

1 **Communication**

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3 **Rapid inactivation of SARS-CoV-2 variants by continuous and intermittent irradiation**
4 **with a deep-ultraviolet light-emitting diode (DUV-LED) device**

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31 SARS-CoV-2, Variants, UV-LED, Viral inactivation, COVID-19
32

33 **Abstract**

34 More than 1 year has passed since social activities have been restricted due to the spread
35 of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). More recently, novel
36 SARS-CoV-2 variants have been spreading around the world, and there is growing concern
37 of higher transmissibility of the variants and weaker protective efficacy of vaccine against the
38 variants. Immediate measures are needed to reduce human exposure to the virus. In this
39 study, the antiviral efficacy of deep-ultraviolet light-emitting diode (DUV-LED) irradiation (280
40 ± 5 nm, 3.75 mW/cm²) against three SARS-CoV-2 variants was evaluated. For the B.1.1.7,
41 B.1.351, and P.1 strains, the infectious titer reduction rates of 96.3%, 94.6%, and 91.9%,
42 respectively, were already recognized with the irradiation of virus stocks for 1 s, and the rates
43 increased to 99.9%, 99.9%, and 99.8%, respectively, with irradiation for 5 s. We also tested
44 the effect of pulsed DUV-LED irradiation (7.5 mW/cm², duty rate: 50%, frequency: 1 KHz)
45 under the same output conditions as continuous irradiation, and found that the antiviral
46 efficacy of pulsed and continuous irradiation was the same. These findings suggest that
47 SARS-CoV-2 may be instantly inactivated by DUV-LED irradiation if the DUV-LED device is
48 further developed and optimized to increase its output.

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50

51 **Introduction**

52 The global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has
53 placed countries in a difficult and ever-evolving situation for over a year. More than 140 million
54 cases of coronavirus disease (COVID-19) and 3.0 million deaths due to COVID-19 have been
55 reported to the World Health Organization (WHO) as of April 18, 2021 [1]; these numbers
56 represent increases of more than approximately 30- and 10-fold, respectively, when
57 compared to the numbers last year. Although vaccinations have begun around the world,
58 COVID-19 has not yet been completely suppressed. At the end of last year, three variants of
59 SARS-CoV-2, that is, the United Kingdom (UK) strain (B.1.1.7) [2,3], South African strain
60 (B.1.351) [4,5], and Brazilian strain (P.1) [6,7], were confirmed, and they have recently spread
61 all over the world. These variants threaten society as a whole, since the variants may have
62 higher transmissibility [2,3,8-10], protective efficacy of vaccine on the variants be weak [10-
63 15] and the patients infected with the variants may be more likely to develop severe medical
64 conditions [16,17].

65 However, governments worldwide are attempting to balance economic activity and
66 medical care as much as possible. Although the development of therapeutic agents and
67 vaccines is an important strategy for bringing an end to the pandemic, it is also necessary to
68 devise measures to reduce virus exposure to prevent the spread of infection due to droplets

69 and droplet nuclei.

70 A deep-ultraviolet light-emitting diode (DUV-LED) instrument that generates around 250-
71 to 300-nm wavelengths has been reported to effectively inactivate microorganisms, including
72 SARS-CoV-2 [18-22]; however, its effect on SARS-CoV-2 variants has not yet been
73 evaluated. Recently, the inactivating effects of pulse patterns of a UV-LED device, which
74 enables pulsed irradiation as the radiation can be turned on and off at a high frequency, on
75 microorganisms have been shown to be as effective as continuous irradiation [23]. In this
76 study, we examined whether continuous and intermittent (pulsed) DUV-LED irradiation can
77 inactivate the three types of SARS-CoV-2 variants (B.1.1.7, B.1.351, and P.1).

78

79 **Materials and Methods**

80 *• Materials*

81 1. Cells: VeroE6/TMPRSS2 cells were obtained from the Japanese Collection of Research
82 Bioresources (JCRB) Cell Bank in Japan (<https://cellbank.nibiohn.go.jp/english/>; JCRB no.
83 JCRB1819). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing
84 10% fetal bovine serum (FBS), penicillin/streptomycin, and 1 mg/ml G418 (Thermo Fisher
85 Scientific, Tokyo).

86 2. Viral stocks: Three types of SARS-CoV-2 variants, that is, the variants that were first
87 described in the UK (hCoV-19/Japan/QHN001/2020 (B.1.1.7)), South Africa (hCoV-
88 19/Japan/TY8-612/2021 (B.1.351),) and Brazil (hCoV-19/Japan/TY7-501/2020 (P.1)), were
89 obtained from the National Institute of Infectious Diseases of Japan. These viruses were
90 propagated in VeroE6/TMPRSS2 cells cultured in DMEM containing 10% FBS and
91 penicillin/streptomycin. At 48 h or 72 h after infection, virus stocks were collected by centrifuging
92 the culture supernatants at 3,000 rpm for 10 min. Clarified supernatants were kept at -80°C until
93 use.

94 3. DUV-LED: The DUV-LED apparatus, which generates a narrow-range wavelength (280
95 ± 5 nm), was obtained from Nikkiso Co. Ltd. (Tokyo, Japan). This wavelength was selected with
96 consideration for practicality due to the high output (radiation) power and longer durability of the
97 LED device during the developmental stage. In addition to conventional continuous irradiation,
98 this DUV-LED instrument enables pulsed irradiation as the radiation can be turned on and off at
99 a high frequency. We used a signal generator (AIMEX Corporation, Tokyo, Japan) to irradiate
100 DUV-LED light.

101 For the evaluation of DUV-LED inactivation of the target virus, aliquots of virus stock (150 µl)
102 adjusted to 5.0×10^4 PFU/ml were placed in the center of a 60-mm Petri dish and irradiated with
103 3.75 mW/cm^2 of continuous irradiation or with 7.5 mW/cm^2 of pulsed irradiation (duty rate: 50%;
104 frequency: 1 KHz) at a work distance of 20 mm for various times (1, 5, or 10 s; n = 3 each). We

105 set the duty rate and frequency of the pulsed irradiation to be the same as the output per time of
106 the continuous irradiation (Supplement 1).

107

108

109 • *Method*

110 The antiviral efficacy of DUV-LED irradiation against the SARS-CoV-2 variants was evaluated.
111 After DUV-LED irradiation, approximately 120 μ l of each virus stock was collected with a 200- μ l
112 tip. Virus solutions were serially diluted in 10-fold steps in serum-free DMEM in a 1.5-ml tube,
113 then inoculated onto VeroE6/TMPRSS2 monolayers in a 12-well plate. After adsorption of virus
114 for 2 h, cells were overlaid with MEM containing 1% carboxymethyl cellulose and 2% FBS (final
115 concentration). The cells were incubated for 72 h in a CO₂ incubator, then observed under a
116 microscope for cytopathic effects. A non-irradiated virus suspension was used as a negative
117 control. To calculate the PFU, cells were fixed with 10% formalin for 30 min, and stained with a
118 2% crystal violet solution.

119 The antiviral effects of DUV-LED irradiation were assessed using the logPFU ratio calculated as
120 $\log_{10}(N_t / N_0)$, where N_t is the PFU count of the UV-irradiated sample, and N_0 is the PFU count
121 of the sample without UV irradiation. In addition, the infectious titer reduction rate was calculated
122 as $(1 - 1 / 10^{\log \text{PFU ratio}}) \times 100$ (%). All experiments were performed in a biosafety level 3
123 laboratory.

124

125

126 **Results**

127 • *Inactivating effects of continuous irradiation with a DUV-LED device*

128 We observed a marked cytopathic effect in all cells that were infected with the UK, South African,
129 or Brazilian strain and were not irradiated with DUV-LED light (Figure 1a). The infected cells that
130 were irradiated for 1 s showed an obvious reduction in the cytopathic effect (Figure 1b), and the
131 morphology of the cells that were irradiated for 5 s was largely comparable to that of the mock
132 cells (Figure 1c, d).

133 The plaque assay revealed that a short irradiation time inactivated SARS-CoV-2 variants
134 rapidly (Figure 2). Of note, for the UK, South African, and Brazilian strains, the infectious titer
135 reduction rates of 96.3%, 94.6%, and 91.9%, respectively, were already recognized with the
136 irradiation of virus stocks for 1 s, and the rates increased to 99.9%, 99.9%, and 99.8%,
137 respectively, with irradiation for 5 s (Table 1 and Figure 3). These results suggested that DUV-
138 LED irradiation for a very short time can drastically inactivate SARS-CoV-2 variants.

139

140 • *Inactivating effects of pulsed irradiation with a DUV-LED device*

141 For the UK, South African, and Brazilian strains, the infectious titer reduction rates of 94.4%,
142 93.4%, and 84.4%, respectively, were already recognized with the irradiation of virus stocks for 1
143 s, and the rates increased to 99.9%, 99.9%, and 99.8%, respectively, with irradiation for 5 s (Table
144 1 and Figure 4). These results were almost the same as those obtained with continuous irradiation.

145
146

147 **Discussion**

148 Recently, there has been growing concern around the world, including at the WHO, regarding
149 the emergence of new SARS-CoV-2 variants since they may have longer infectivity periods [24],
150 stronger infectivity, including in children [2,8,10,25,26], and protective efficacy of vaccine on these
151 variants may be weak [12-15]. It has also been pointed out that patients infected with SARS-CoV-
152 2 variants may be more likely to develop severe medical conditions and have a higher risk of
153 death [8,10,16]. Therefore, in parallel with advances in vaccines and therapeutic agents,
154 measures to reduce virus exposure to prevent the spread of SARS-CoV-2 infection are desired.

155 The present study demonstrated for the first time that DUV-LED irradiation can rapidly
156 inactivate three types of SARS-CoV-2 variants, that is, the ones that were first described in the
157 UK, South Africa, and Brazil [2-7,9,10,26]. Additionally, continuous and pulsed DUV-LED
158 irradiation showed similar degrees of rapid virus inactivation.

159 UV-LED devices that can provide irradiation at various peak emission wavelengths, such as
160 UV-A (320 – 400 nm), UV-B (280 – 320 nm), and UV-C (100 – 280 nm), have been adopted to
161 inactivate various pathogenic species, including bacteria, viruses, and fungi. UV-C is considered
162 to be the most effective germicidal region of the UV spectrum as it causes the formation of
163 photoproducts in DNA and RNA [27]. These pyrimidine dimers interrupt the transcription,
164 translation, and replication of DNA and RNA, and eventually lead to the death of the
165 microorganism [28]. Last year, we reported for the first time that irradiation with DUV-LED at a
166 wavelength of 280 ± 5 nm rapidly inactivated wild-type SARS-CoV-2 that was obtained from a
167 COVID-19 patient [22]. The effect of DUV-LED irradiation on the wild-type SARS-CoV-2
168 (infectious titer reduction rates of 87.4% for 1 s and 99.9% for 10 s of irradiation) was similar to
169 that on the SARS-CoV-2 variants in the present study. Since the SARS-CoV-2 variants also have
170 a lipophilic outer membrane (envelope protein), the inactivating effects of DUV-LED irradiation on
171 the UK, South African, and Brazilian variants were as expected, and similar effects are also
172 expected for other variants that may emerge in the future. Unlike enveloped viruses, non-
173 enveloped viruses that do not have the envelope protein, such as norovirus, are known to be
174 highly resistant to disinfectants, but DUV-LED irradiation is expected to be effective against non-
175 enveloped viruses as well (unpublished observations).

176 In this study, we also tested the effect of pulsed irradiation with a DUV-LED device. As shown

177 in Table 1 and Figure 4, the degree of virus inactivation by continuous and intermittent irradiation
178 was comparable when the device outputs were the same (power X radiation time). This suggested
179 that SARS-CoV-2 may be instantly inactivated by DUV-LED irradiation if the DUV-LED device is
180 further developed and optimized to increase its output [23].

181 Despite the significant inactivating effects of DUV-LED reported here, this study has some
182 limitations. First, these effects may be limited to the test conditions applied in this study, including
183 the irradiation distance and output (work distance of 20 mm; irradiation at 3.75 mW/cm² for
184 continuous irradiation and 7.5 mW/cm² for pulsed irradiation (duty rate: 50%; frequency: 1 KHz)).
185 In addition, it is necessary to also evaluate multiple parameters, such as the frequency and duty
186 ratio, to clarify the effectiveness of pulse irradiation. The influence of the material and the power
187 consumption for the high amplitude were also not evaluated. In the future, we will examine in
188 more detail whether various conditions of DUV-LED irradiation may affect the degree of the
189 inactivation of microorganisms.

190 In addition to community settings, healthcare settings are also vulnerable to the invasion and
191 spread of SARS-CoV-2 and its variants, and the stability of SARS-CoV-2 in aerosols and on
192 surfaces [19] likely contributes to the transmission of the virus in medical environments. It is
193 important to create an environment that minimizes virus exposure to suppress the spread of
194 SARS-CoV-2 in a sustainable and efficient manner. It was confirmed in our study that SARS-
195 CoV-2, including its variants, is highly susceptible to DUV-LED irradiation. By devising appropriate
196 and optimized irradiation methods, it is conceivable that DUV-LED irradiation can be adapted and
197 applied in various settings. This study provides useful baseline data for securing a safer
198 community and medical environment. The development of devices equipped with DUV-LED is
199 expected to prevent virus spread through the air and from contaminated surfaces.

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202

203 **Contributors**

204 H.I., H.S. and A.S. conceived the study and wrote the manuscript. A.S., C.K., and T.O.
205 conducted the experiments dealing with the viruses. S.F. contributed to the study design,
206 study supervision, and manuscript revision.

207

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220

221 **Declaration of interest statement**

222 H.S. receives part of his salary from Nikkiso Co., Ltd., Tokyo, Japan. Nikkiso Co., Ltd.
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224 had no role in the study design, data collection and analysis, decision to publish, or
225 preparation of the manuscript. The other authors declare no conflicts of interest.
226

227 **Figure legends**

228 **Figure 1.** Inhibitory effects of continuous DUV-LED irradiation on three types of SARS-CoV-
229 2 variants (the UK, South African, and Brazilian strains). Cytopathic changes in virus-infected
230 VeroE6/TMPRSS2 cells without DUV-LED irradiation (a), with DUV-LED irradiation for 1 s (b)
231 or 5 s (c) corresponding to 3.75 or 18.75 mJ/cm², respectively. (d) Mock cells.
232

233 **Figure 2.** Plaque formation in VeroE6/TMPRSS2 cells. Virus solutions were treated with
234 continuous DUV-LED irradiation for 0, 1, or 5 s, then diluted 100-fold and inoculated onto
235 VeroE6/TMPRSS2 cells. Representative results are shown.
236

237 **Figure 3.** Log reduction of the infectious titer by continuous irradiation with DUV-LED for the
238 UK, South African, and Brazilian strains.

239 DUV-LED: continuous irradiation (current: 0.35 A).

240 Time-dependent inactivation of SARS-CoV-2 by DUV-LED irradiation. The results shown are
241 the means and standard deviations of triplicate measurements.
242

243 **Figure 4.** Relative value (percentage of the value of the cells irradiated for 0 s) of the
244 infectious titer after continuous and pulsed irradiation with DUV-LED for the UK, South African,
245 and Brazilian strains.

246 DUV-LED: continuous irradiation (current: 0.35 A) or pulsed irradiation (current: 0.7 A; duty
247 ratio: 50%; frequency: 1 KHz). The inactivating effects were almost the same between the
248 continuous and pulsed DUV-LED irradiation.

249

250 **Table caption**

251 **Table 1.** Differences in the infectious titer after continuous and pulsed DUV-LED irradiation
252 for the UK, South African, and Brazilian strains irradiated with different patterns of DUV-LED
253 light for 0, 1, 5, or 10 s.

254

255 **Supplement caption**

256 **Supplement 1.** Output diagrams of two patterns of DUV-LED irradiation. A) Continuous
257 irradiation with a current of 0.35 A for 1, 5, or 10 s. B) Intermittent (pulsed) irradiation with a
258 current of 0.7 A for 1, 5, or 10 s (frequency: 1 KHz; duty rate: 50%). The output per time was
259 set to be the same in continuous irradiation (A, 3.75 mW/cm² × time) and intermittent
260 irradiation (B, 7.5 mW/cm² × time).

261

262

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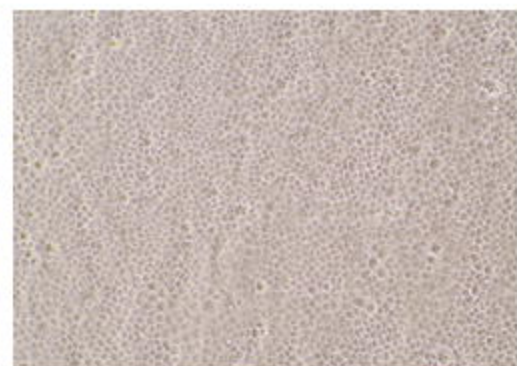
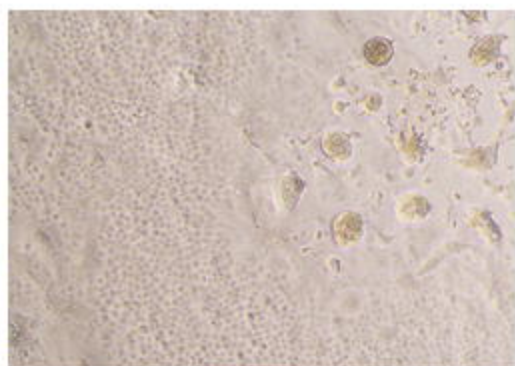
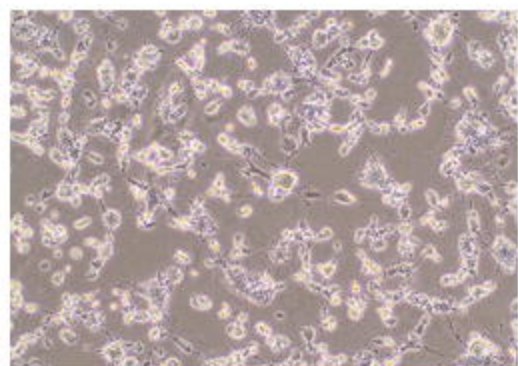
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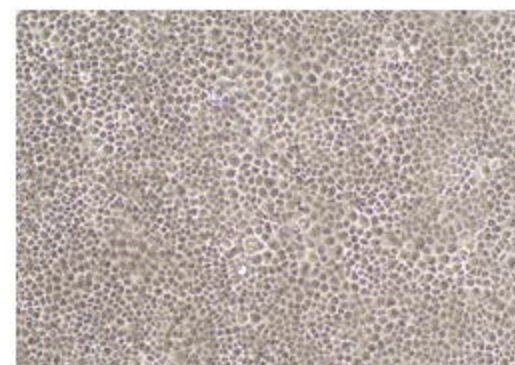
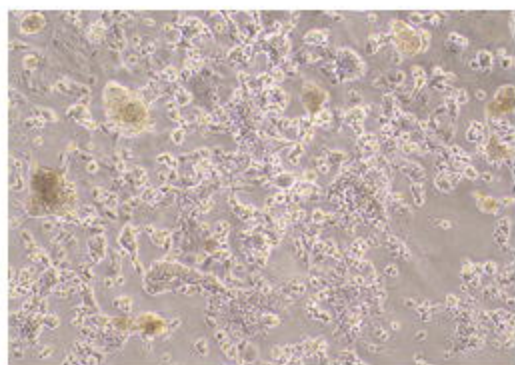
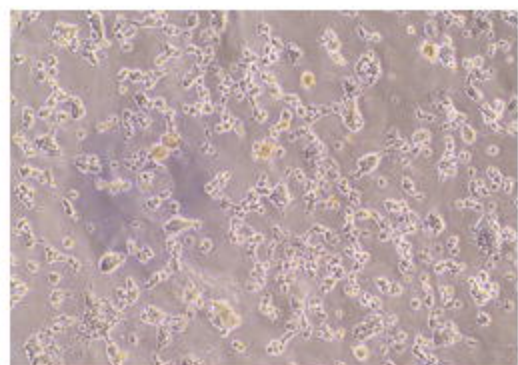
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Figure 1

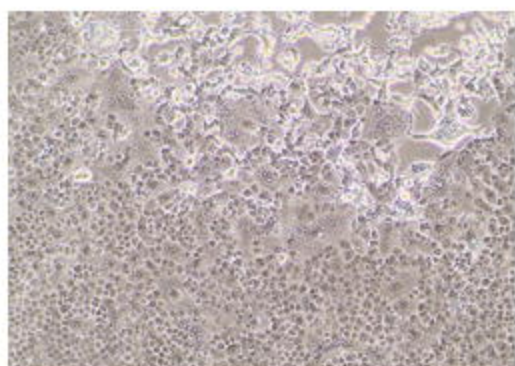
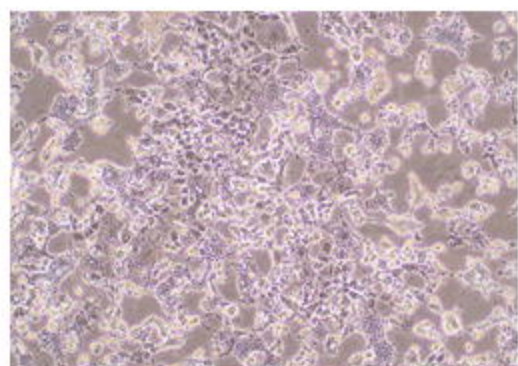
UK strain



South African strain



Brazilian strain



(a) 0 sec

(b) 1 sec

(c) 5 sec

(d) Mock

Figure 2

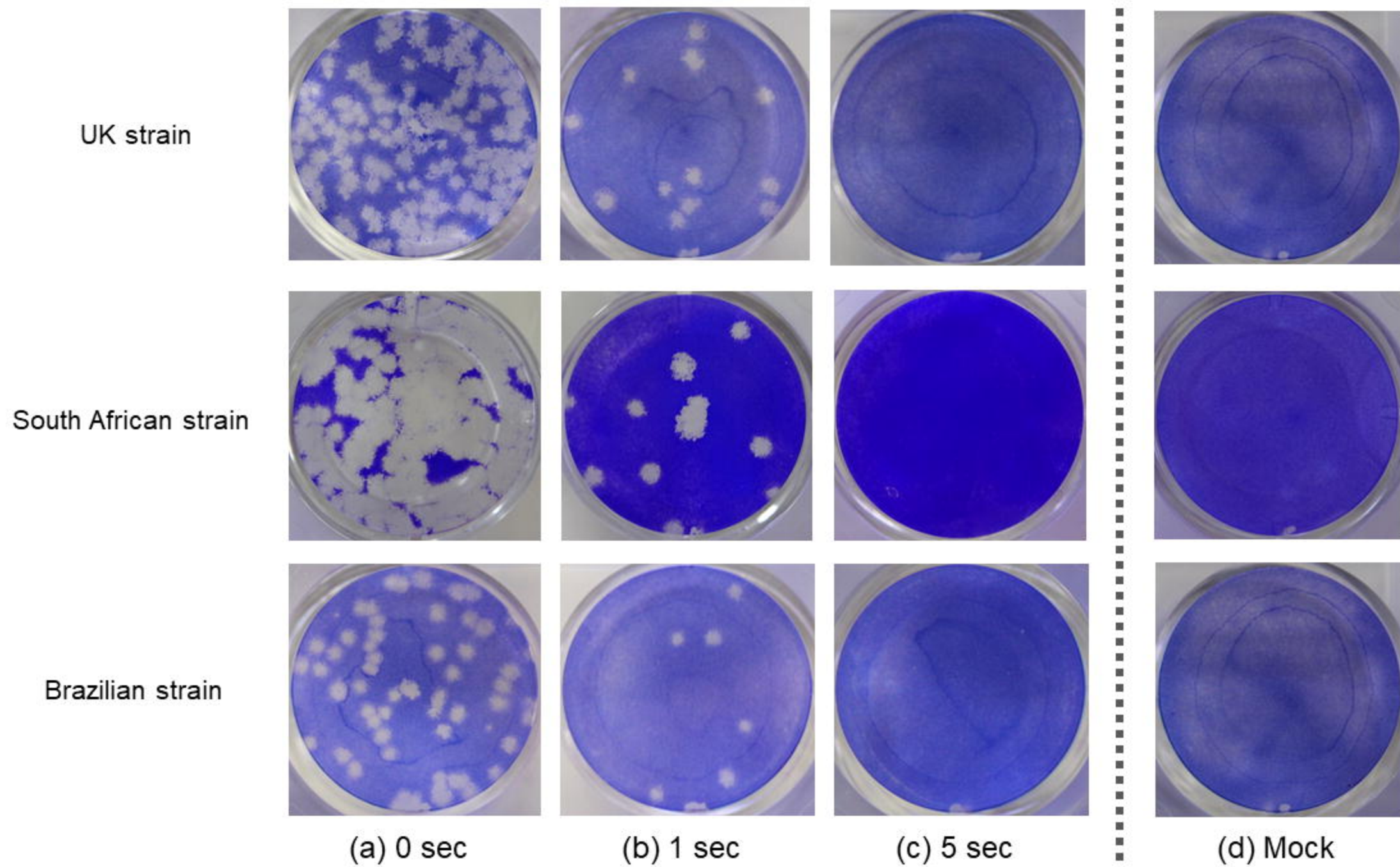


Figure 3

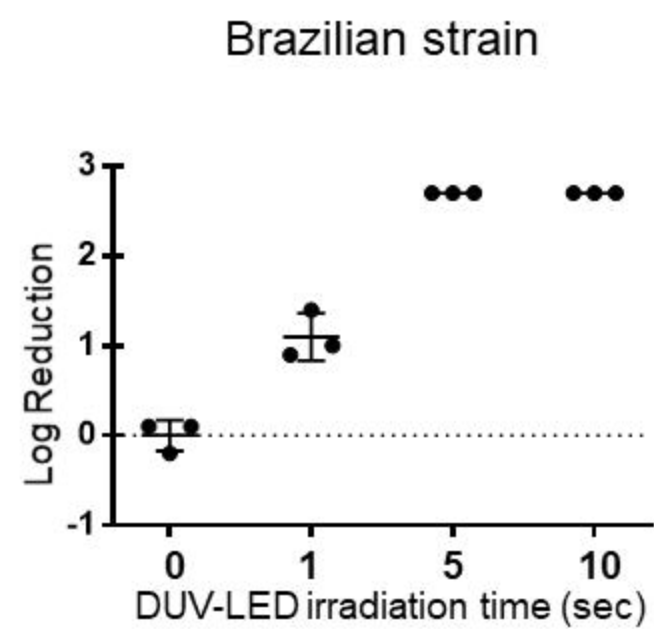
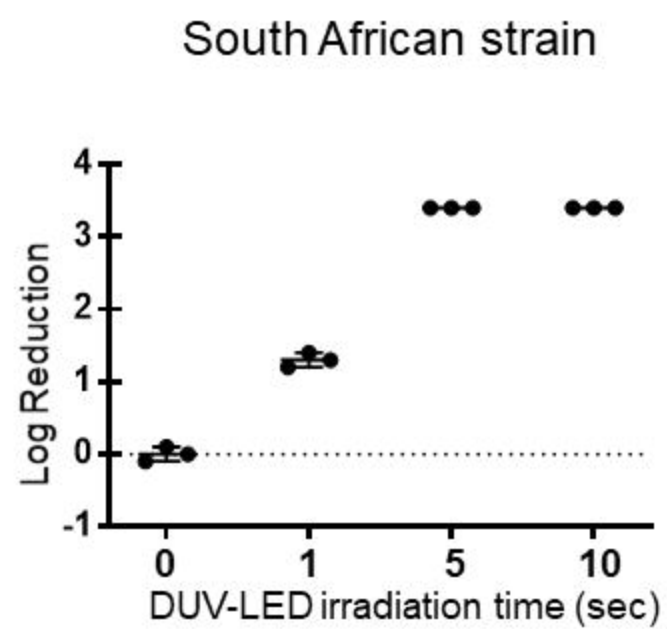
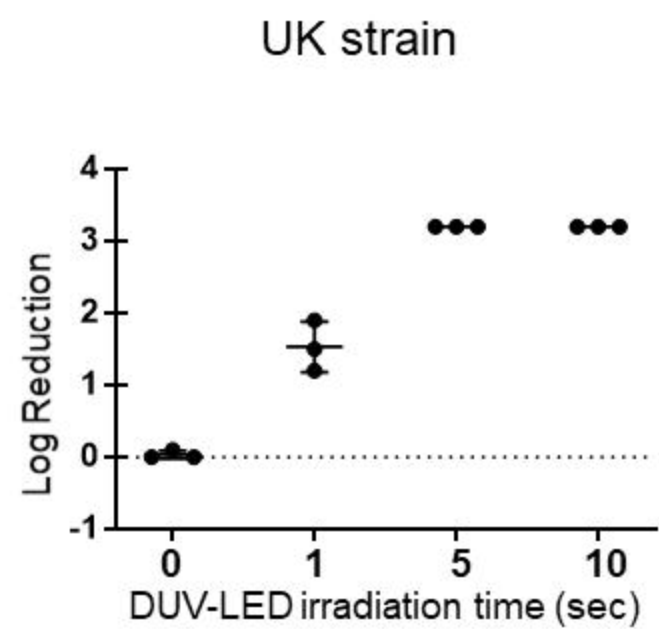
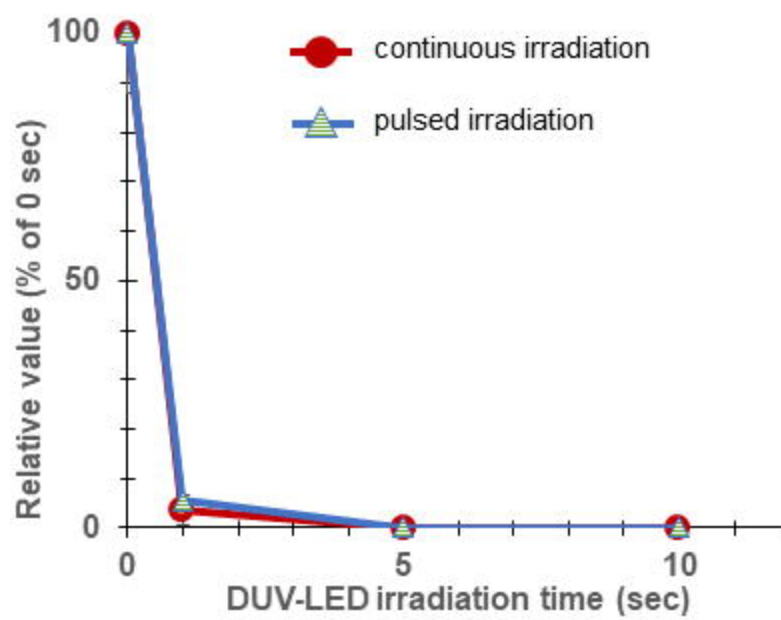
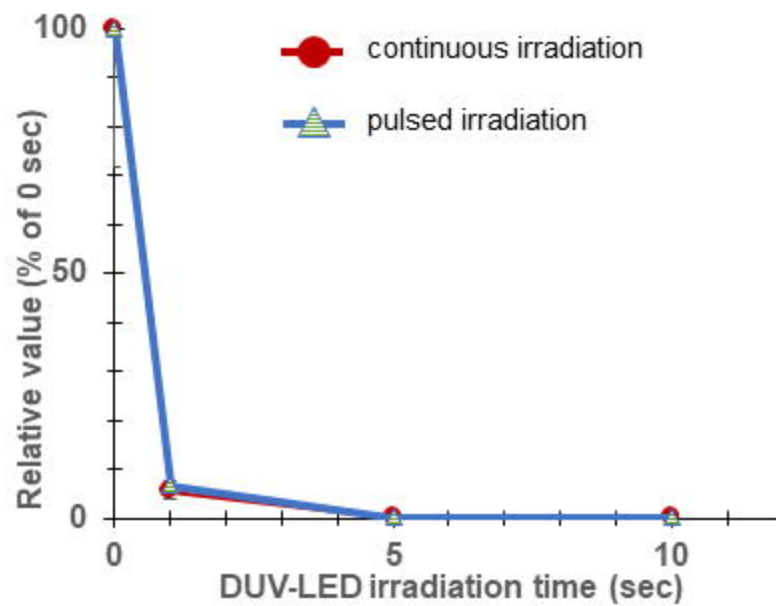


Figure 4

UK strain



South African strain



Brazilian strain

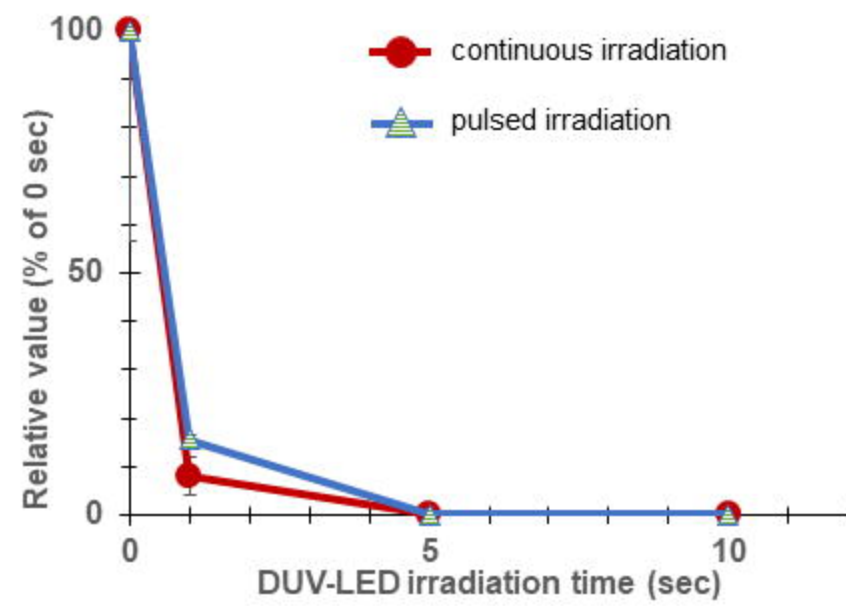


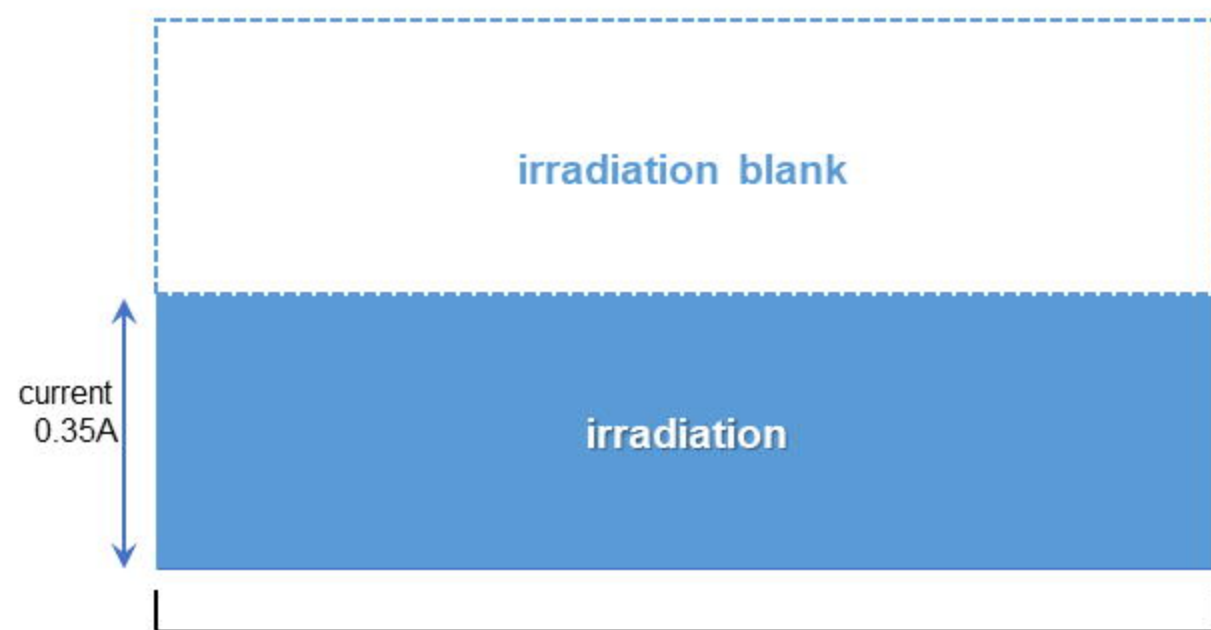
Table 1

		Control (no irradiation)	DUV-LED irradiation time					
			1 sec		5 sec		10 sec	
			continuous irradiation	pulsed irradiation	continuous irradiation	pulsed irradiation	continuous irradiation	pulsed irradiation
UK strain	PFU (PFU/mL)	3.5×10^4	1.3×10^3	1.9×10^3	< 20	< 20	< 20	< 20
	Log PFU ratio ^a	—	1.4	1.3	> 3.2	> 3.2	> 3.2	> 3.2
	Infection titer reduction ratio ^b (%)	—	96.3	94.4	> 99.9	> 99.9	> 99.9	> 99.9
South African strain	PFU (PFU/mL)	5.3×10^4	2.9×10^3	3.5×10^3	< 20	5.3×10^1	< 20	< 20
	Log PFU ratio ^a	—	1.3	1.2	> 3.4	3.1	> 3.4	> 3.4
	Infection titer reduction ratio ^b (%)	—	94.6	93.4	> 99.9	99.9	> 99.9	> 99.9
Brazilian strain	PFU (PFU/mL)	1.1×10^4	8.7×10^2	1.7×10^3	< 20	< 20	< 20	< 20
	Log PFU ratio ^a	—	1.1	0.8	> 2.7	> 2.7	> 2.7	> 2.7
	Infection titer reduction ratio ^b (%)	—	91.9	84.4	> 99.8	> 99.8	> 99.8	> 99.8

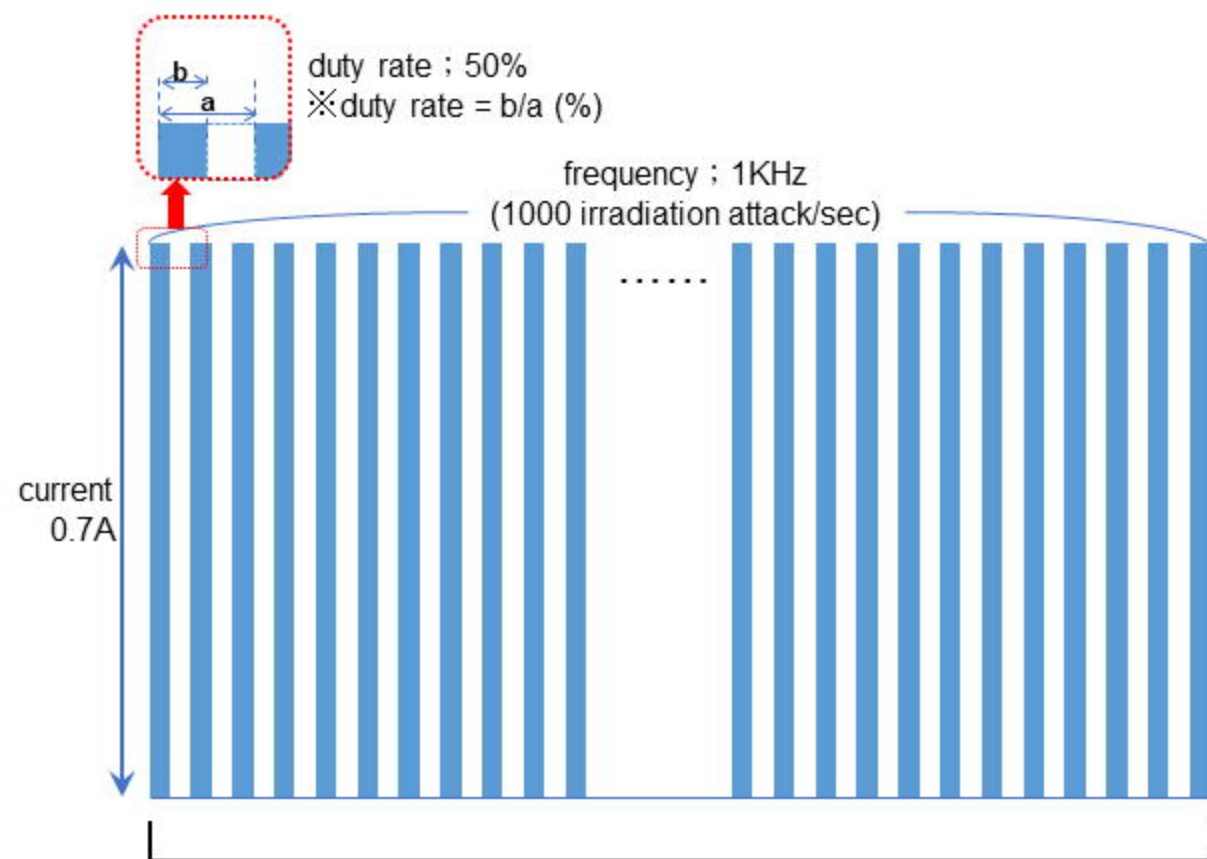
^a $\log_{10} (N_t/N_0)$ where N_t is the PFU count of the UV-irradiated sample and N_0 is the PFU count of the sample without UV irradiation.

^b $(1 - 1/10^{\log \text{PFU ratio}}) \times 100$ (%).

Supplement 1



A) continuous irradiation



B) intermittent irradiation