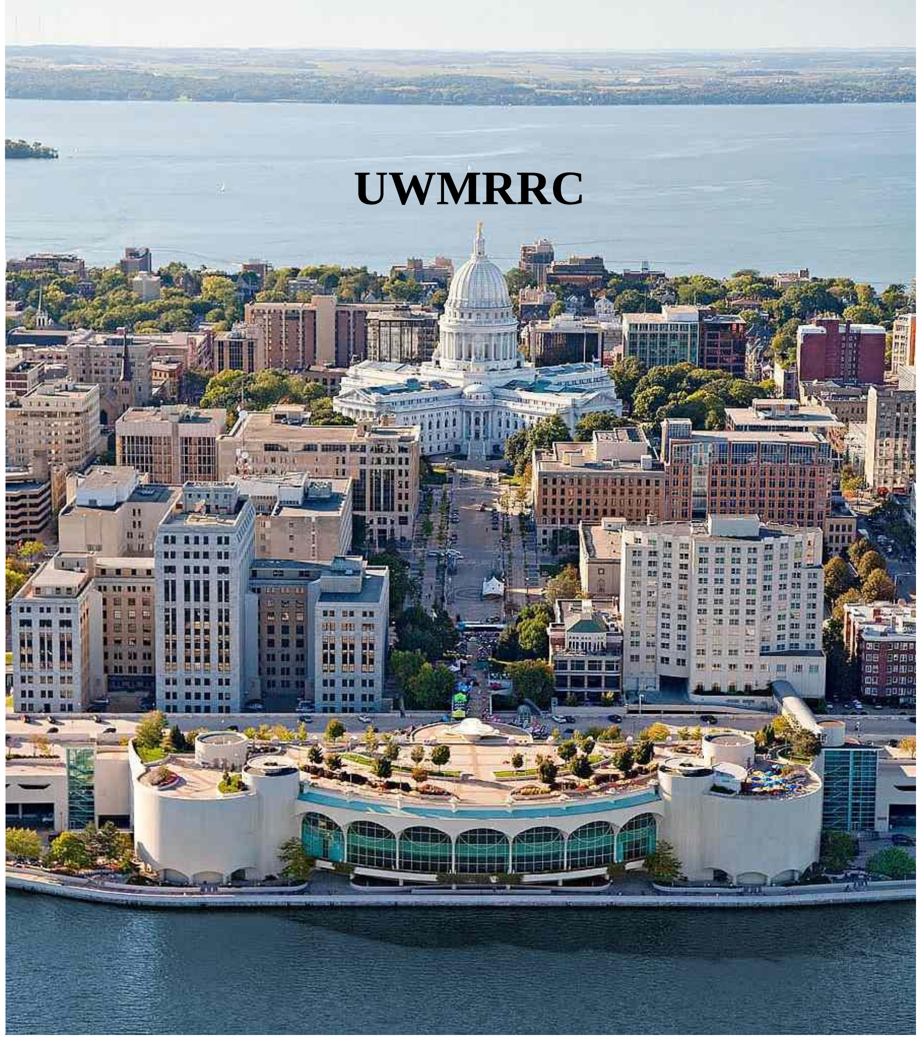

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