Quantum Beam Engineering E 量子ビーム発生工学特論E

Laser-tissue interaction and its medical applications

レーザーの生体組織への影響と医療応用

based on and using figures from **M. Niemz, "Laser-Tissue Interactions," Springer**

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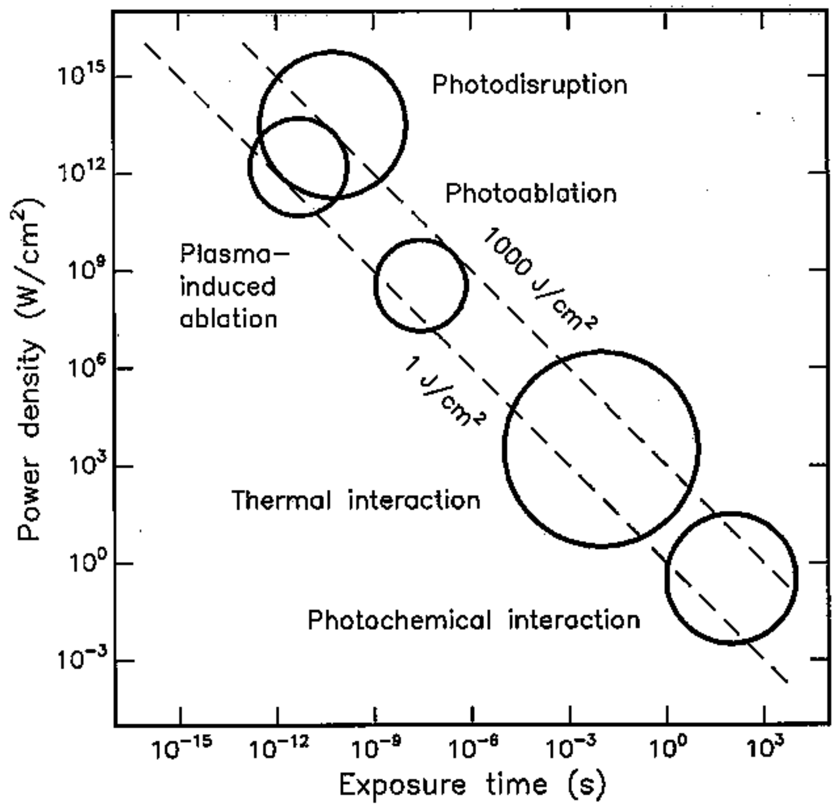
Interaction mechanisms

- Photochemical interaction
- Thermal interaction
- Photoablation
- Plasma-induced ablation
- Photodisruption

All these seemingly different interaction types share the energy density (fluence) ranges between 1 and 1000 J/cm^2 → Exposure duration largely matters!



Map of laser-tissue interactions

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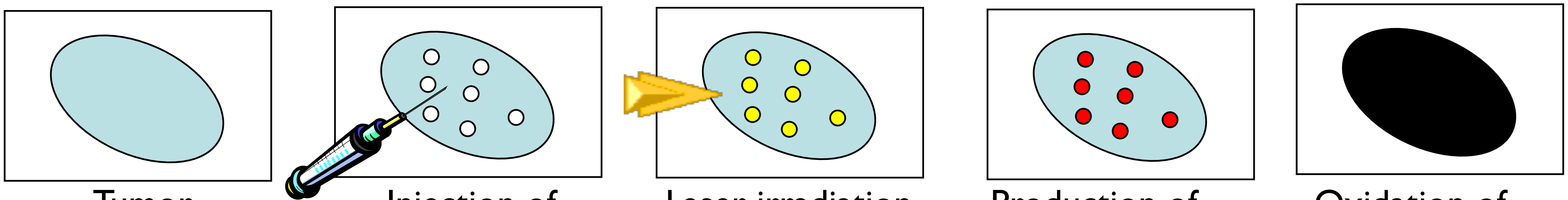
Photochemical interaction

Light can induce chemical effects and reactions within macromolecules or tissues.

- In nature → photosynthesis
- Medical application → significant role during photodynamic therapy (PDT)
- takes place at very low intensity ~ 1 W/cm^2 and long exposure (seconds to CW)
- in the visible ranges – high efficiency and optical penetration depth

Photodynamic therapy (PDT)



Tumor

Injection of photosensitizer

↙ chromophore compound causing light-induced reactions in other non-absorbing molecules

Laser irradiation

⇩

Excitation of photosensitizer

Production of highly cytotoxic reactants through intramolecular transfer reactions

Oxidation of essential cell structures

⇩

Necrosis

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Kinetics of photosensitization

Excitation

- Singlet state absorption $^1S + h\nu \Rightarrow {}^1S^*$

Decays

- Fluorescence $^1S^* \Rightarrow {}^1S + h\nu'$
- Nonradiative singlet decay $^1S^* \Rightarrow {}^1S$
- Intersystem crossing $^1S^* \Rightarrow {}^3S^*$
- Phosphorescence $^3S^* \Rightarrow {}^1S + h\nu''$
- Nonradiative triplet decay $^3S^* \Rightarrow {}^1S$

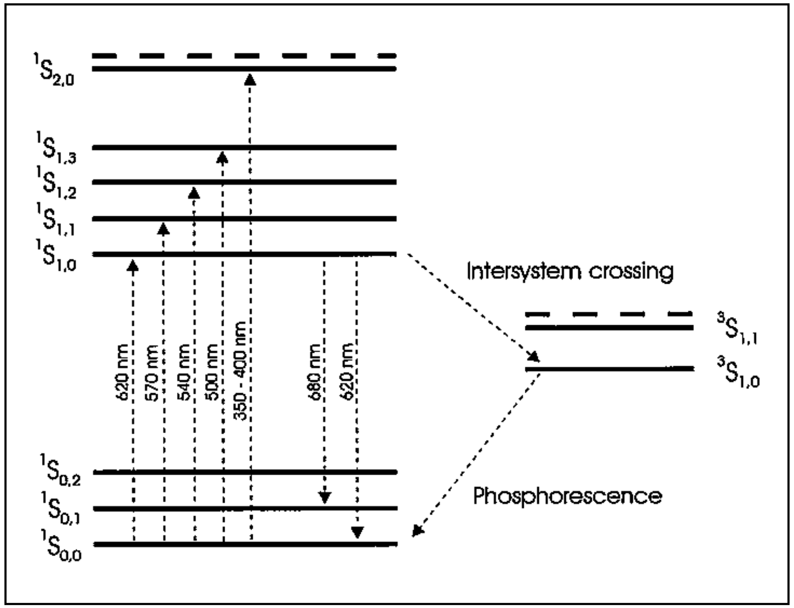
Type I reactions

- Hydrogen transfer $^3S^* + RH \Rightarrow SH^\bullet + R^\bullet$
- Electron transfer $^3S^* + RH \Rightarrow S^{\bullet -} + RH^{\bullet +}$
- Formation of HO_2 radicals $SH^\bullet + {}^3O_2 \Rightarrow {}^1S + HO_2^\bullet$
- Formation O_2^- radicals $S^{\bullet -} + {}^3O_2 \Rightarrow {}^1S + O_2^{\bullet -}$

Type II reactions

- Intramolecular exchange $^3S^* + {}^3O_2 \Rightarrow {}^1S + {}^1O_2^*$
- Cellular oxidation $^1O_2^* + \text{cell} \Rightarrow \text{cell}_{ox}$

cytotoxic



Energy level diagram of hematoporphyrin derivative (HpD)

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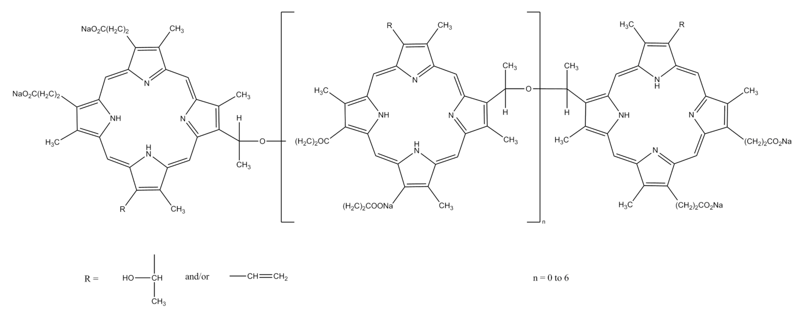
Photodynamic therapy (PDT)

a form of cancer therapy using nontoxic light-sensitive compounds that are exposed selectively to light, whereupon they become toxic to targeted tumor cells.

method

- Intravenous injection of photosensitizer (typically porfimer sodium, sold as photofrin)
  - Photofrin concentration in tumor is ca. four times higher than in healthy tissues.
  - Photofrin stays in tumor longer than 48 hours.
  - Photofrin is excreted from healthy tissues (except for liver and kidney) within 24 hours.
- Laser irradiation after 48-72 hours after Photofrin injection
  - 630 nm wavelength
  - introduced to the tumor by optical fiber

Photofrin (Porfimer sodium)



https://en.wikipedia.org/wiki/Porfimer_sodium

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Summary of photochemical interaction

- Main idea
  - use a photosensitizer acting as catalyst
- Observations
  - no macroscopic observations
- Typical lasers
  - red dye lasers, semiconductor lasers
- Pulse exposure duration
  - 1 sec ~ CW
- Intensity
  - 0.01 ~ 50 W/cm^2
- Medical application
  - Photodynamic therapy of cancer

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Thermal interaction

Laser & optical tissue parameters → **Heat generation**

Thermal tissue parameters → **Heat transport**

Type of tissue → **Heat effects**

Heat generation → Heat transport → Heat effects

Microscopic two-step process

1. Absorption: $\mathrm{A} + h\nu \rightarrow \mathrm{A}^*$
   - Absorption of a photon promotes molecule A to an excited state A*
   - Free water molecules, proteins, pigments, and other macromolecules have many vibrational levels, leading to efficient photoabsorption.
2. Deactivation: $\mathrm{A}^* + \mathrm{M}(E_{\mathrm{kin}}) \rightarrow \mathrm{A} + \mathrm{M}(E_{\mathrm{kin}} + \Delta E_{\mathrm{kin}})$
   - Inelastic collisions with some partner M of the surrounding medium
   - deactivation of A* and simultaneous increase in kinetic energy of M

Transfer of photon energy to kinetic energy

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Thermal interaction

Laser & optical tissue parameters		Thermal tissue parameters		Type of tissue
↓		↓		↓
Heat generation	→	Heat transport	→	Heat effects

凝固(coagulation)	60°C
蒸発・気化(vaporization)	100°C
炭化(carbonization)	>100°C
融解(melting)	>300°C

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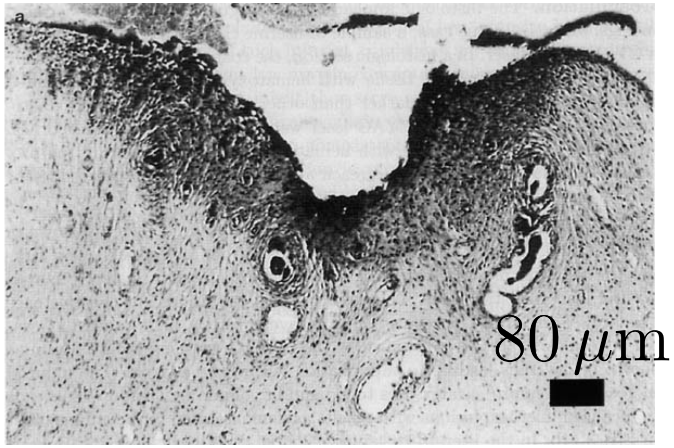
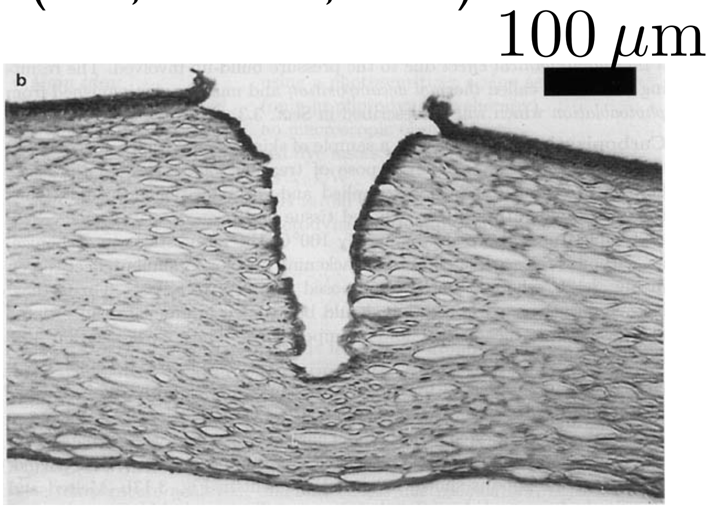
coagulation

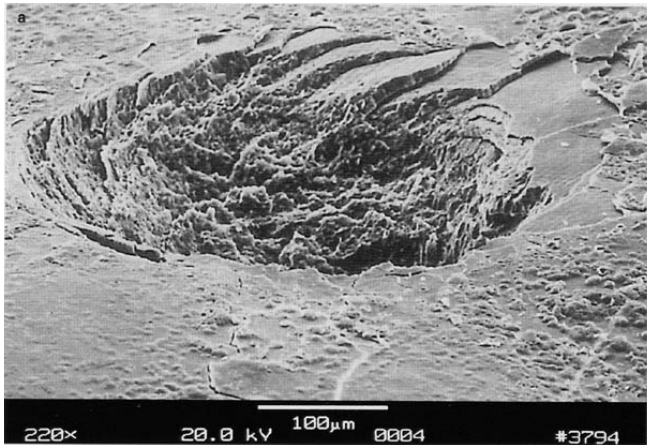


Uterine tissue of a wistar rat (CW, Nd:YAG, 10 W)

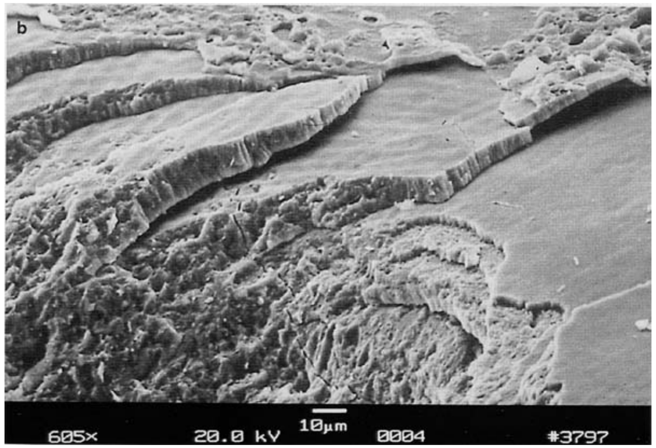


Human cornea (120 pulses, Er:YAG, 90 μs, 5 mJ, 1 Hz)

vaporization



Human tooth (20 pulses, Er:YAG, 90 μs, 100 mJ, 1Hz)



Human tooth (Enlargement)

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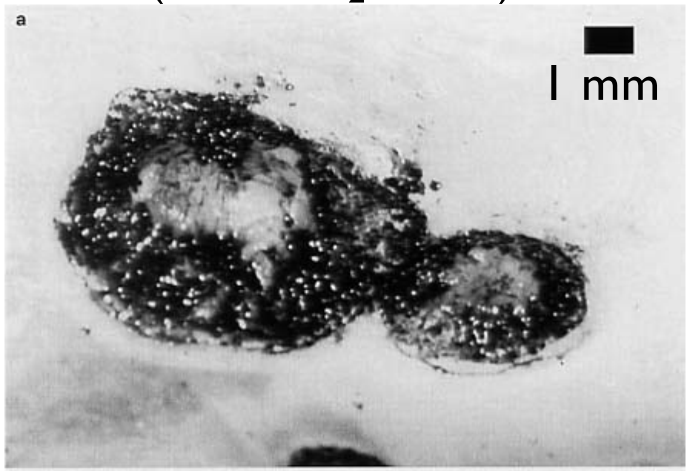
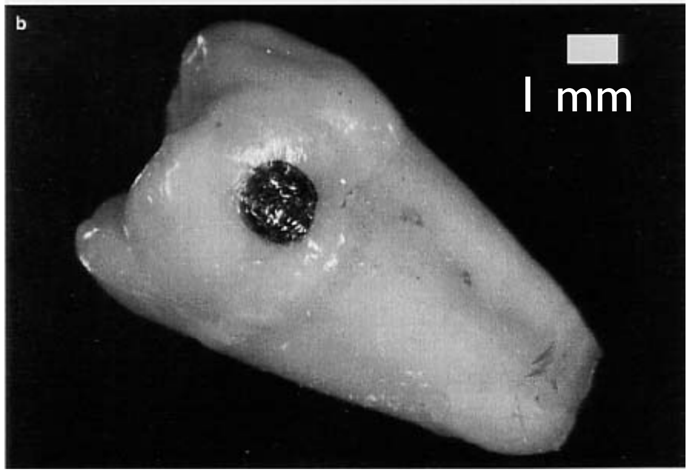
carbonization

Tumor metastases on human skin (CW CO_2, 40 W)

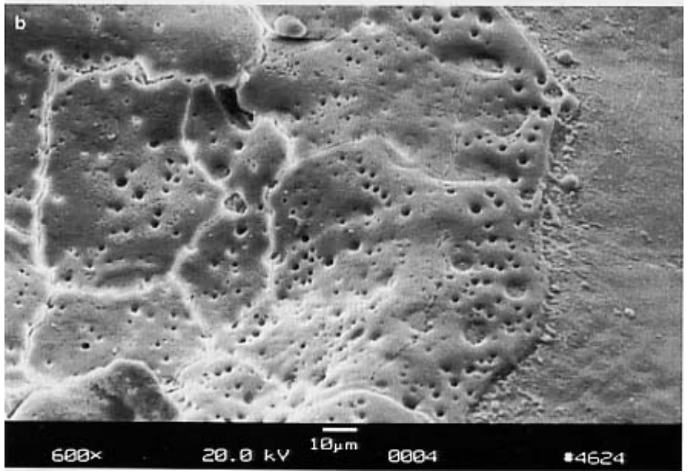




Human tooth (CW CO_2, 1W)

melting

Human tooth (100 pulses, Ho:YAG, 3.8 μs, 18 mJ, 1Hz)



Human tooth (Enlargement)

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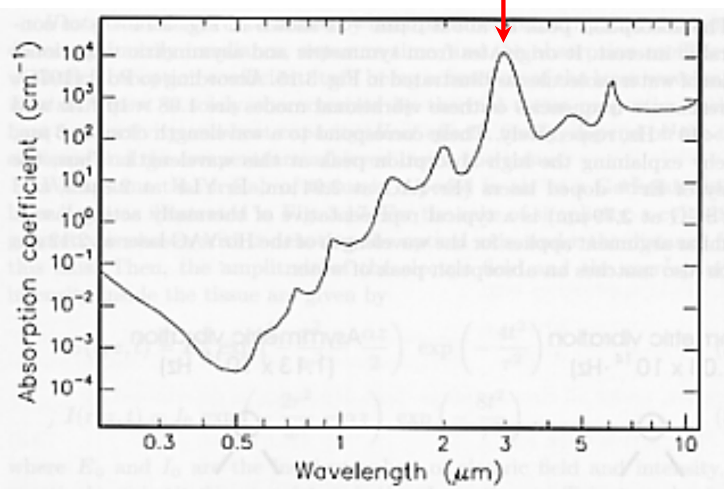
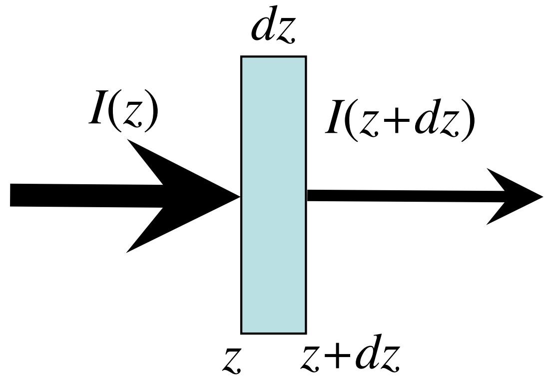
Heat generation

- Absorption mainly by free water molecules, proteins, pigments, and other macromolecules
- Absorption governed by Lambert-Beer's law
- Absorption by water molecules plays a significant role.
  - Peak at 3μm due to symmetric and asymmetric vibrational modes
  - Er:YAG@2.94μm, Er:YLF@2.8μm, Er:YSGG@2.79μm



Absorption spectrum of water



Energy deposition per unit area and time $S\Delta z$ (W/cm^2)

$$S(z,t)\Delta z = I(z,t) - I(z+\Delta z)$$

$$S(z,t) = -\frac{\partial I(z,t)}{\partial z} = \alpha I(z,t) \quad (\mathrm{W/cm^3})$$

heat source

absorption coefficient

heat content change dQ vs temperature change dT

$$dQ = mcdT \qquad m: \text{mass},\ c: \text{specific heat capacity}$$

Good approximation for most tissues

$$c = \left(1.55 + 2.8\frac{\rho_W}{\rho}\right)\frac{\mathrm{kJ}}{\mathrm{kg\cdot K}}$$

ρ : tissue density (kg/m^3)

ρ_W : water content (kg/m^3)

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Heat transport

Mainly due to heat conduction, except for that due to blood flow (heat convection)

Heat flux $\mathbf{j}_Q$ (diffusion equation) $\mathbf{j}_Q = -k\nabla T$ k : heat conductivity

Good approximation for most tissues $k = \left(0.06 + 0.57\frac{\rho_W}{\rho}\right)\frac{\mathrm{W}}{\mathrm{m\cdot K}}$ ρ : tissue density, ρ_W : water content

Equation of continuity

$$\mathrm{div}\,\mathbf{j}_Q = -\frac{\rho}{m}\frac{\partial Q}{\partial t} = -\rho c\frac{\partial T}{\partial t}$$

Heat conduction equation

$$\frac{\partial T}{\partial t} = \frac{k}{\rho c}\nabla^2 T \quad \Rightarrow \quad \frac{\partial T}{\partial t} = \kappa\nabla^2 T$$

$$\kappa \equiv \frac{k}{\rho c} \approx 1.4\times 10^{-7}\ \mathrm{m}^2/s$$

(in water and most tissues)

Heat conduction with heat source S $\frac{\partial T}{\partial t} = \kappa\nabla^2 T + \frac{S}{\rho c}$

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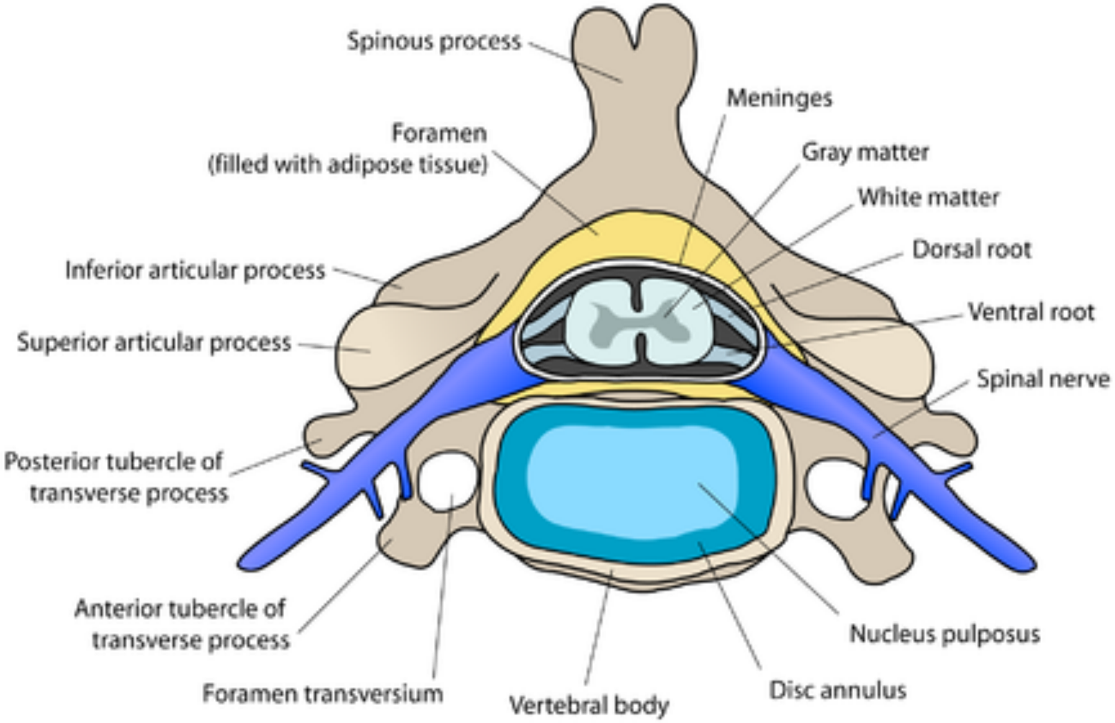
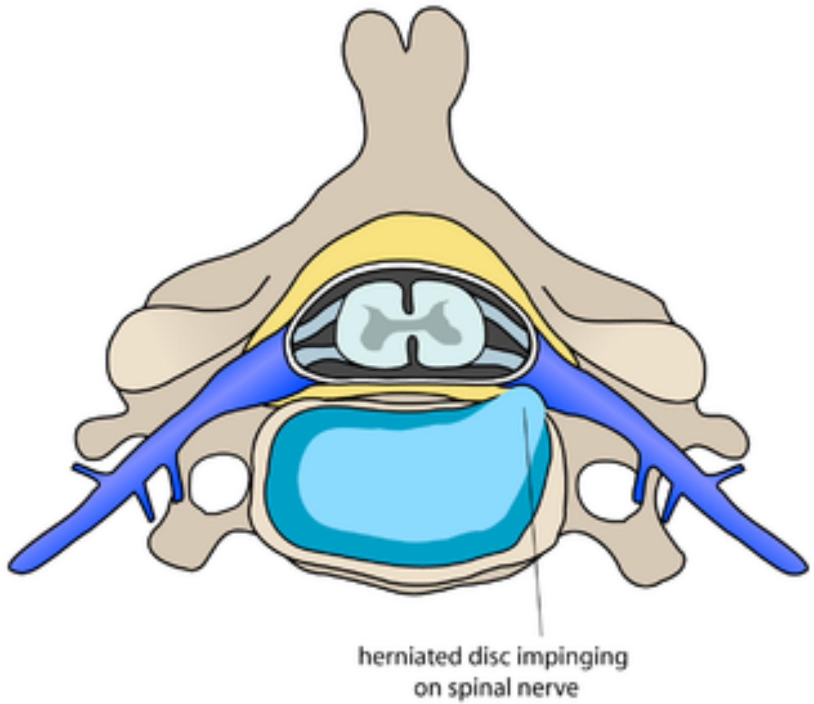
Treatment of lumbar disk herniation



normal



disk herniation

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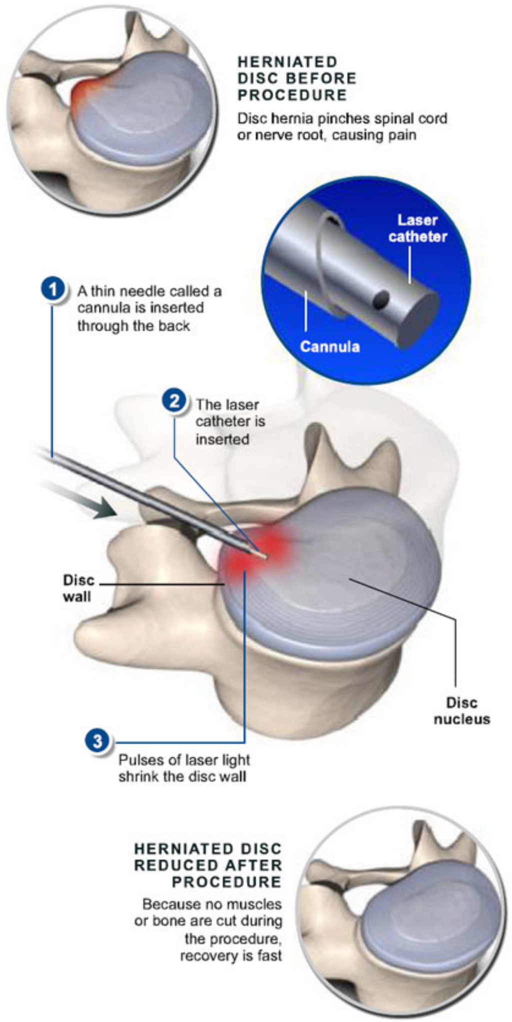
Percutaneous Laser Disc Decompression (PLDD)

“minimally invasive” treatment modalities for lumbar disk herniation



on an outpatient basis using a gentle, relaxing medicine and local anesthetic

STEP 1 : After some anesthetic is injected to numb the area, a thin needle called a cannula is inserted through the back and into the herniated disc.
STEP 2 : A small laser probe is carefully inserted through the cannula and into the disc. Pulses of laser light are shined into the problem area of the disc.
STEP 3 : The laser light creates enough heat to shrink the disc wall area.
END OF PROCEDURE : The probe and needle are removed, and the insertion area in the skin is covered with a small bandage. Because no muscles or bone are cut during the procedure, recovery is fast and scarring is minimized.

http://www.spinesurgeon.co.uk/content/laserdiscoplasty/

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Summary of thermal interaction

- Main idea: Achieving a certain temperature which leads to the desired thermal effect
- Observation：coagulation, vaporization, carbonization, melting
- Typical lasers：CO_2, Nd:YAG, Er:YAG, Ho:YAG, argon ion, semiconductor lasers
- Pulse duration：1μs～1min
- Intensity：$10 \sim 10^6$ W/cm^2
- Medical application
  - Laser-induced interstitial themotherapy (LITT)
  - Treatment of retinal detachment
  - Laser bruise treatment

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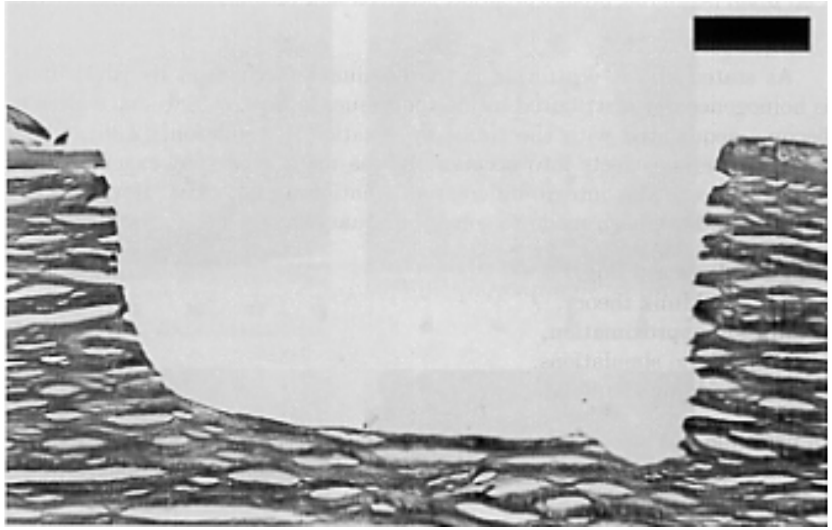
Photoablation



Cross section of corneal tissue (ArF excimer @6.4eV (193nm), 14 ns, 180 mJ/cm^2)

- Removal of tissue in a very clean and exact fashion without thermal damage
- Tissue is very precisely "etched."
- Takes place over threshold intensity (10^7～10^8 W/cm^2)

Advantages

- Precision of the etching process
- Excellent predictability
- No thermal damage to adjacent tissue

Medical application

- Laser-Assisted in situ Keratomileusis (LASIK) - myopia, hypermetropia, and astigmatism.

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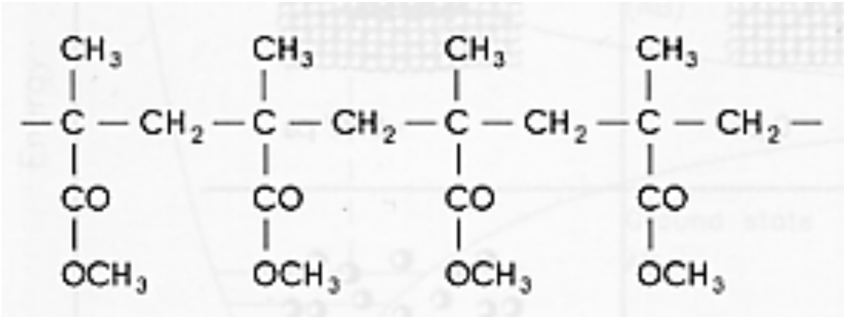
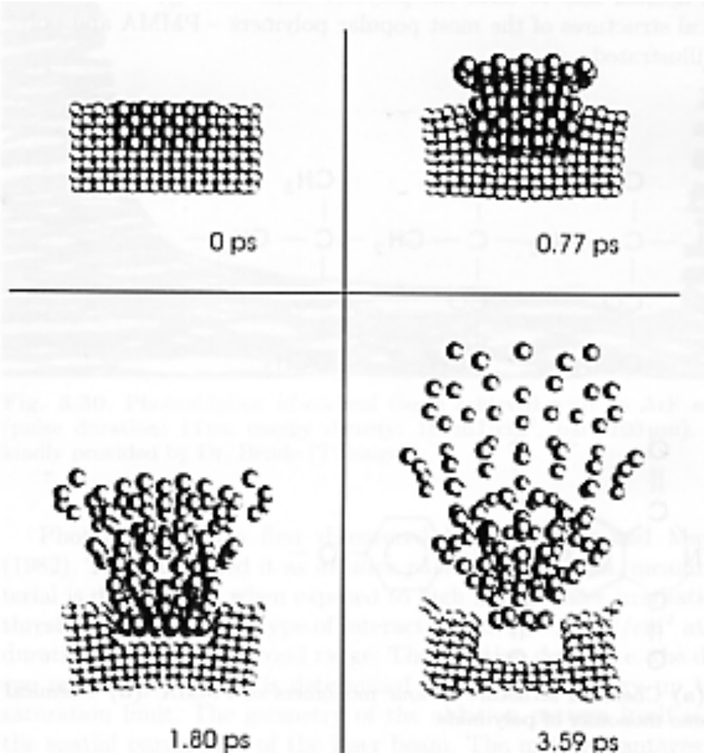
Mechanism of photoablation



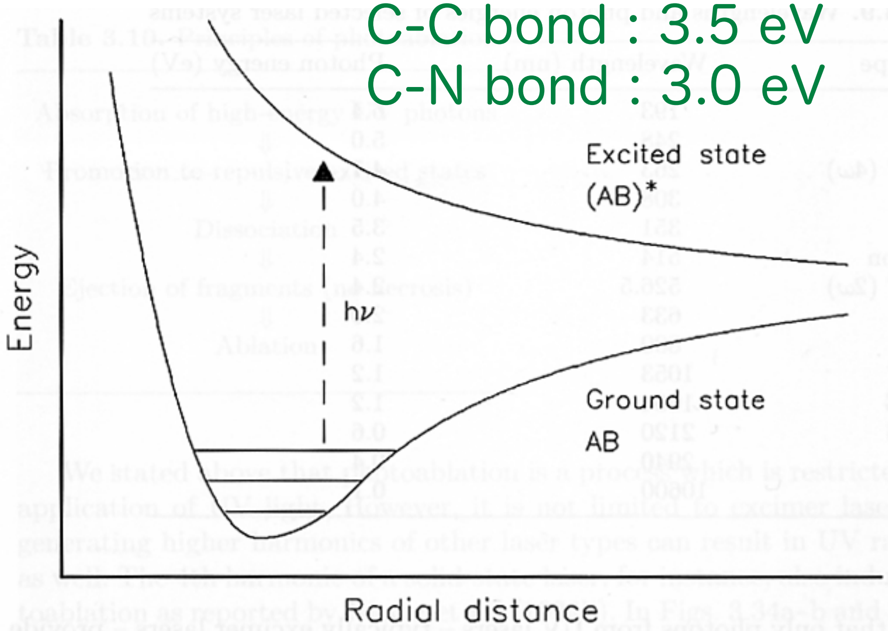
Polymethyl-metacrylate (PMMA)



needs UV light

C-C bond : 3.5 eV

C-N bond : 3.0 eV



1. Absorption of a UV photon
2. Excitation of repulsive states
   - AB + $h\nu \rightarrow$ (AB)*
3. Dissociation
   - (AB)* → A + B + E_{kin} (~ 3 – 7 eV)
4. Ejection of fragments

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Ablation depth

Lambert-Beer's law

$$I(z) = I_0 \exp(-\alpha z)$$

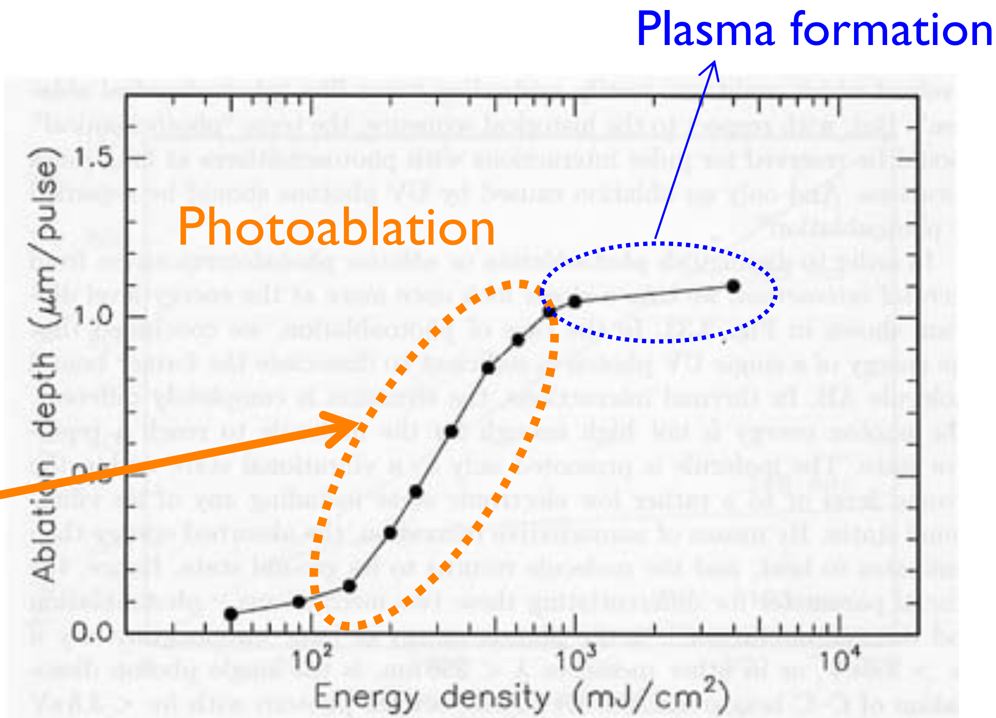
I_0 : incident intensity α : absorption coefficient

Photoablation takes place only when $I(z)$ is above a certain threshold I_{th} .

Ablation depth d

$$I_0 \exp(-\alpha d) = I_{th}$$

$$d = \frac{1}{\alpha} \ln \frac{I_0}{I_{th}} = \frac{2.3}{\alpha} \log_{10} \frac{I_0}{I_{th}}$$



Ablation curve of rabbit cornea
(ArF excimer, 14ns)

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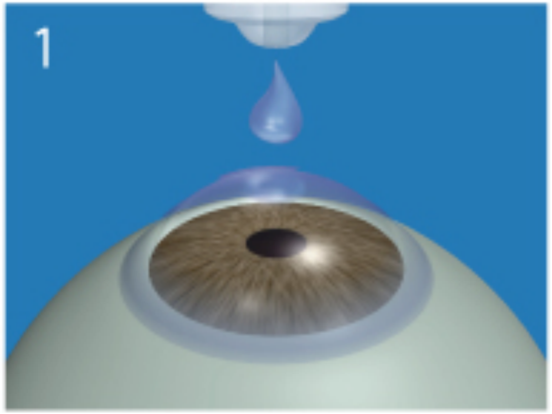
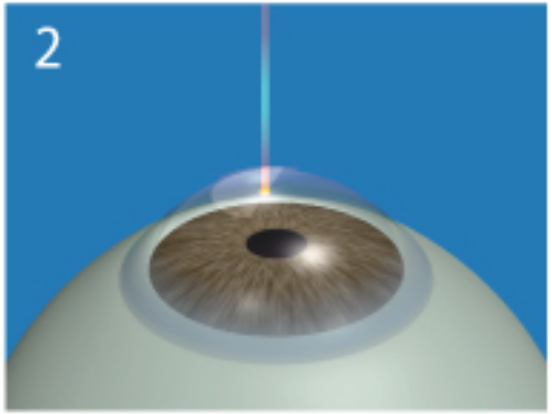
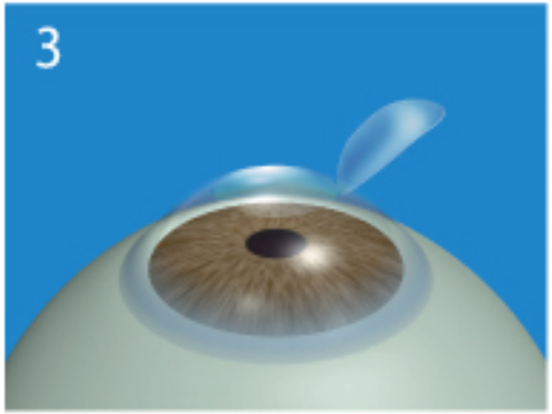
Laser in situ Keratomileusis (LASIK)



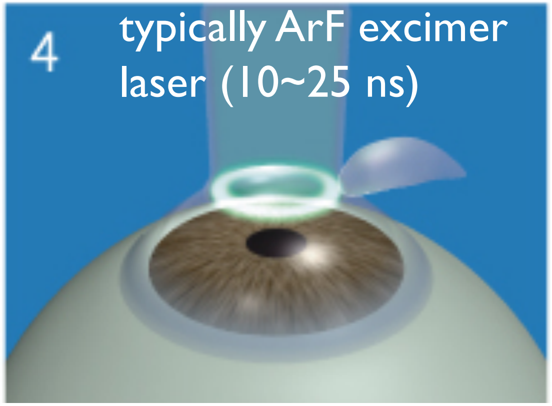
anesthetic (eye drop)



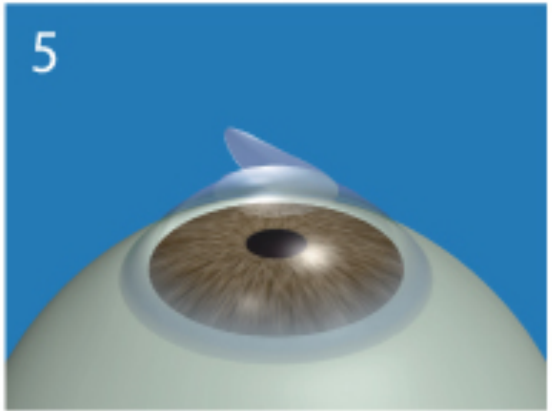
fs laser is used to create a thin, hinged flap of the cornea (15 sec exposure per eye)



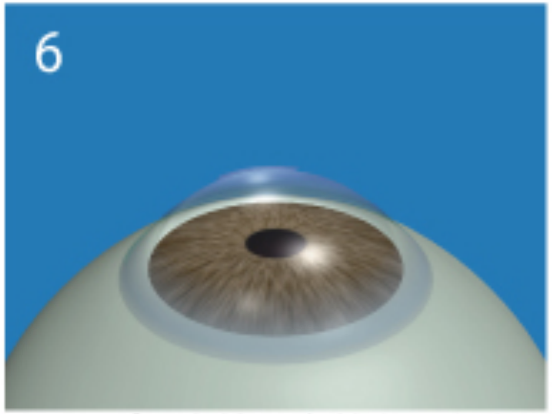
corneal flap is flipped open



excimer laser is used to remove tissue from the center of the cornea to correct the refractive error



the flap is replaced



the flap is allowed to heal naturally without stitches

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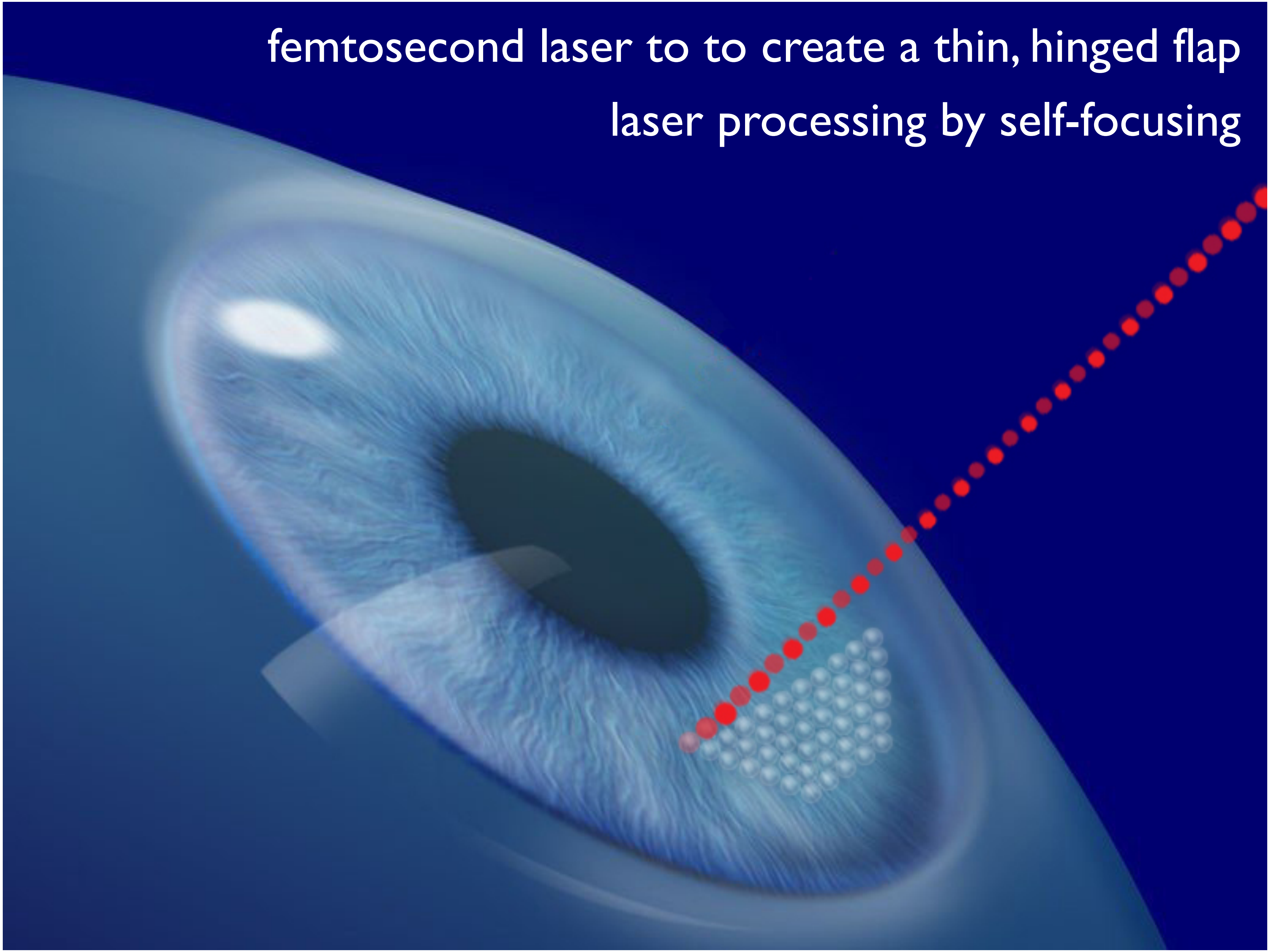

femtosecond laser to to create a thin, hinged flap
laser processing by self-focusing

Summary of photoablation

- Main idea : direct breaking of molecular bonds by UV photons
- Observations : very clean ablation, associated with audible report and visible fluorescnece
- Typical lasers : excimer lasers such as ArF, KrF, XeCl, XeF
- Pulse duration : 10〜100 ns
- Intensity : 10^7〜10^{10} W/cm^2
- Medical application : vision correction (LASIK)

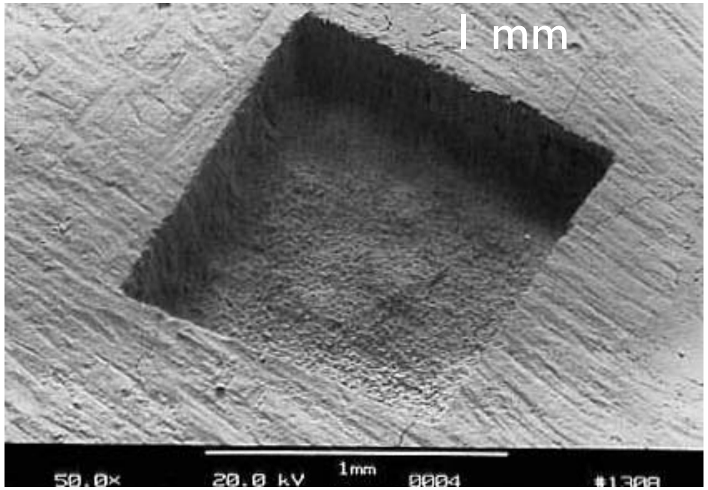
Plasma-induced ablation

- Optical breakdown at laser intensity exceeding 10^{11}W/cm^2 in solid and 10^{14} W/cm^2 in air
- Ablation is primarily caused by plasma ionization itself.
- Very clean and well-defined removal of tissue without evidence of thermal or mechanical damage by choosing appropriate laser parameters.

Medical application

- Refractive corneal surgery
- Caries therapy

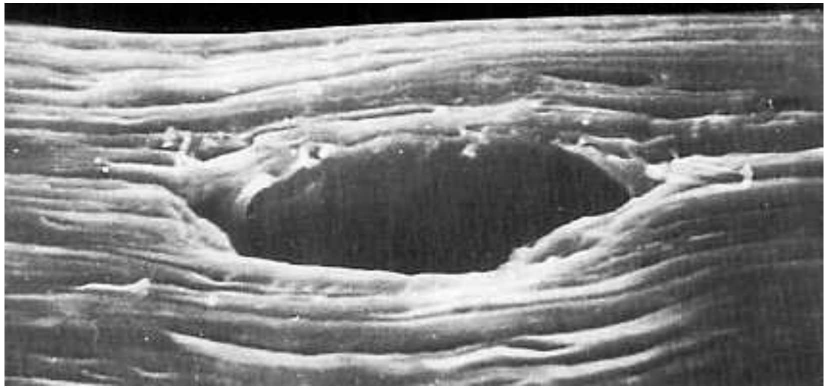
Plasma sparking on tooth surface (Nd:YLF, 30 ps, 1 mJ, 5×10^{12} W/cm^2)



After 16,000 pulses

Photodisruption

- At even higher laser energy density, shock waves and other mechanical side effects become more significant.
- Shock waves, cavitation bubble, jet formation → mechanical damage to (adjacent) tissue



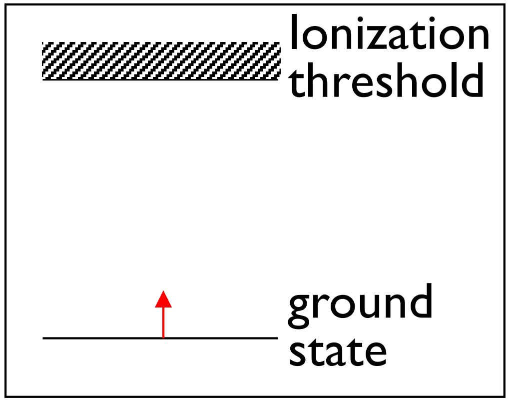
Cavitation bubble within a human cornea (single pulse, Nd:YLF, 30 ps, 1 mJ)

Medical application

- Lithotripsy

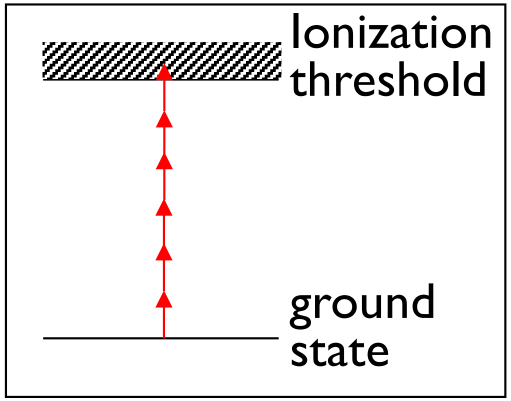
Plasma formation by optical breakdown

Step I : multi-photon ionization



Low intensity

No ionization



High intensity

Multiphoton ionization

Step II : avalanche ionization

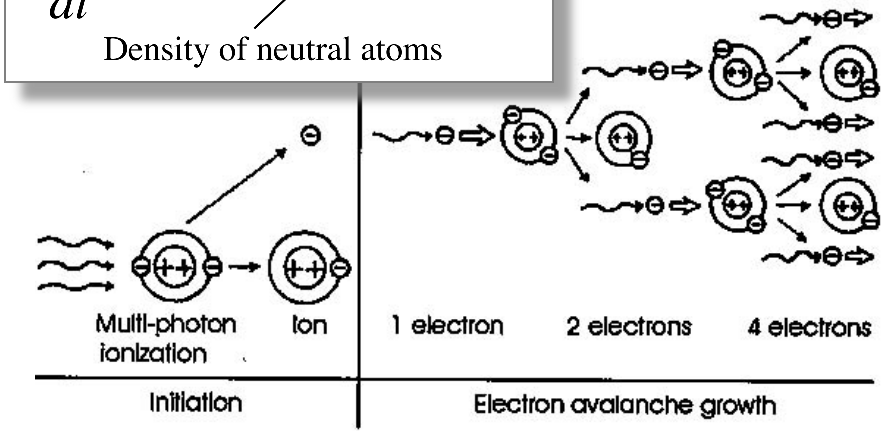
Ejected electrons are accelerated in laser fields (inverse Bremsstrahlung)

$$h\nu + e + \mathrm{A}^+ \rightarrow e + \mathrm{A}^+ + E_{\mathrm{kin}}$$

Accelerated electrons collide with other atoms and induce further ionization

$$\frac{d\rho_e}{dt} = \sigma_N I^N \rho_{\mathrm{atom}} + \eta(I)\rho_e$$

Electron density (ρ_e); Density of neutral atoms (ρ_{atom})



Plasma formation by optical breakdown

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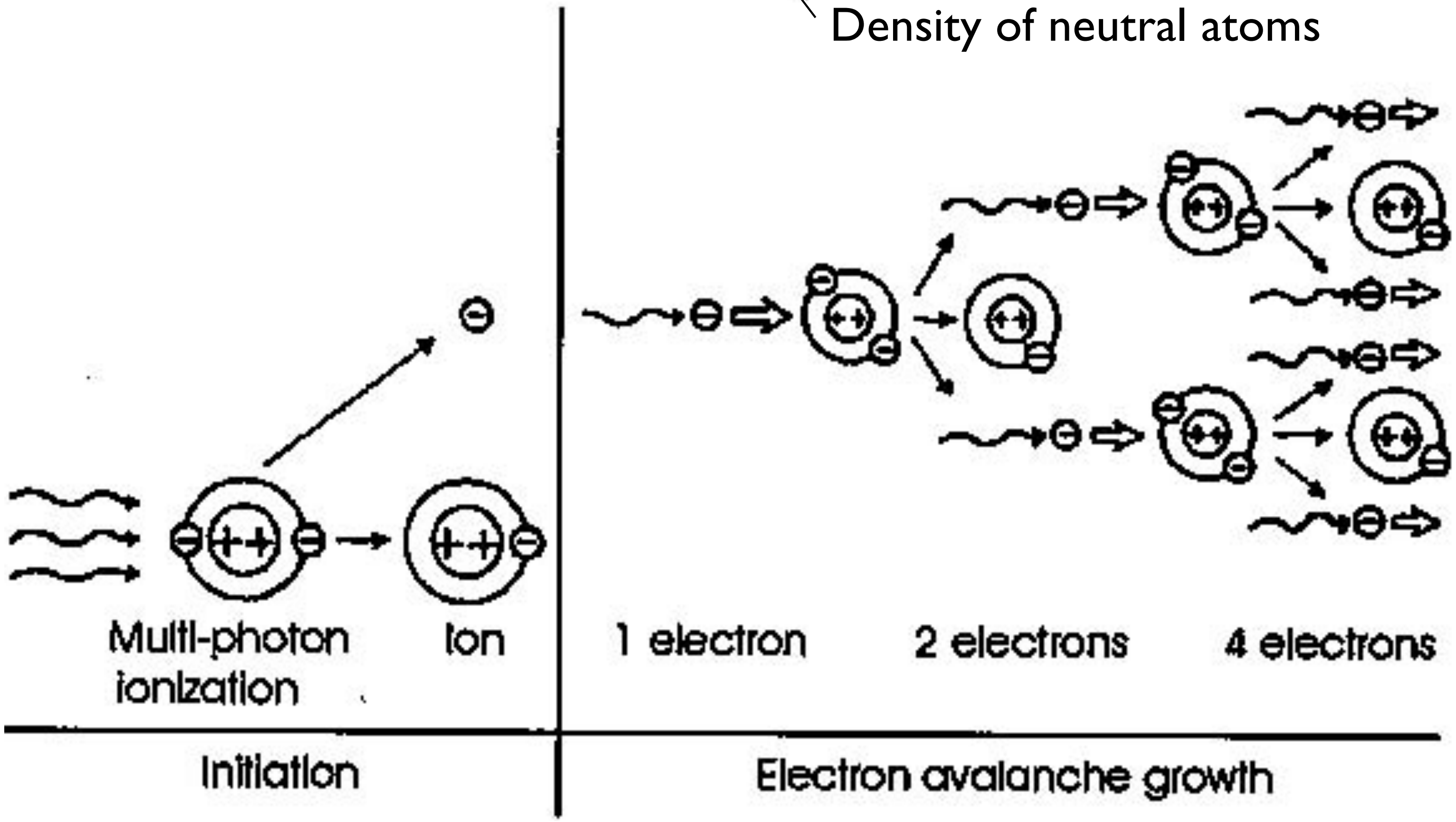
Plasma formation by optical breakdown

$$\frac{d\rho_e}{dt} = \sigma_N I^N \rho_{\rm atom} + \eta(I)\rho_e$$

Electron density

Density of neutral atoms



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Progress of plasma-induced ablation and photodisruption

Laser irradiation

Optical breakdown ↓

Plasma formation and expansion → Tissue removal (Plasma-induced ablation)

supersonic →deceleration ↓

Shock wave generation ↓

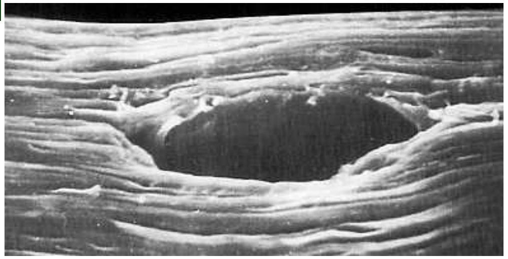
Cavitation bubble formation ↓

Bubble expansion

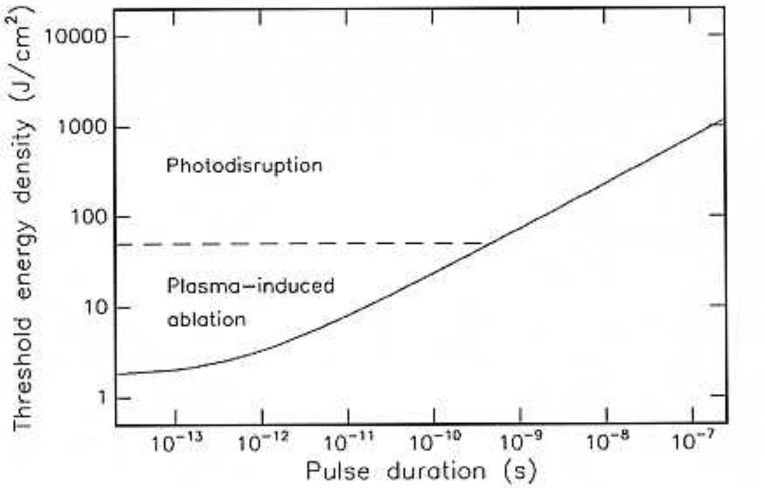
bubble collapse ↓

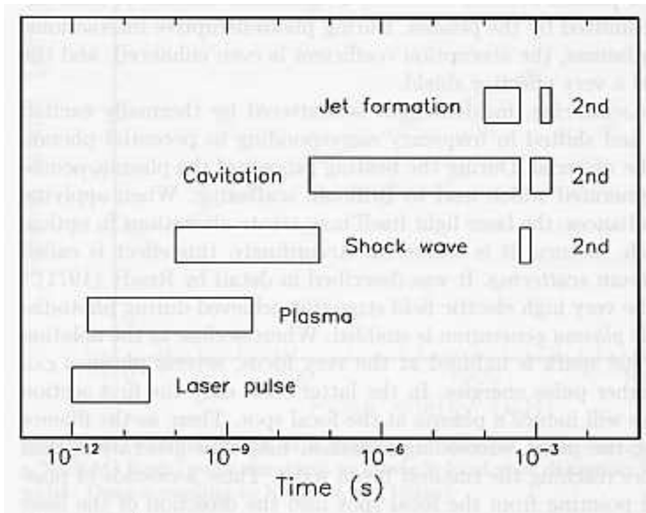
(Liquid) jet formation

Shock wave generation, Cavitation bubble formation, Bubble expansion, (Liquid) jet formation → Damage to adjacent tissues (Photodisruption)



Cavitation bubble within a human cornea





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Summary of plasma-induced ablation

- Main idea : ablation by ionizing plasma formation
- Observation: very clean ablation, associated with audible report and blueish plasma spaking
- Typical lasers
  - Nd:YAG
  - Nd:YLF
  - Ti:Sapphire
- Pulse duration : 100 fs ～ 500 ps
- Intensity : 10^{11}～10^{13} W/cm^2
- Medical application : refractive corneal surgery, caries therapy

Summary of photodisruption

- Main idea : fragmentation and cutting of tissue by mechanical forces
- Observation: plasma sparking, generation of shock waves, cavitation, jet formation
- Typical lasers
  - Nd:YAG
  - Nd:YLF
  - Ti:Sapphire
- Pulse duration : 100 fs ～ 100 ns
- Intensity : 10^{11}～10^{16} W/cm^2
- Medical application : lithotripsy

Chat your student ID number and full name.
This lecture is recorded.

Report Assignment

Pick up and summarize a biological and/or medical application of laser that was NOT presented in the lecture. Describe (at least) its relevant interaction mechanism, principle, advantages/disadvantages, and future prospects.

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