Dosimetry of the biological studies on MMW thermal effects in Japan

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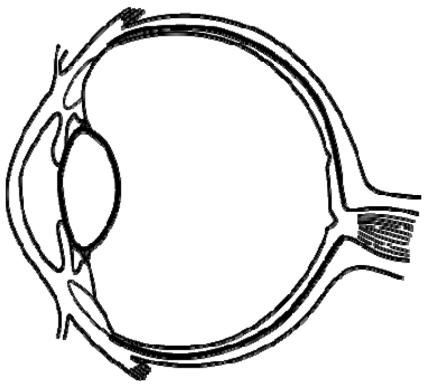
Outline

- Exposure setup and Experimental dosimetry.
- Threshold analysis for cornea damage.
- Numerical dosimetry and Mathematical modeling to estimate the threshold of cornea damage.
- Study on over 100GHz.

INTRODUCTION

Searching threshold level of corneal damage exposed to MMW EMF

- Eye ball is sensitive tissue in living body
  - Especially, we have to consider thermal effect due to MMW exposure
- Performing exposure experiment with rabbit eye and numerical analysis to investigate threshold level of power density.

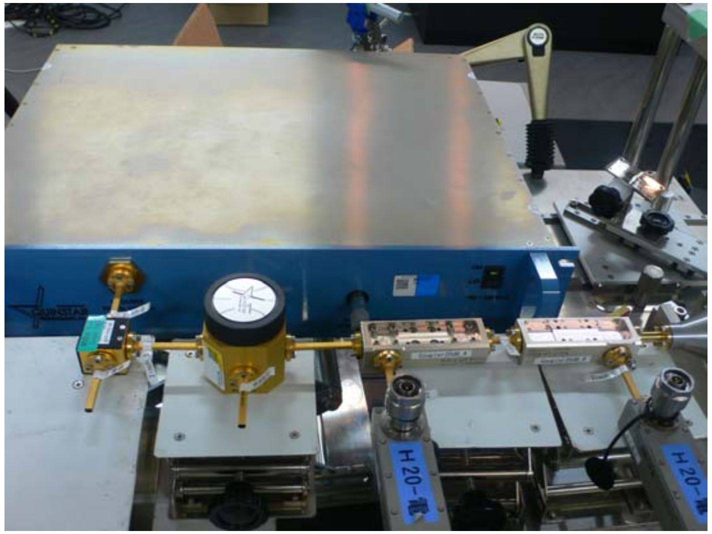


Reports of millimeter wave

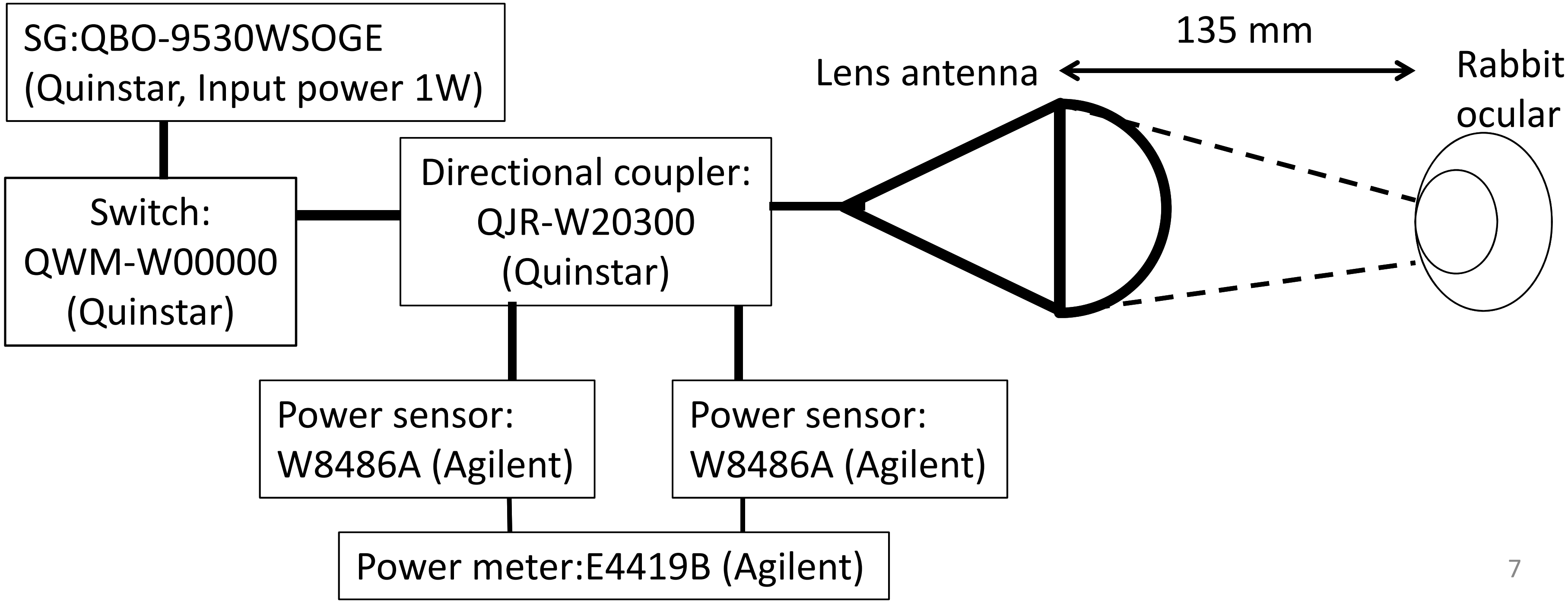
	Frequency	Exposure conditions	Animal	Results
Rosenthal (1977)	35 GHz 107 GHz CW	• <50 mW • 15~80 min (Single exposure) • Anesthetize＋ • Eye lids open by tape • Circular horn applicator in contact with eye	Rabbit	• 107GHz: immediate corneal stromal damage, it was gone by next day. • 35GHz: persistent corneal damage, almost always present the next day.
Kues (1999)	60 GHz CW	• 10 mW/cm^2 • 8 hr (Single Exposure) • 4 hr × 5 days • Circular horn antenna	Rabbit & Monkey	Neither microscopic examinations nor the diagnostic procedures performed on the eyes of acute and repeatedly exposed rabbits found any ocular changes that could be attributed to millimeter-wave exposure at 10 mW/cm^2.
Chalfin (2002)	35 GHz 94 GHz PW	• 0~11J/cm^2 • Anesthetize ＋ • 2 W/cm^2 35GHz:1.5~5.0s 94GHz:2.0~4.0s • ~8W/cm^2, 1.0s • Open ended waveguide • Retained ocular blink reflex	Monkey	The threshold of the cornea injury (epithelial edema, fluorescein staining) • 35GHz: 7.5 J/cm^2 • 94GHz: 5 J/cm^2 Endothelial cell counts remained unchanged.

EXPOSURE SETUP AND EXPERIMENTAL DOSIMETRY

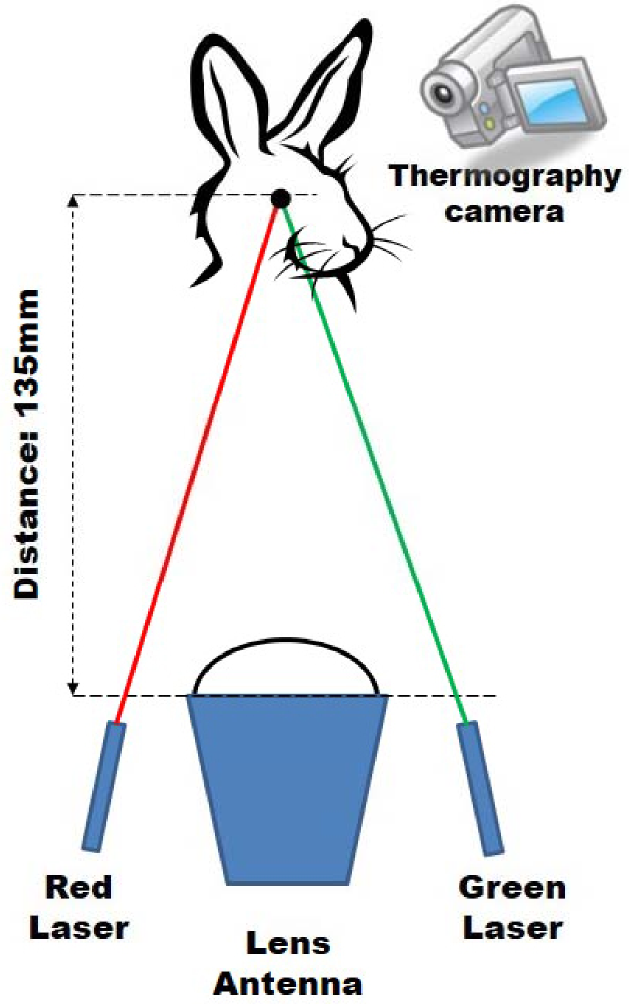
Example of Exposure system at 95 GHz

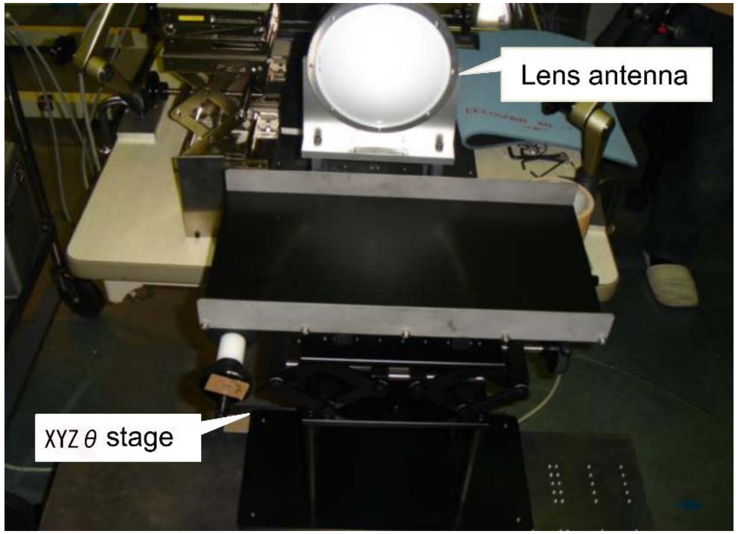


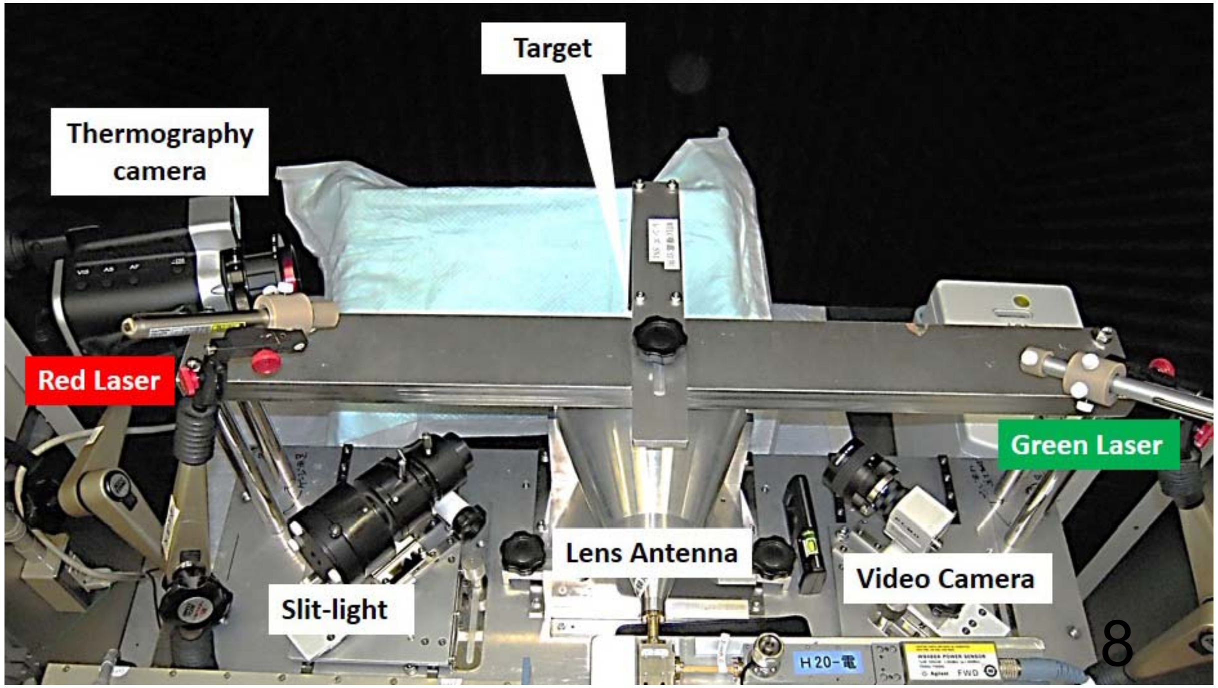
- Maximum input power at the lens antenna: approximately 450 mW
  - It comes from insertion loss at waveguides.
- Maximum incident power density: 200mW/cm^2
- Exposure on/off is controlled with switch.



Standardized exposure system

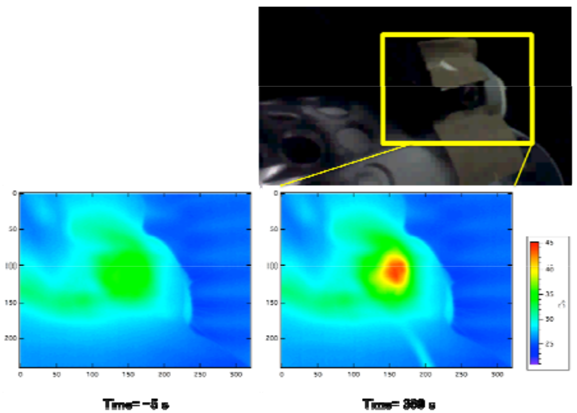




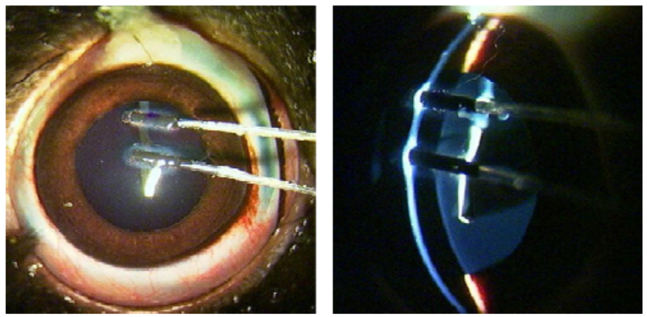


Temperature measurement for ocular tissue

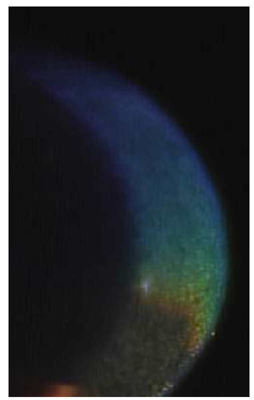
- Temperature measurement was performed by
  - IR thermography (to measure corneal surface)
  - Fiber optic temperature probe (to measure stroma of cornea and lens
  - Micro-Encapsulated Thermo-chromic liquid Crystal (to measure aqueous humor)



IR thermography



Fiber optic temperature probe

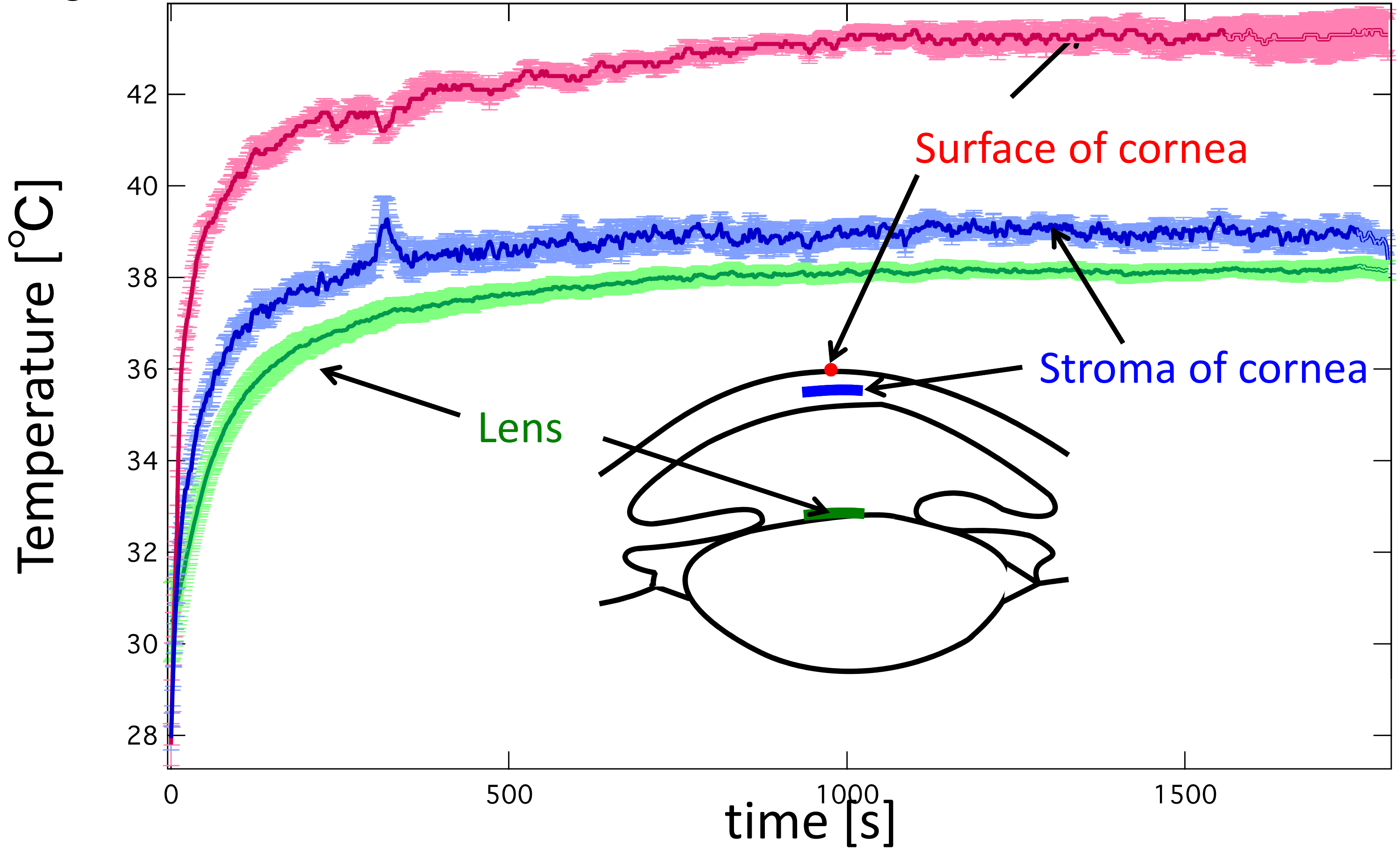


MTLC

Temperature development

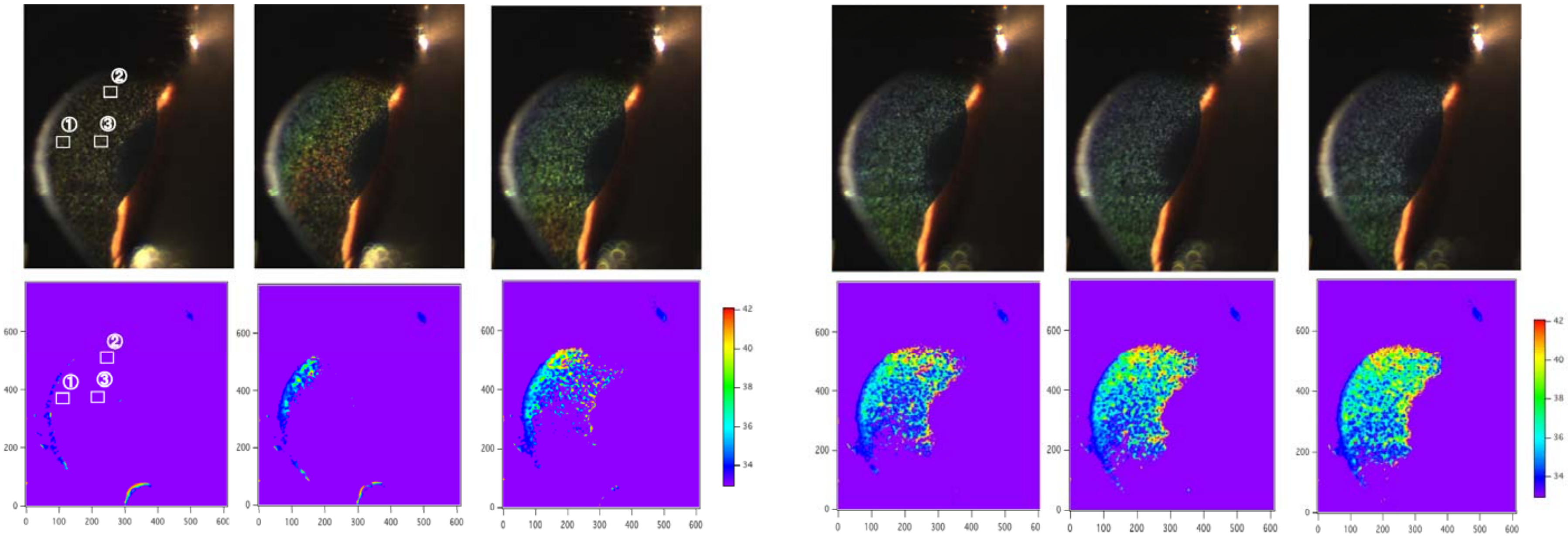
(30min, 75GHz, 200mW/cm²)

Average of 5 rabbits



Temperature rise in the Surface of cornea is the highest of all at 75GHz

Estimation of temperature distribution @150mW/cm^2



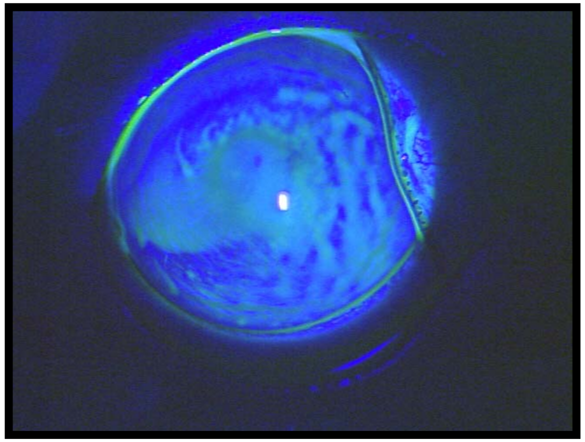
0s 10s 20s 30s 40s 50s

-Upper row: captured images of temperature distribution
-Lower row: 2D temperature distributions estimated from captured image
-Temperature distributions are displayed with very high spatial resolution as 20 x 20 µm

THRESHOLD ANALYSIS FOR CORNEA DAMAGE

Fluorescein staining of damaged cornea epithelial cell

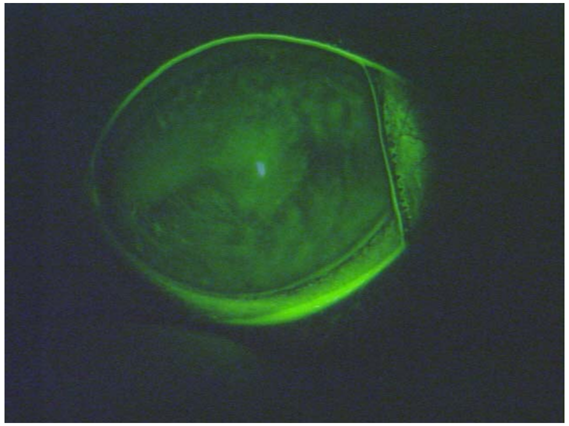
Former methods
S.W. Rosenthal, 1976
S. Chalfin, 2002

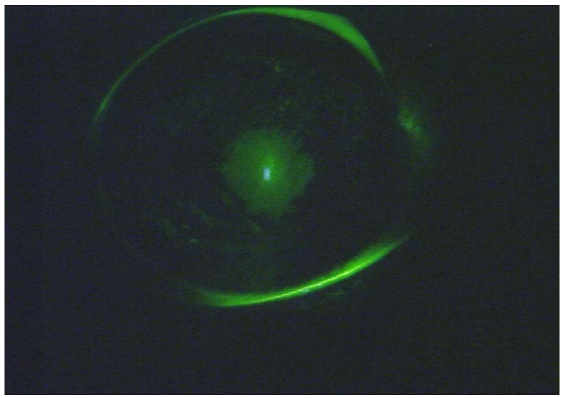


- Rosenthal
- Only the exciter filter
- 2 % Fluorescein, 1 drop
- Surplus fluorescence washing

- Chalfin (No detail)

KMU methods
M. Kojima, et al., 2009





- The exciter filter+ Excitation light cutting filter
- 0.05 % Fluorescein 25 μl instillation

↓

- Surplus fluorescence washing

maximum likelihood estimation with generalized linear model (GLE)

- Hereafter, the values of MMW power density which indicate the threshold of eye damage are defined as damaged dose (DD).
- Maximum likelihood estimation (MLE) were performed with probit model for the experimental data to estimate the threshold level for cornea damage.
  - “R” language is used for the MLE.

Cumulative distribution function(CDF) for the probit analysis

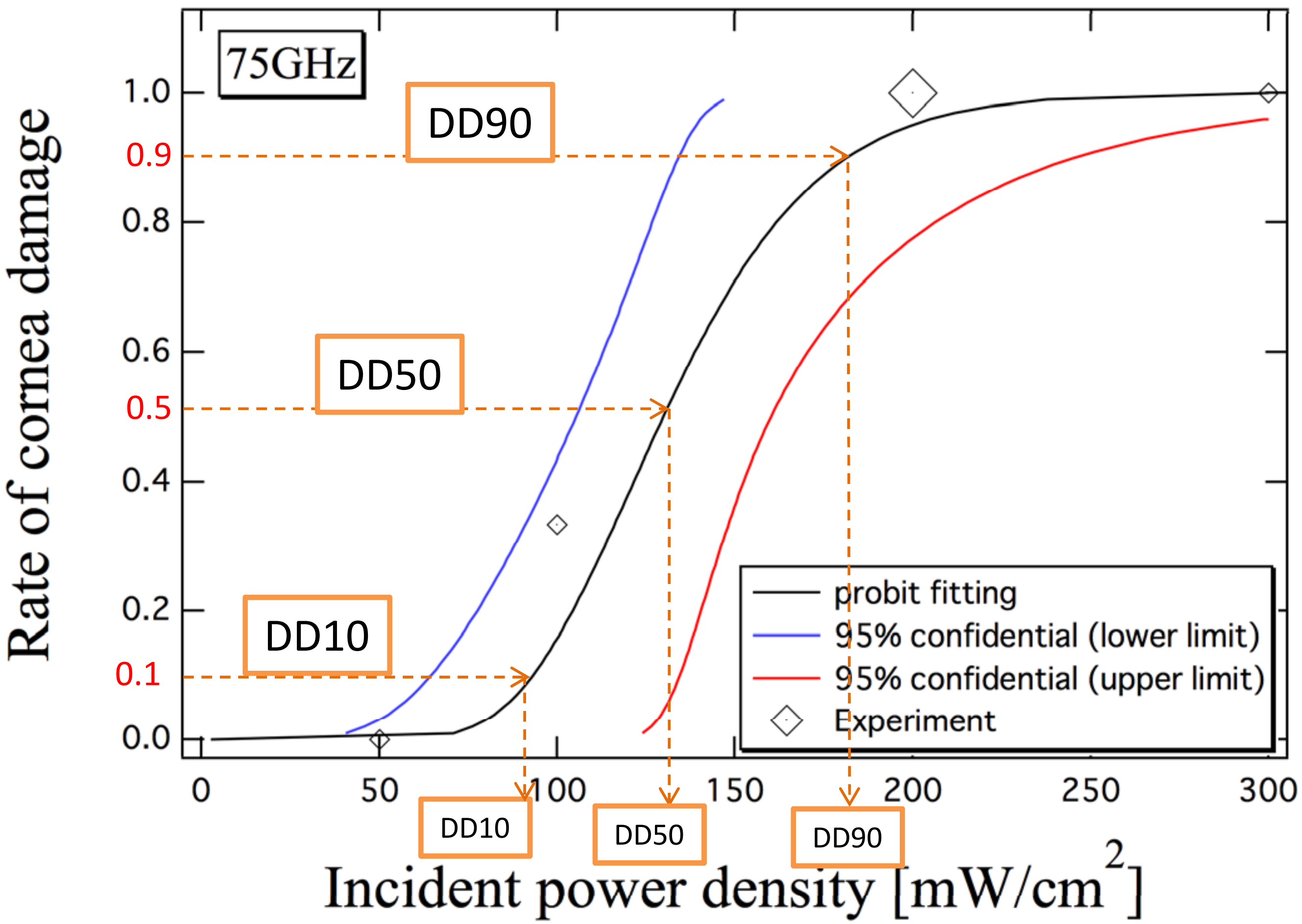
$$p(x) = \int_{-\infty}^{\alpha+\beta x} \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} dz$$

$$x = \log_e w_{in}$$

Here w_{in} is incident power density.

Coefficients of α and β are determined by the method of maximum likelihood.

Fitting result for 75GHz, 6min exposure (Corneal Epithelium Damage)

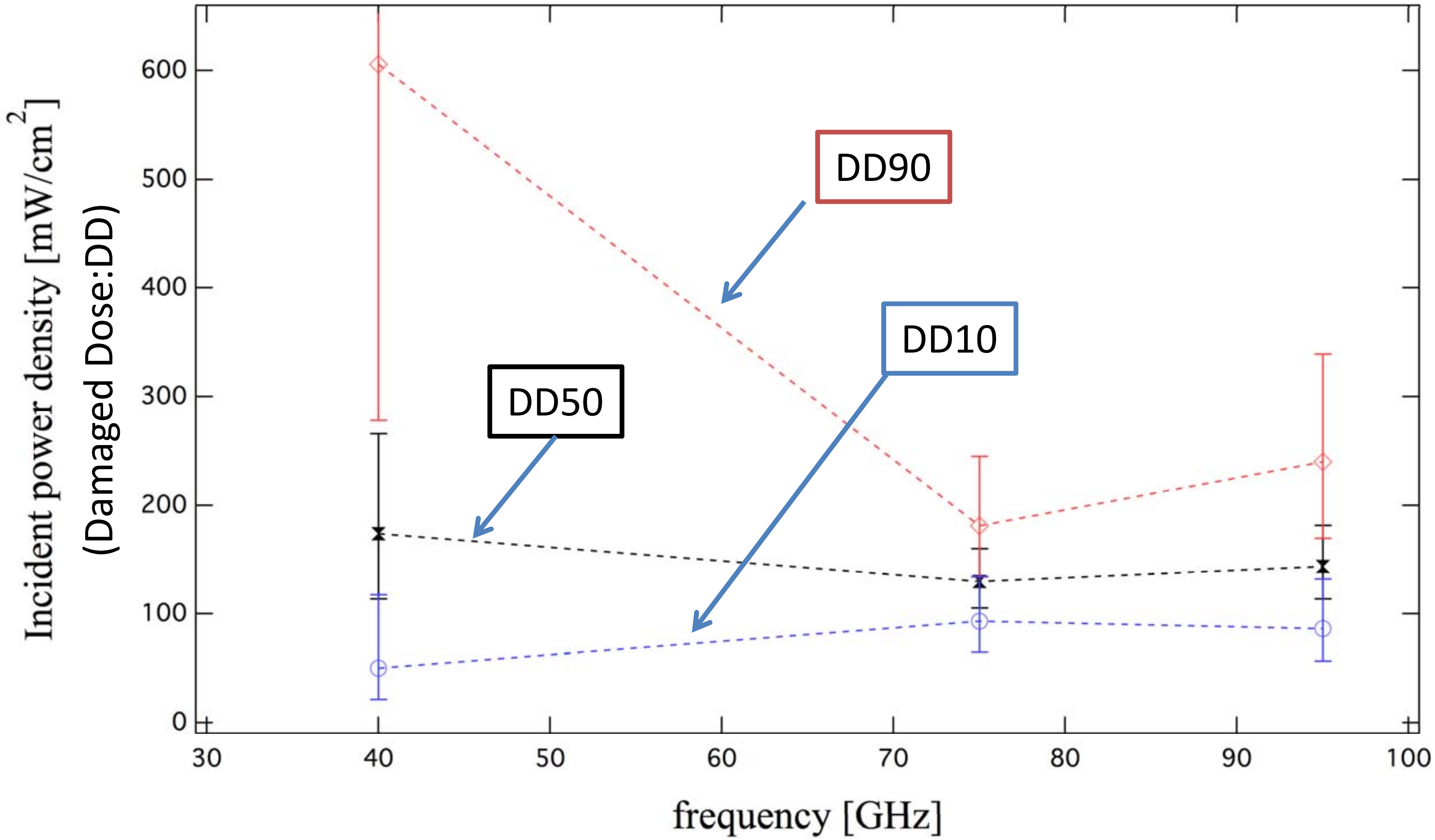


Estimation of damaged dose for corneal epithelium damage

Frequency[GHz]	DD10 [mW/cm^2]		DD50 [mW/cm^2]		DD90 [mW/cm^2]	
40GHz	50.0	+67.6	174	+92.0	605	+712
		-28.7		-60.2		-327
75GHz	93.1	+41.3	130	+30.3	181	+63.8
		-28.6		-24.6		-47.2
95GHz	86.2	+45.9	144	+37.8	240	+99.3
		-29.9		-29.9		-70.2

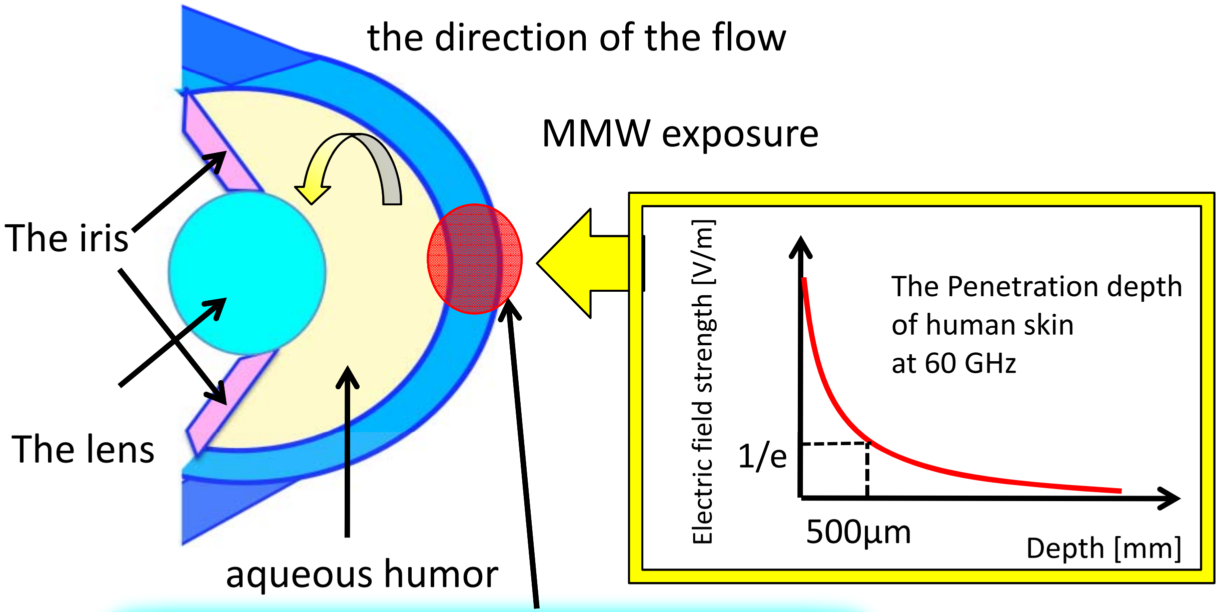
- DD10, DD50, and DD90 is estimated from each result of MLE for 40, 75, and 95GHz exposure.
- "+" and "-" denotes upper and lower limit of 95% confidence interval, respectively.

The dependence of DD on frequency (corneal epithelium damage)



NUMERICAL DOSIMETRY AND MATHEMATICAL MODELING TO ESTIMATE THE THRESHOLD OF CORNEA DAMAGE

Heat transport mechanism



Energy absorption is occurred .

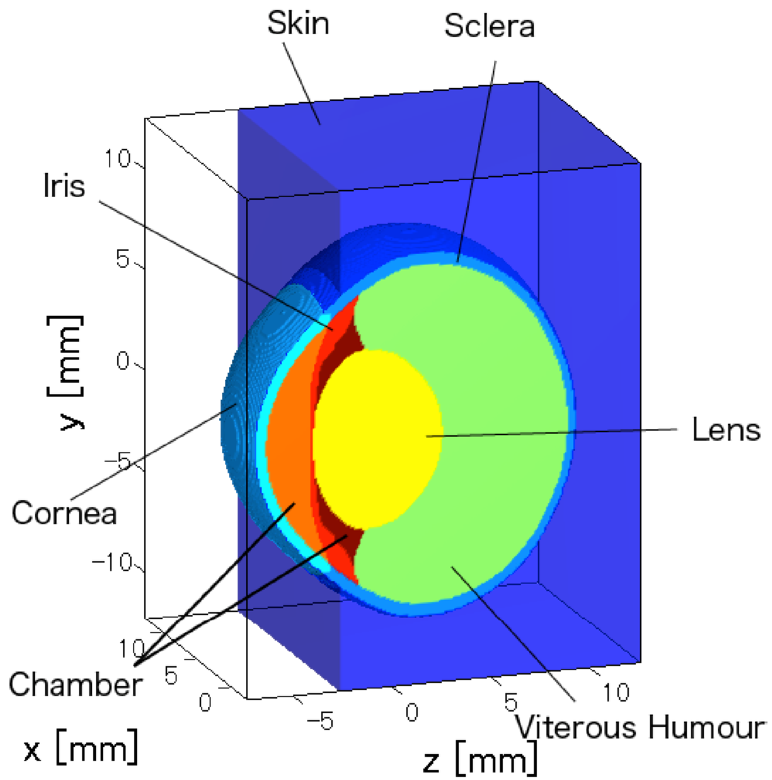
heating transportation pattern { conduction / convection

•The temperature elevation is highly localized within several hundred µm depth from the surface of the cornea.

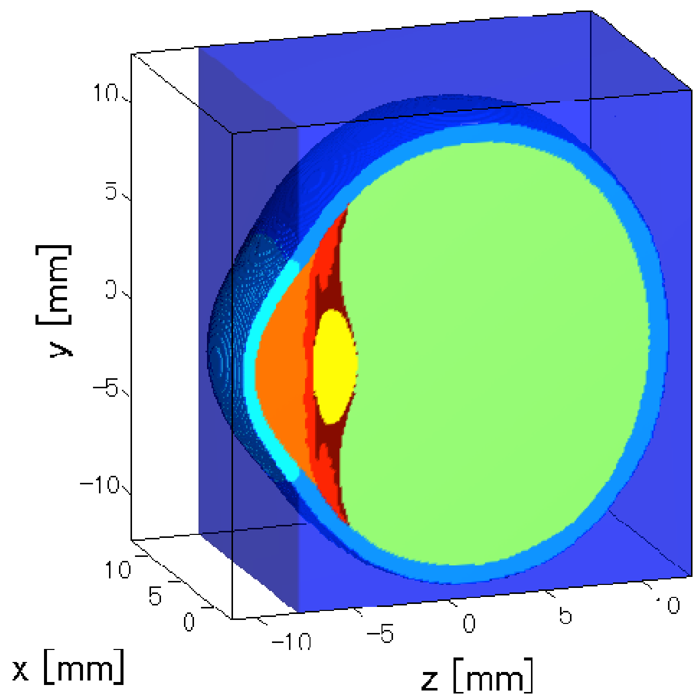
•Heat transport become complex in anterior chamber because of the existence of the aqueous humor and such a heating process .

Fine voxel models for rabbit and human

<u>Rabbit eye model</u>



<u>Human eye model</u>

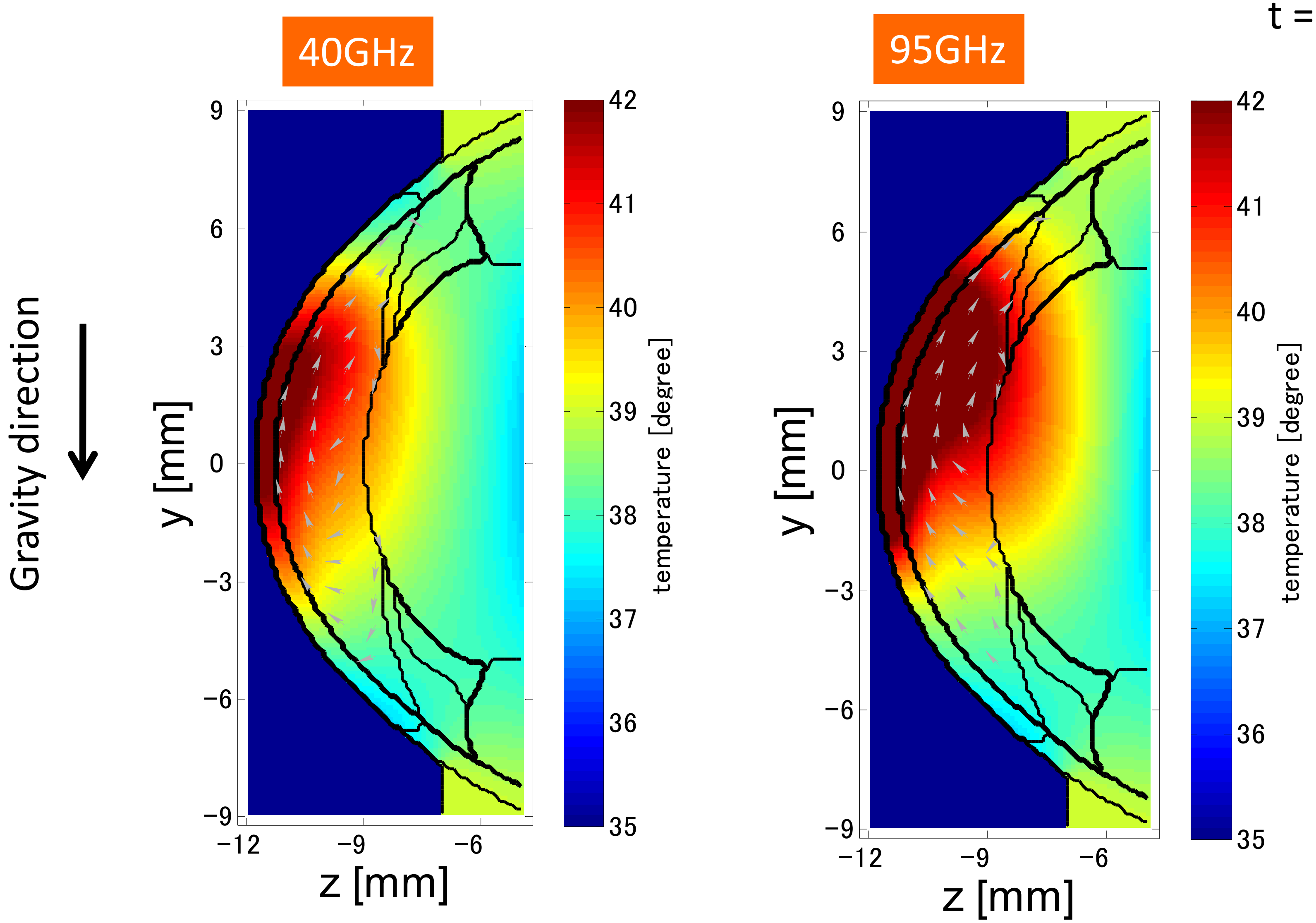


-These models are medically supervised.
-Mesh size is 50µm.
-These models are consists of 7 tissues, cornea, aqueous humor, iris, lens, vitreous humor, sclera, and skin.

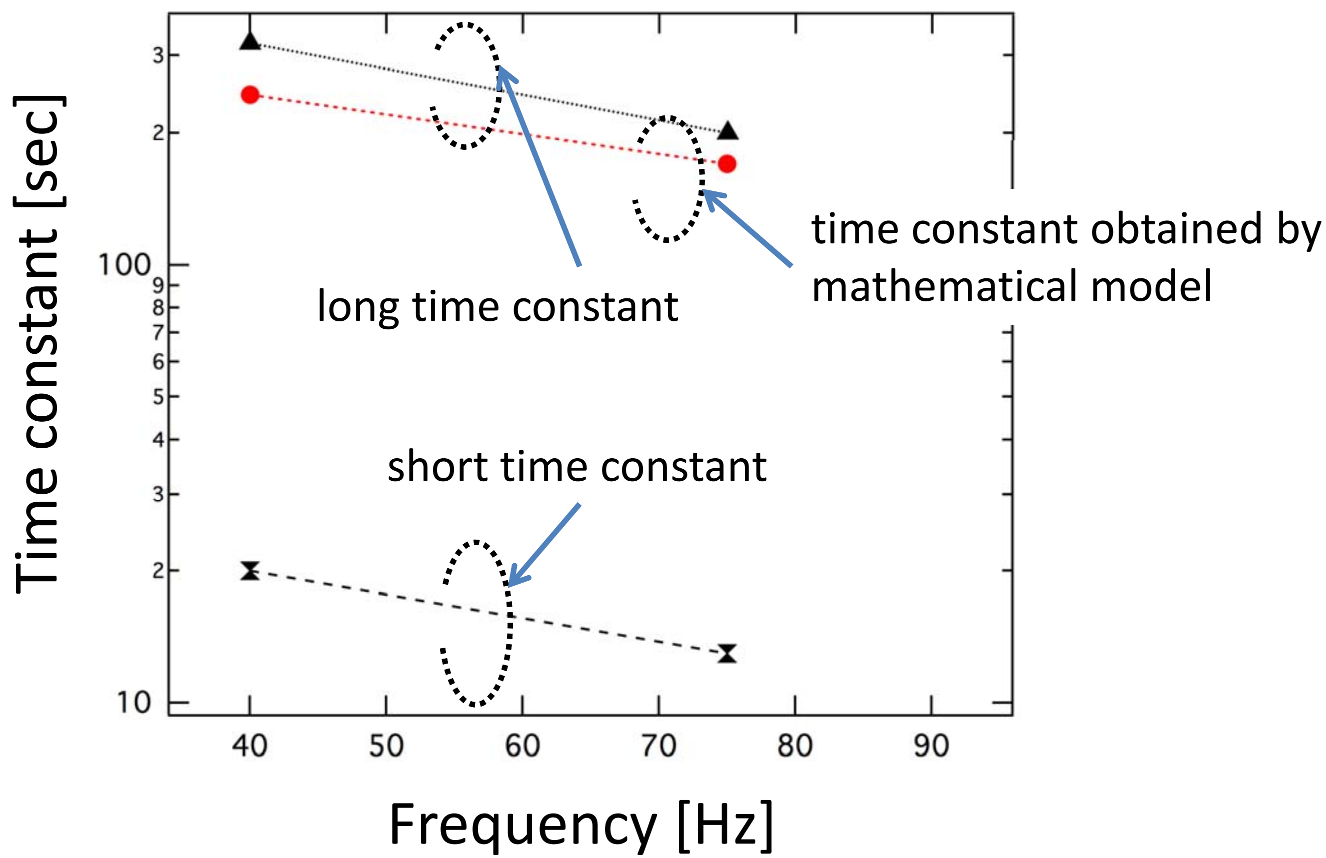
Dependence of T and V on the frequency

200mW/cm^2 40GHz, 95GHz

t = 360s

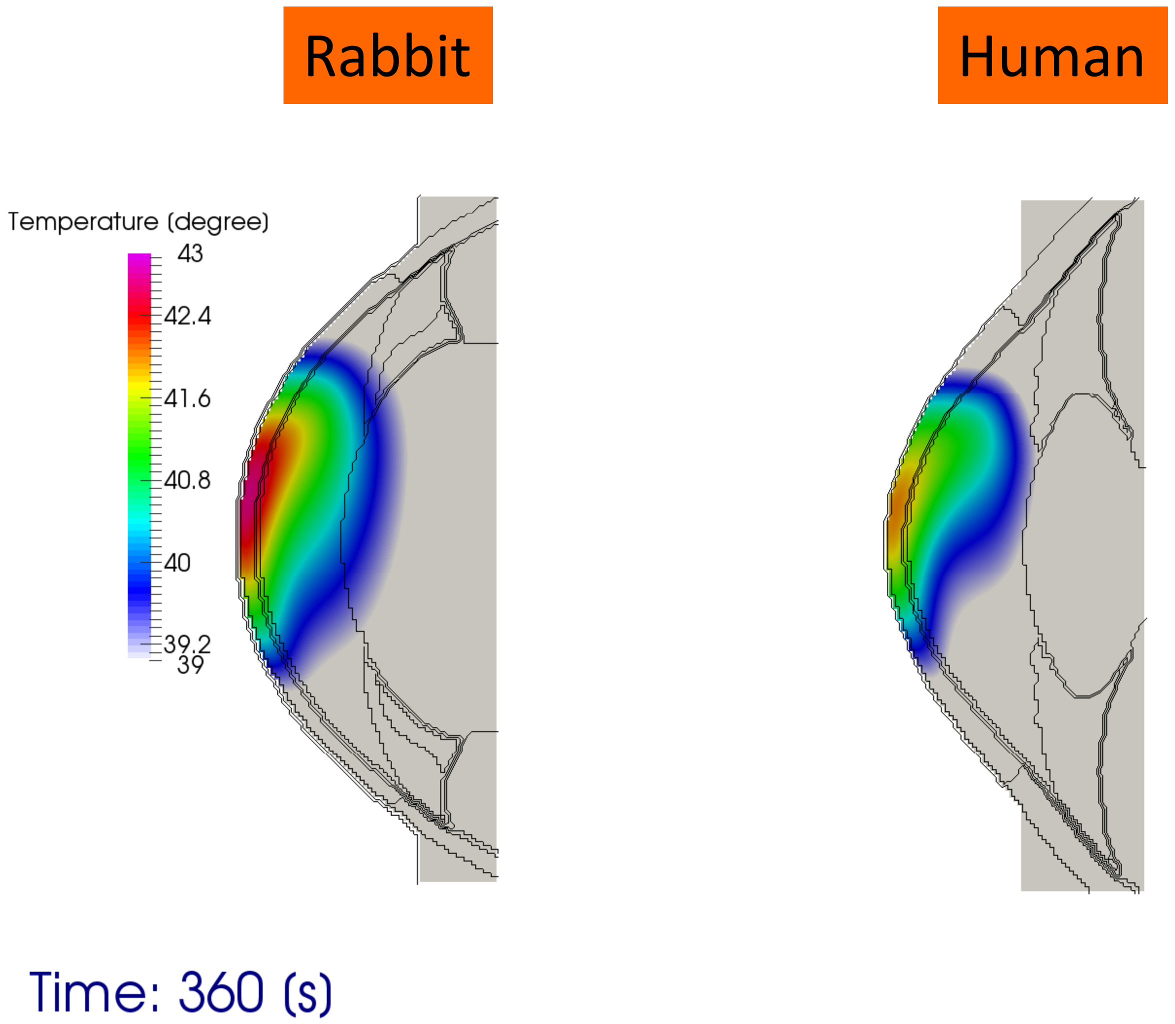


Dependence of time constant on the frequency

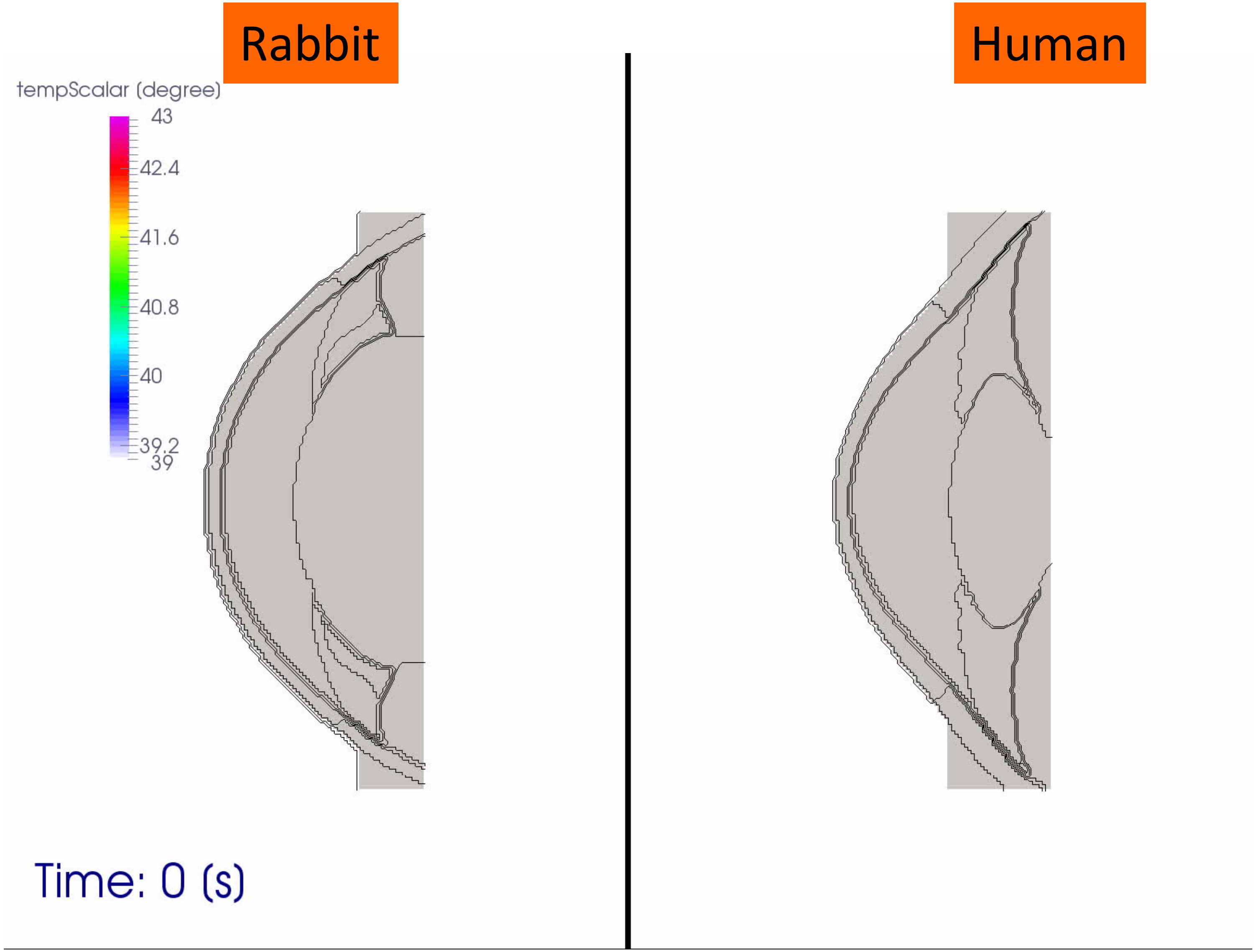


-As for time constant, result by mathematical model is consistent with long time constant obtained by experiment data.

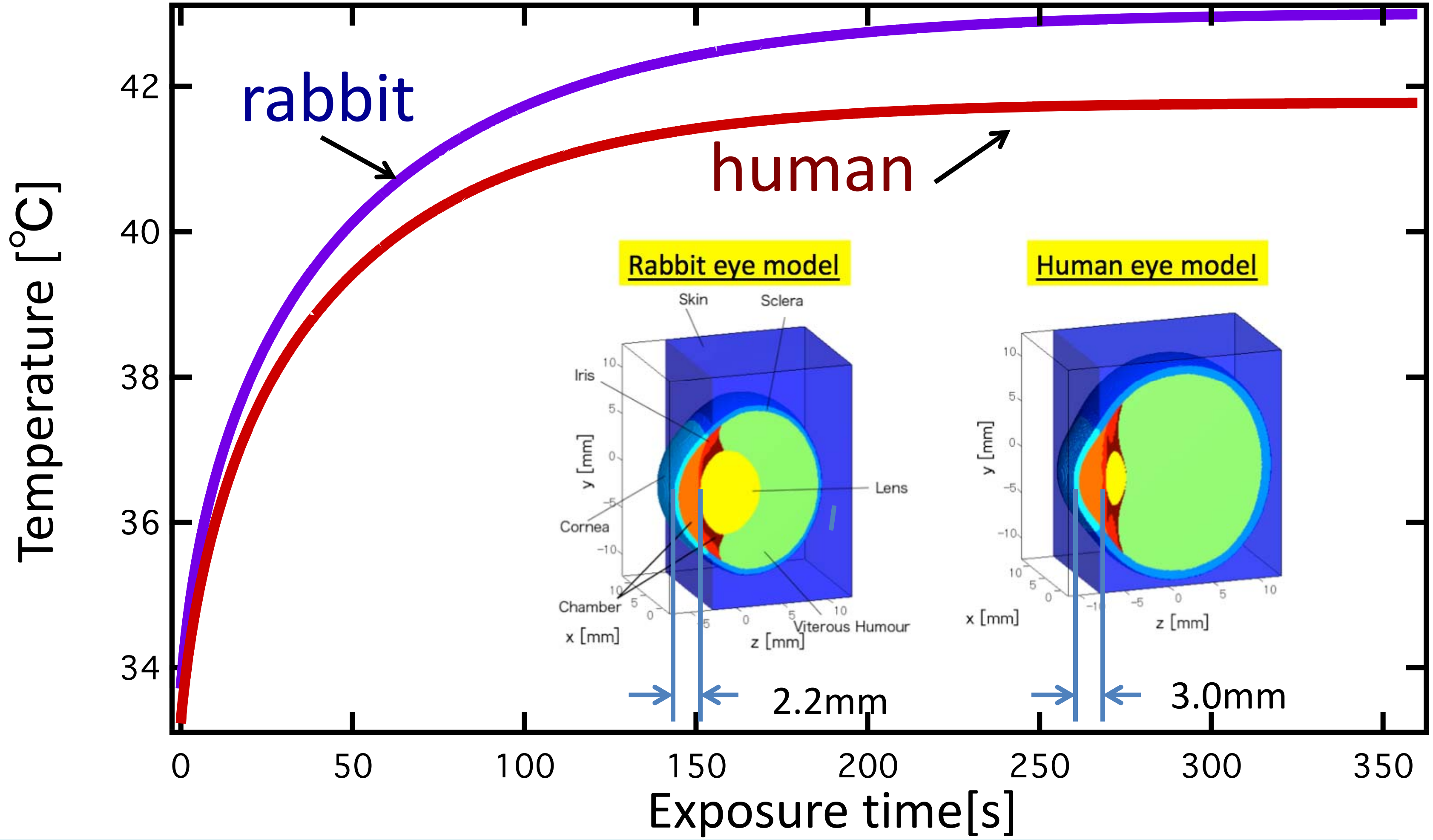
Temperature distribution 40GHz@200mW/cm^2



Temperature distribution   40GHz@200mW/cm^2



Comparison of temperature change between rabbit and human (40GHz@200mW/cm^2)



Human eye is superior in the heat transport ability, because of its deeper anterior chamber depth.

Quantification of thermal dose

- The method to determine the thermal dose has been proposed for cancer therapy from 1984.[1-3]
  - This method is termed "thermal isoeffective dose"
  - Recently this method is considered to apply to estimating threshold caused by thermal effect of MRI equipment.[4]
- The time–temperature data are converted to an equivalent number of minutes at 43ºC
  - 43ºC is the near the break point for CHO and several other cell lines.

[1]Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys 1984; 10: 787–800.
[2]Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia. 2003; 19:267–294.
[3] Yarmolenko PS, Moon EJ, Landon C, Manzoor A, Hochman DW, Viglianti BL, Dewhirst MW, "Thresholds for thermal damage to normal tissues: an update", Int J Hyperthermia. 2011;27(4):320-43.
[4] van Rhoon GC1, Samaras T, Yarmolenko PS, Dewhirst MW, Neufeld E, Kuster N, "CEM43° C thermal dose thresholds: a potential guide for magnetic resonance radiofrequency exposure levels?", Eur Radiol. 2013 Aug;23(8):2215-27

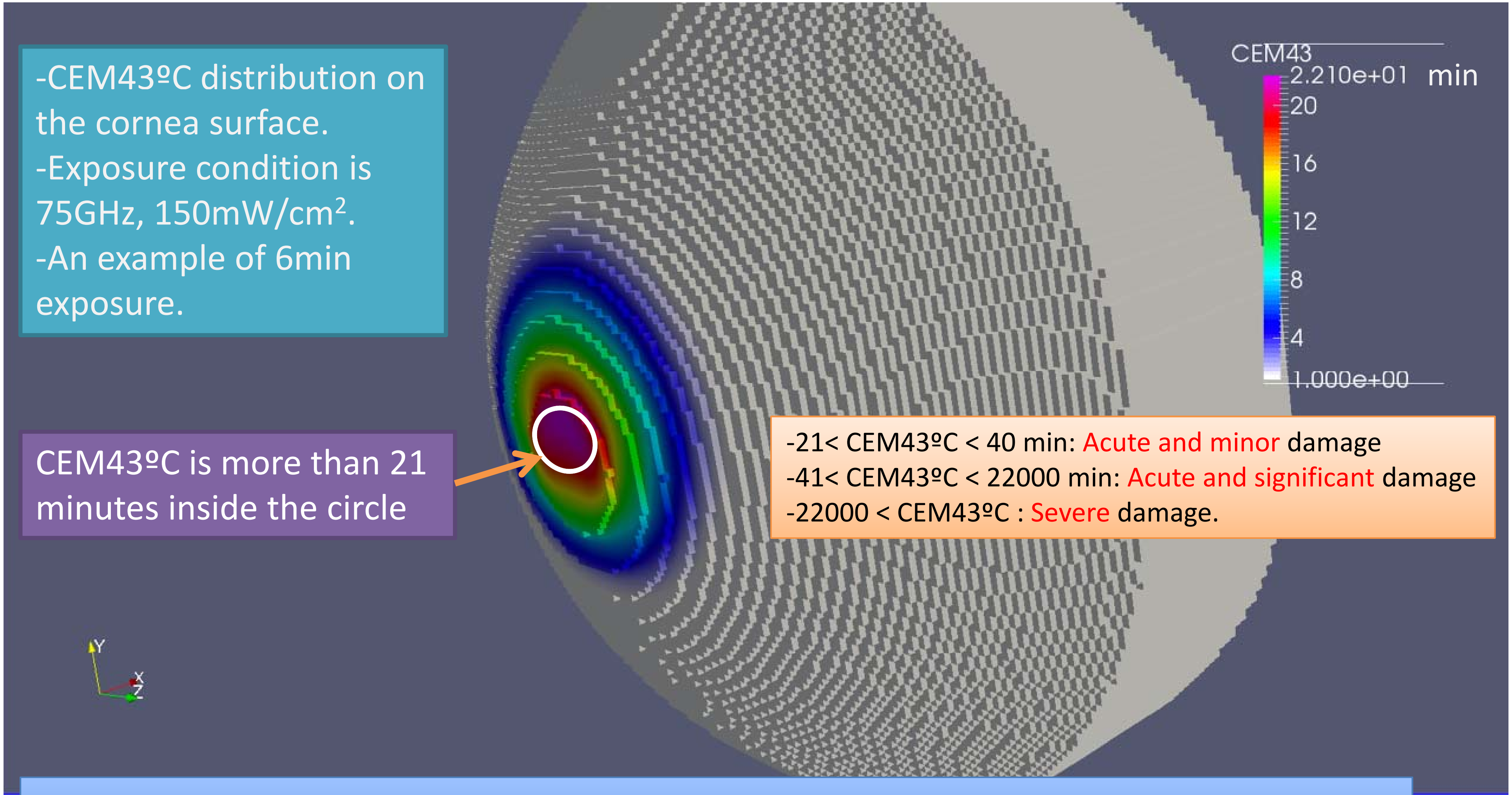
CEM43ºC

- Index of thermal isoeffective dose originally defined as follows.

$$CEM\,43^{o}\,C = tR^{(43-T)}$$

  - CEM 43ºC:cumulative number of equivalent minutes at 43ºC
  - t: time interval (min)
  - T: average temperature during time interval t.
  - R: the number of minutes needed to compensate for a 1º temperature change either above or below the breakpoint.
- As for cornea, thermal exposure causes
  - 21< CEM43ºC < 40 min: Acute and minor damage
  - 41< CEM43ºC < 22000 min: Acute and significant damage
  - 22000 < CEM43ºC : Severe damage.

CEM43ºC distribution at 6min (75GHz 150mW/cm^2)



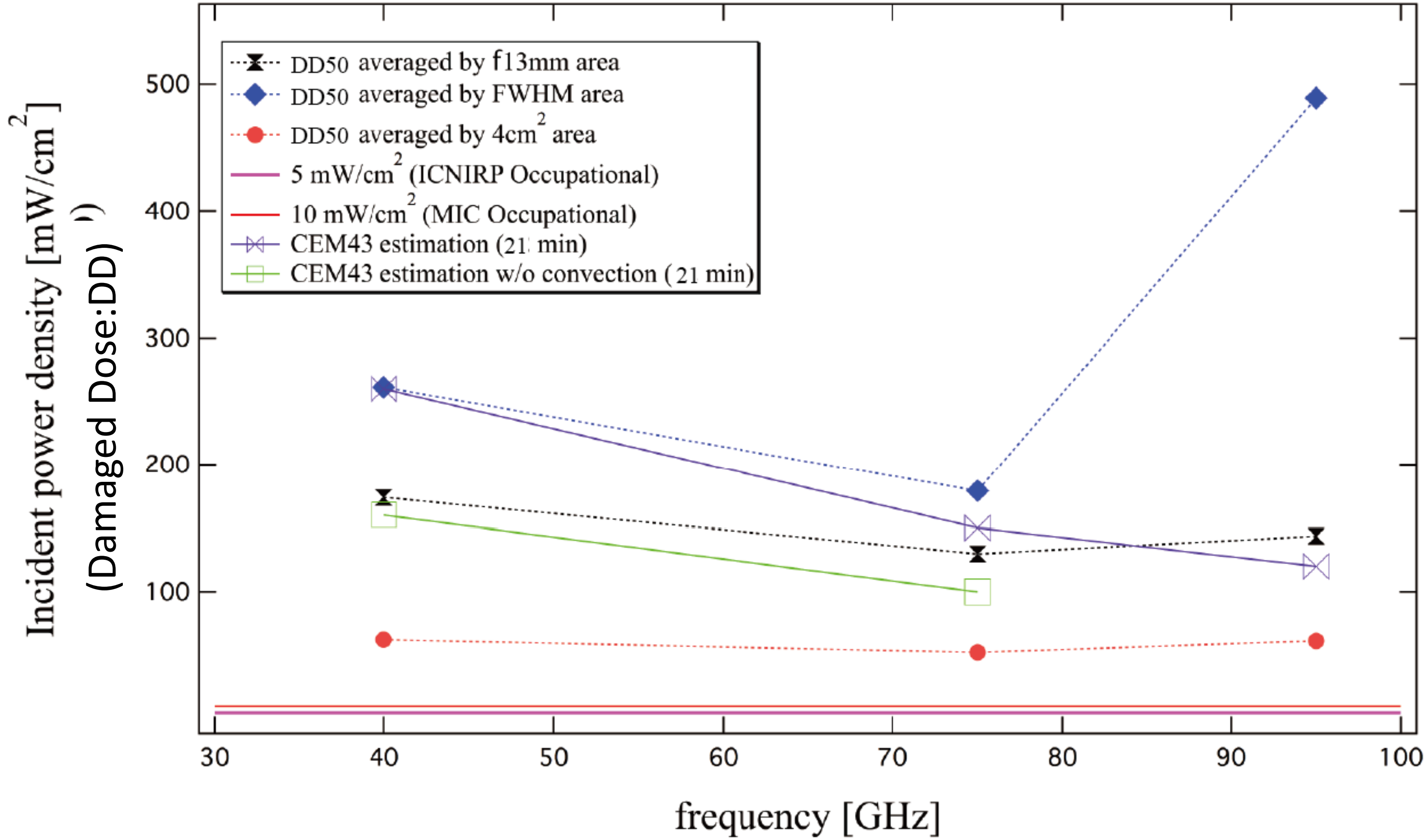
- -CEM43ºC distribution on the cornea surface.
- -Exposure condition is 75GHz, 150mW/cm^2.
- -An example of 6min exposure.

CEM43ºC is more than 21 minutes inside the circle

-21< CEM43ºC < 40 min: Acute and minor damage
-41< CEM43ºC < 22000 min: Acute and significant damage
-22000 < CEM43ºC : Severe damage.

Cornea damage is predicted inside the circle by CEM43ºC analysis.

Comparison between experiment and mathematical model (CEM43ºC)

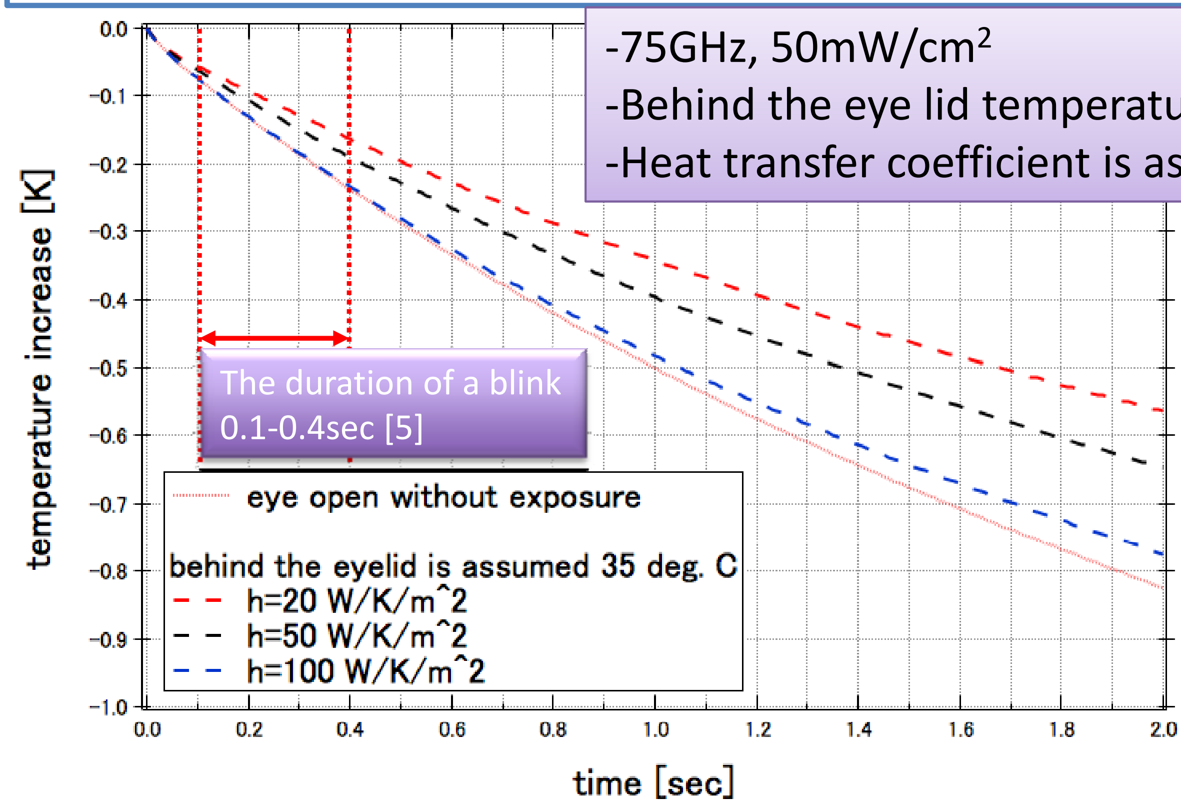


Threshold dose level predicted by CEM 43ºC model is fairly agree with the DD50 dose level.

Preliminary investigation for blinking

Blinking effect on the cornea surface temperature is investigated to discuss actual condition.

-75GHz, 50mW/cm²
-Behind the eye lid temperature is assumed 35ºC
-Heat transfer coefficient is assumed 20-100 W/Km²



-For the duration of blinking, cornea surface temperature decreases 0.1-0.3 ºC in rough estimation

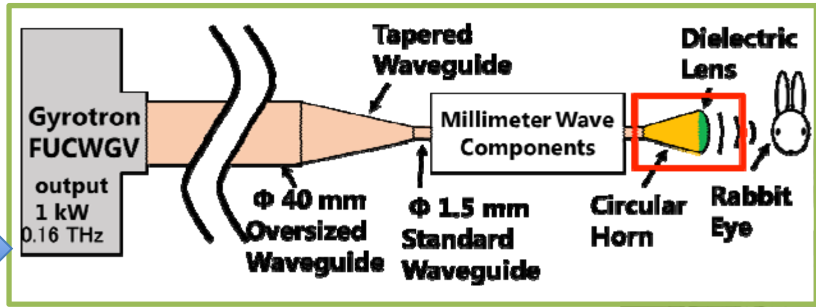
-We will conduct more investigation for the effect of eye blinking.

[5]Schiffman, H.R., Sensation and Perception. An Integrated Approach, New York: John Wiley and Sons, Inc., 2001

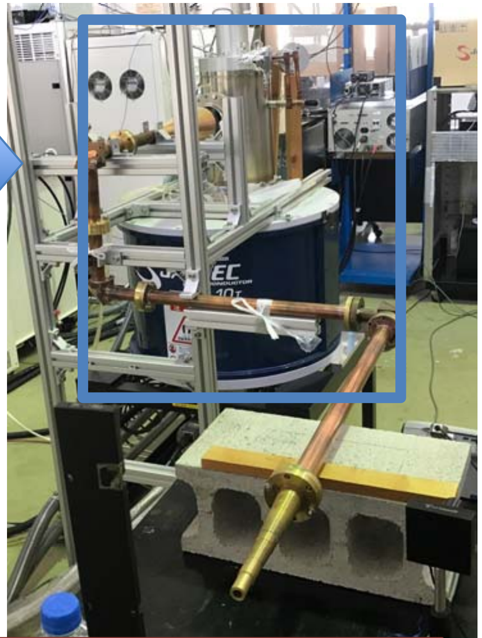
STUDY ON OVER 100GHZ

0.16THz exposure system (tentative and preliminary)

The concept of high power exposure system with the Gyrotron



Gyrotron FU CW G V @Fukui Univ.



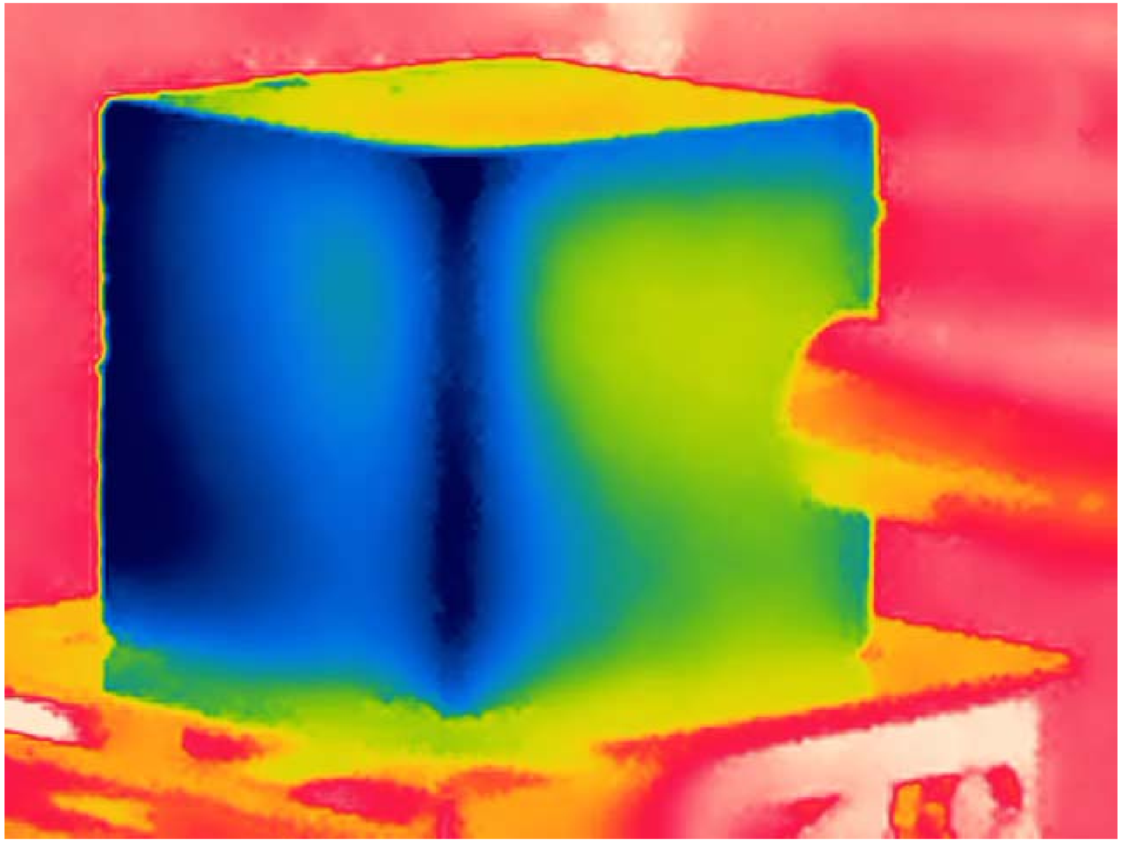
Establishment of the animal breeding facility

Preliminary exposure experiment @ 0.16THz

- 0.16THz high power exposure apparatus is being developed with the Gyrotron to observe cornea (eye) damage.
  - ➢ Preliminary experiment is performed by exposing agar phantoms to the 0.16THz electromagnetic wave.
- Tentative animal breeding facility is also being developed at Fukui Univ.
  - ➢ Adjustment of environment is examined near the Gyrotron facility .

0.16THz exposure example of ager phantom

Peak Power >10W, duty ratio:10%, pulse cycle:1s



-We observed about 100ºC temperature elevation with this condition.
-By using Gyrotron system, we can investigate cornea damage for short time exposure.

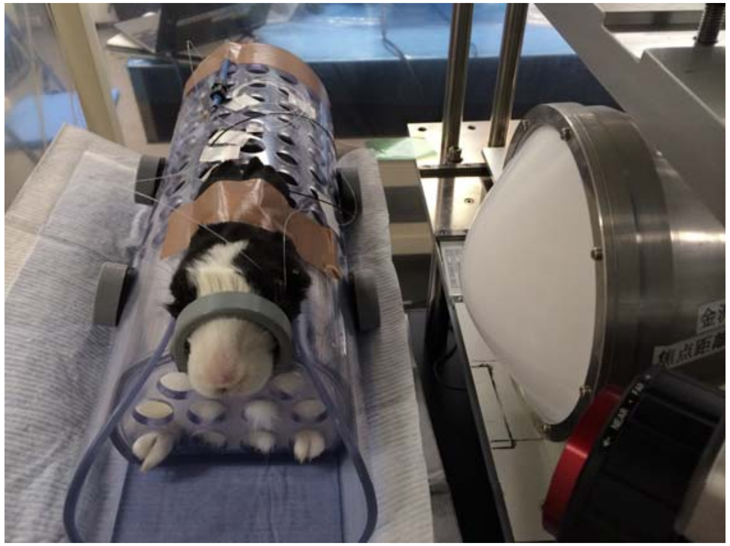
Summary

- We have performed experimental and numerical dosimetry for 40, 75, and 95GHz.
  - Temperature elevation of human is smaller than that of rabbit.
- By performing probit model analysis, DD10, DD50, and DD90 are obtained based on in vivo exposure experiment.
  - This analysis is useful to decide the threshold dose.
- Threshold dose level predicted by CEM 43ºC model is fairly agree with the DD50 dose level.
- We will plan over 100GHz (THz) in vivo exposure experiment in future work.

Thank you for kind attention.

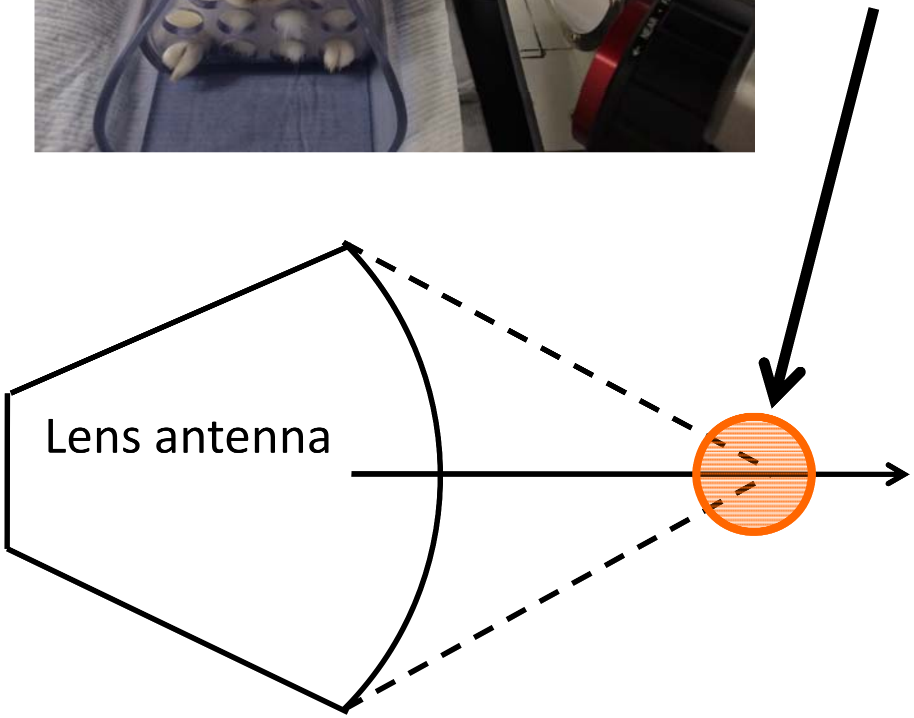
APPENDIX

MMW Exposure condition



Frequency [GHz]	40, 75, 95
Power density [mW/cm^2]	200

-The position of corneal surface is adjusted to the focal point of the lens antenna.
-The incident power density is spatially averaged over a region of ϕ -13 mm. (which is the average size of the rabbit ocular area, and this value is used to determine exposure level.)



The configuration of multi-physics simulation system

The system is consists of 2 part:

EMF analysis

3D electromagnetic field

Method :

3D scattered-field FDTD (**F**inite **D**ifference **T**ime **D**omain) method

＋rabbit eye model

induced electromagnetic field in the rabbit eye → SAR

Heat Transport analysis

SAR (**S**pecific **A**bsorption **R**ate)

Heat Transportation — **Heat Convection** / **Heat Conduction**

Method : SMAC (Simplified marker and cell) method

➡ Temperature and flow velocity + (pressure)

Equations for heat transport simulation

- Non-compressive fluid
- Boussinesq approximation
- SMAC (Simplified marker and cell) method is used

Continuity equation

$$\nabla \cdot \vec{V} = 0$$

Navier-storkes equation

$$\frac{\partial \vec{V}}{\partial t} + (\vec{V} \cdot \nabla)\vec{V} = -\frac{1}{\rho}\nabla p + \nu \Delta \vec{V} + \vec{g}$$

Biological heat transpot equation

$$\rho C_p\left(\frac{\partial T}{\partial t} + (\vec{V} \cdot \nabla)T\right) = \nabla \cdot (K \nabla T) + A_0 - B(T - T_{blood}) + Q$$

$$Q = \rho SAR$$

$$SAR = \frac{\sigma E^2}{\rho}$$

Convective energy transport term

Calculation of pressure

$$\Delta p' = \frac{\rho}{dt} \nabla \vec{V}^*$$

Physical constants
- density: ρ [kg/m^3]
- coefficient of kinematic viscosity: ν
- specific heat : Cp [J/kg・K]
- heat conduction coefficient : K [W/m・K]
- metabolic heat : A_0 [W/m^3]
- Coefficient of blood flow : B [W/m^3・K]
- heat source : Q [W/m^3]
- gravity :**g** [m/s^2]

Variables
- velocity :**V**[m/s]
- temperature:T[°C]
- pressure:p[kg/m^2]

Boundary condition of rabbit eye

Temperature

Sclera and skin: Γ_1

$$T = T_{const}$$

isothermal boundary

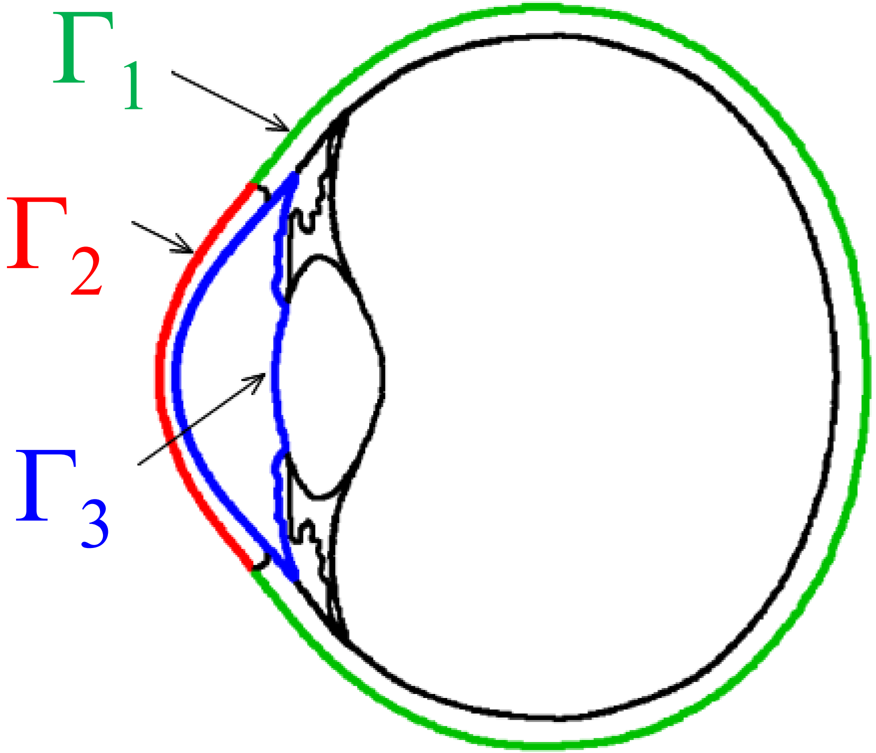
Body temperature : $T_{const} = 39℃$ [2]

Interface with air: Γ_2

$$\vec{q} \cdot \hat{n} = h\left(T - T_{air}\right)$$

Heat transfer coefficient: $h = 20.0\,\mathrm{W/(m^2 \cdot ℃)}$ [3]

Air temperature : $T_{air} = 22 - 24^{\circ}C$



Velocity

Non slip condition on the boundary: Γ_3

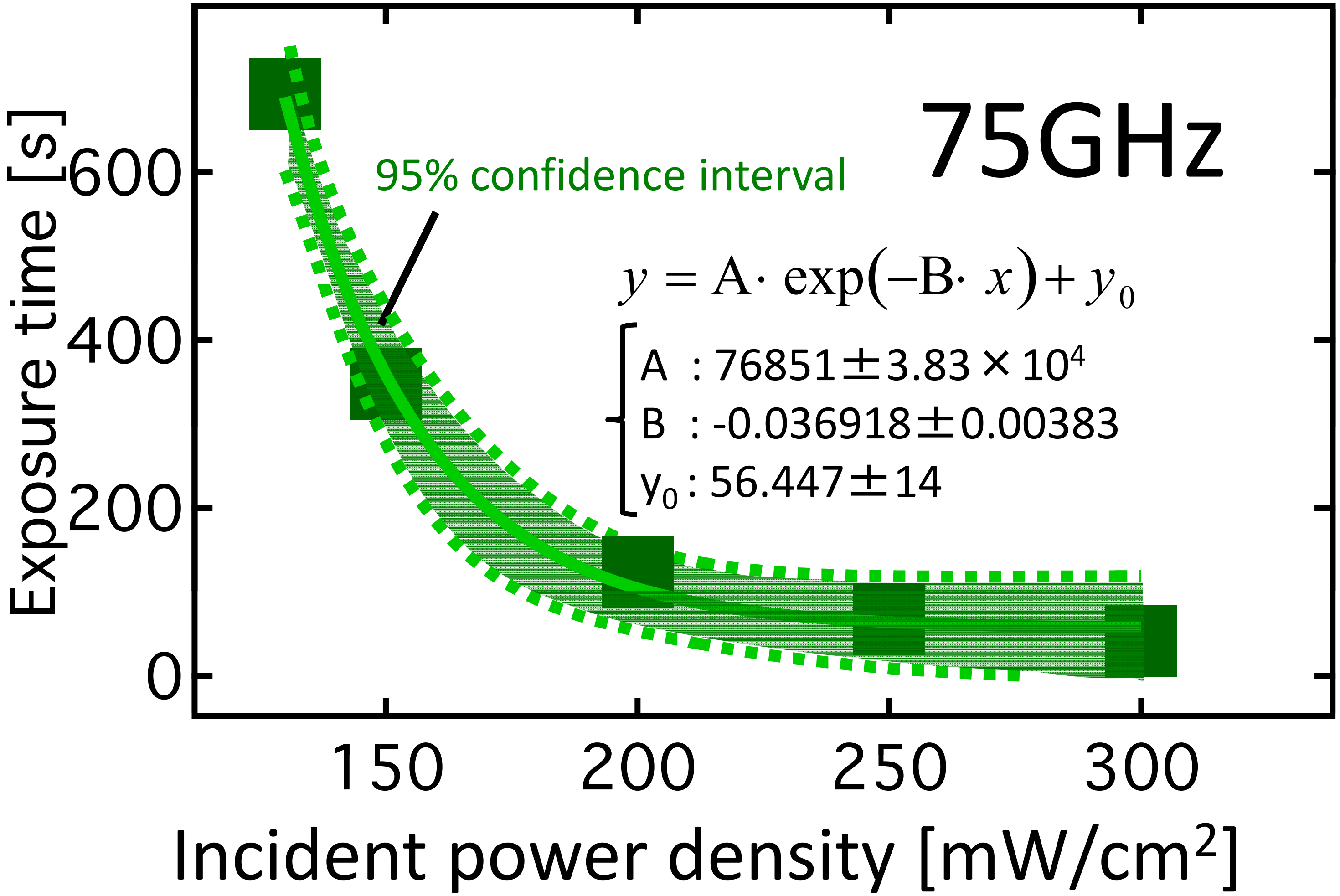
$$\vec{V} = 0$$

pressure

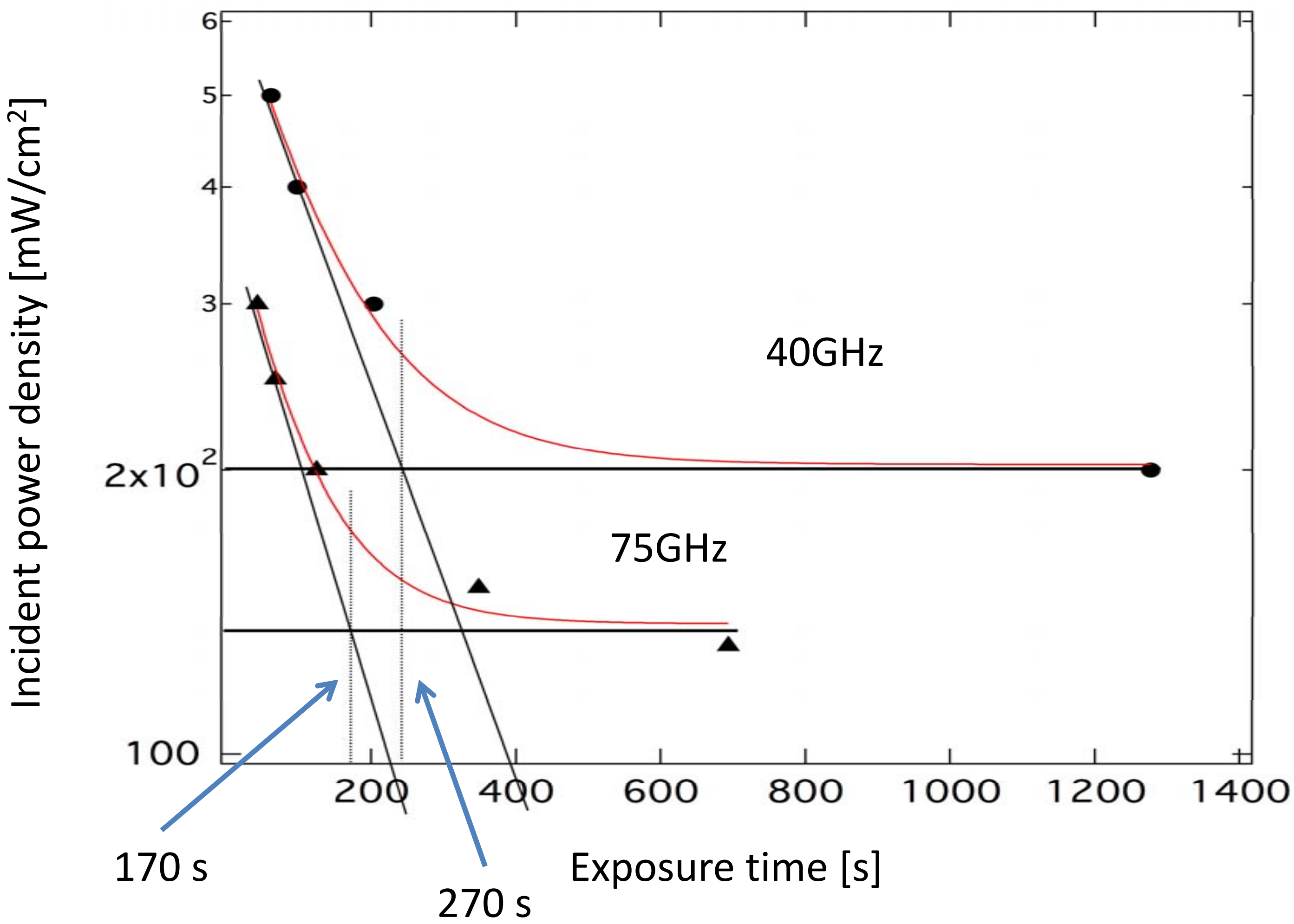
Treat pressure as potential. Explicit boundary condition is not given

[2] A.Hirata et al. ,"Temperature elevation in the eye of anatomically based human head models for plane-wave exposures", 2007.
[3] J.J.W.Lagendijk, "A mathematical model to calculate temperature distributions in human and rabbit eyes during hyperthermic treatment", 1982.

Exposure time and Incident power density of the threshold



Estimation of time constant from mathematical model



-Time constant is estimated from threshold diagram of time and power density.
-Time constant is 270 s and 170s for 40GHz and 75 GHz exposure, respectively.
-The values of time constant become small as the frequency increase.

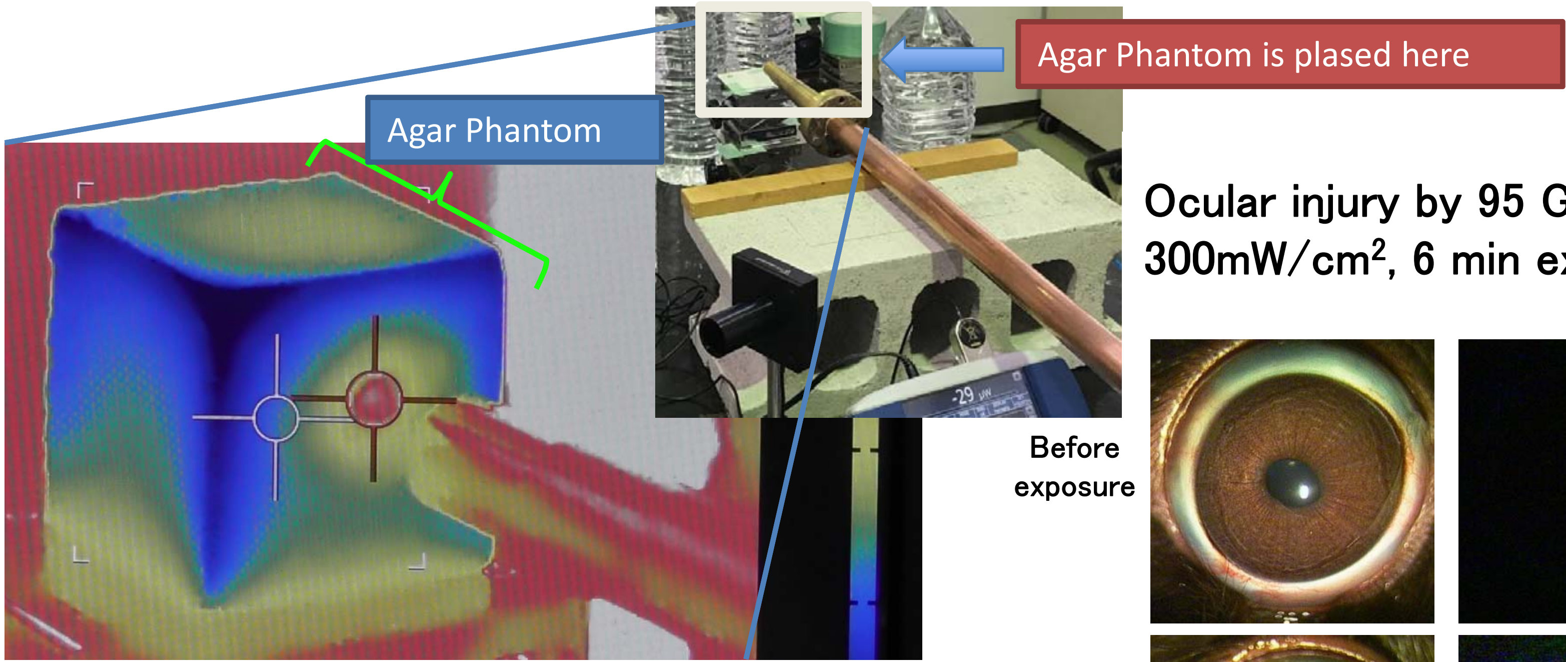
CEM43℃ for MMW exposure

- MMW exposure causes temperature elevation in the ocular tissue as a functions of space and time.
- The history of thermal exposure is required to obtain CEM43℃ index.
- We modified the definition of CEM43℃ as follows

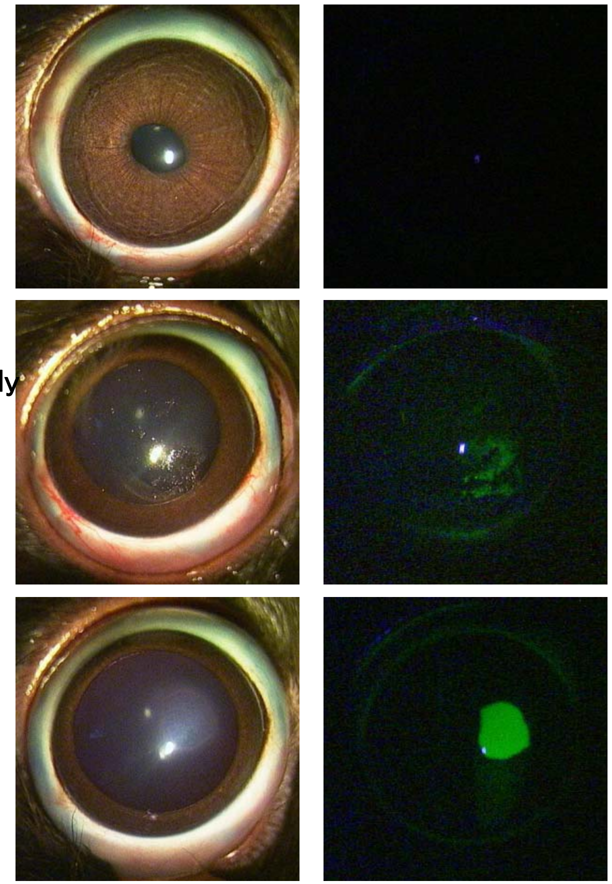
$$CEM\,43^{o}\,C(\vec{r},t) = \int_{0}^{d} R^{(43-T(\vec{r},t'))}\,dt'\,[\mathrm{min}]$$

$T(\vec{r},t)$:Temperature of ocular tissue obtained by computer simulation

t :Exposure duration　　R :（R=0.25 at T<43℃, R=0.5 at T>43℃



Ocular injury by 95 GHz, $300 mW/cm^2$, 6 min exposure



Before exposure

Immediately after exposure

1day after exposure

- For preliminary experiment the Gyrotron is operated at <u>840mW average power</u> under the pulse mode.
  - ✓ Peak power: 1.2W, Duty ratio: 70%, Cycle: 1Hz
- We got a temperature difference (ΔT) between before and during exposure. $\Delta T=16^{\circ}C$ ($34^{\circ}C-18^{\circ}C$)
- This $\Delta T=16^{\circ}C$ is agree on ΔT before and during 95 GHz, $300 mW/cm^2$, 6 min ocular exposure.