LAMELIS 2019
Lasers in Medicine and Life Sciences

Basics of high-energy, short-pulsed lasers

László Égerházi
Department of Medical Physics and Informatics
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What is a laser?

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What is a laser?

L	Light
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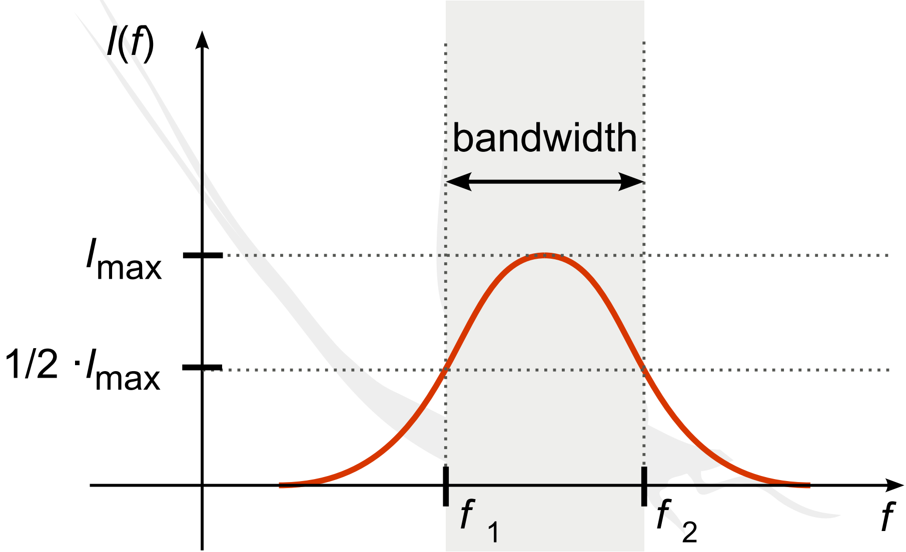
Special properties of lasers

The special properties of lasers are based on a process called **stimulated emission,** during which emission is started by a stimulating radiation and a photon with exactly the same direction, frequency and phase as the stimulating photon is emitted, whilst the stimulating photon is not lost ☛ *coherent amplification of light*

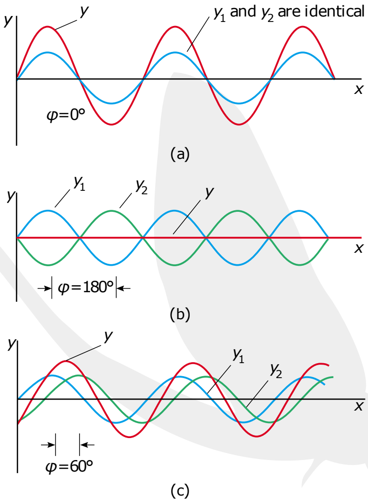
Special properties of lasers

1. Laser beams are **collimated** (can be made very parallel; eg, torch vs laser pointer).
2. Some lasers can produce very **high intensities** ($10^{10} - 10^{18}\,\mathrm{W/cm^2}$).
3. Some lasers can produce very **short pulses** (ps, fs, as).
4. Laser beams are very **monochromatic** (small bandwidth).
5. Lasers are very **coherent.**

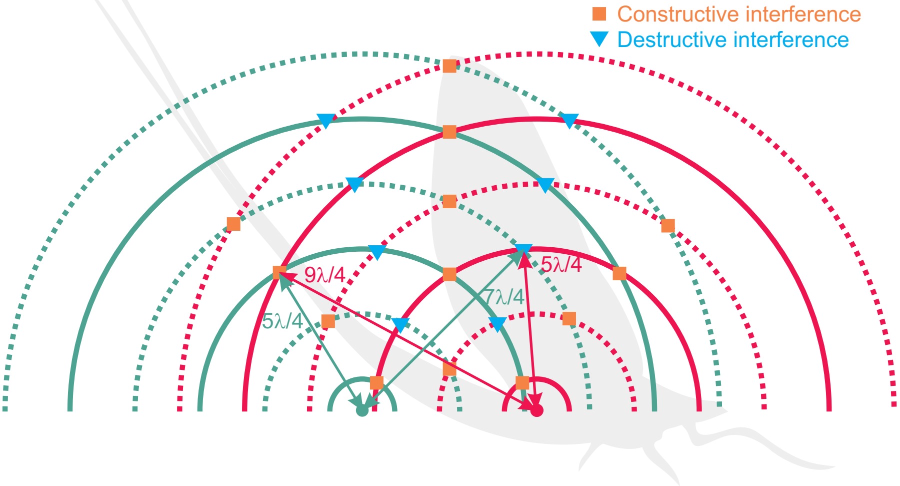
Bandwidth



Superposition of waves



Interference pattern



Coherence I

- light is an electromagnetic wave; the wave function describing the electric field component is
  $$E(x,t) = E_{\max} \cdot \sin(kx - \omega t)$$
  where E is the magnitude of the electric field vector, $k = 2\pi/\lambda$ is the (angular) wave number, $\omega = 2\pi f$ is the angular frequency, t is time and we have assumed that light propagates in one dimension, along the x axis
- if two light waves meet, superposition occurs

Coherence II

- let the two waves be given by

$$E_1(x,t) = E_{\mathrm{max}} \cdot \sin\left(kx - \omega t\right)$$
$$E_2(x,t) = E_{\mathrm{max}} \cdot \sin\left(kx - \omega t + \Delta\phi\right)$$

- $\Delta\phi$: **phase difference** and it determines whether the two waves will amplify or cancel each other
- if the phase difference between the two waves is constant in space and time, their superposition will result in a constant pattern; ☛ **interference**
- **coherence** is the property of waves which tells us whether they can produce a constant interference pattern

Temporal and spatial coherence

- light, as a wave, shows regularities in both space and time
- **coherence in time** can be given by the **coherence time** t_c, which is defined as the longest time interval that passes between two emissions coming from the same light source that can still interfere with each other
- coherence time is connected to the bandwidth Δf of the source by

$$t_c = \frac{1}{\Delta f}$$

Spatial coherence

1. **coherence in space** can be described by the **coherence length** s, which is defined as the longest distance perpendicular to wave propagation at which two emissions coming from the same light source can still interfere with each other
2. coherence length can be given by

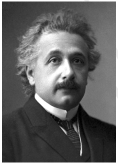
$$s = \frac{\lambda L}{d},$$

in which λ is the wavelength, L is the distance from the observer and d is the diameter of the light source

Role of coherence

- important in interferometric techniques ☛ optical coherence tomography
- key factor in laser speckle flowmetry
- holography: to create holograms, one needs coherent illumination
- why does laser light appear grainy when shone on a surface? ☛ it is so coherent that it produces a diffraction pattern on a not strictly regular surface

History of the laser



1917 Albert Einstein: theory for stimulated emission

1964 Townes | Basov | Prokhorov: practical foundations of lasers (Nobel prize in physics, 1964)

1960 Theodore H Maiman: the first functioning laser (ruby laser)

2018 Donna Strickland | Gérard Mourou: chirped pulse amplification (Nobel prize in physics, 2018)

Einstein's theory (1917)

- transition processes: absorption or emission
- one form of absorption, two types of emission:

Spontaneous emission

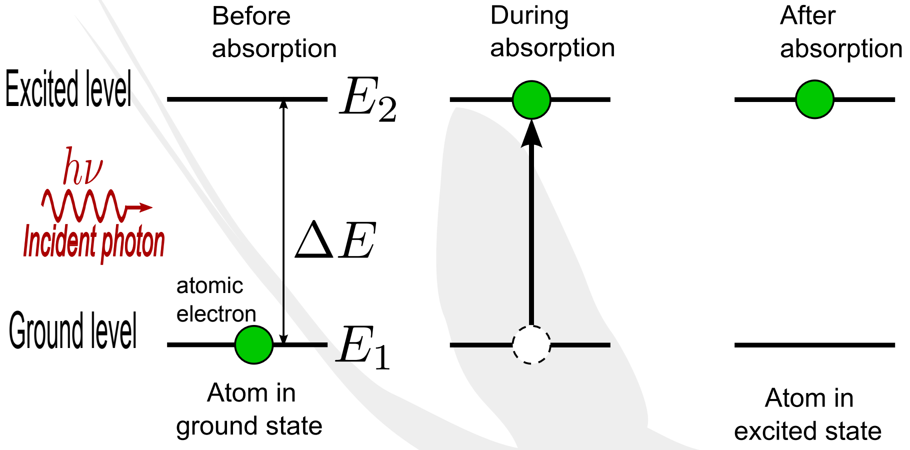
- the atom relaxes **on its own, no** need for **external electromagnetic field**
- the emission of an atom is independent of other atoms
- a photon is emitted in a **random direction**

Stimulated emission

- the atom relaxes **under the effect of an external electromagnetic field** — stimulating photon
- the stimulated photon is not consumed in the process
- the **same direction, frequency** and **phase** as the stimulating photon

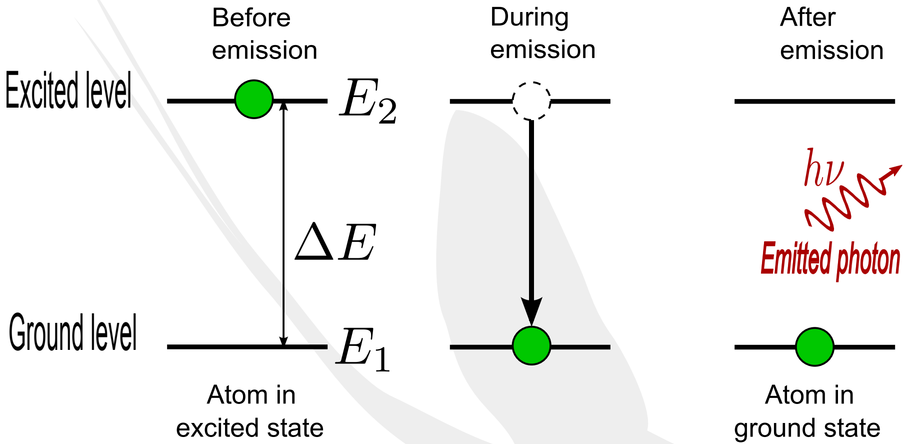
$\Rightarrow$ **very coherent light sources** can be based upon it

Absorption



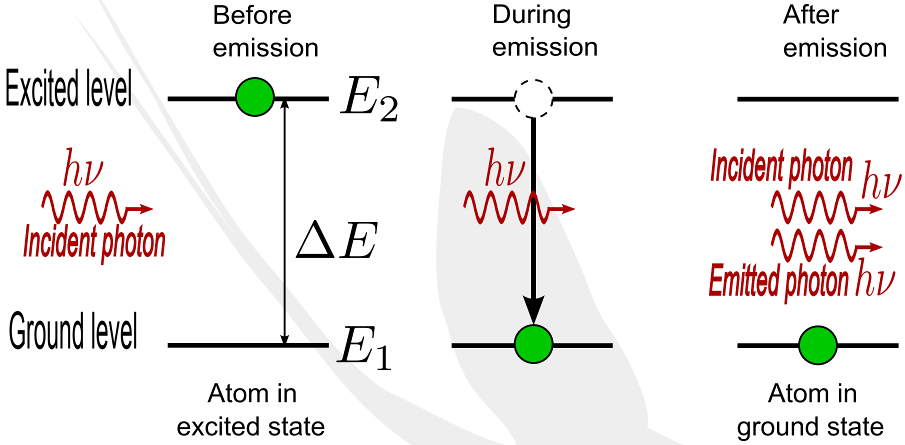
$$E_2 - E_1 = \Delta E = h\nu$$

Spontaneous emission



$$E_2 - E_1 = \Delta E = h\nu$$

Stimulated emission

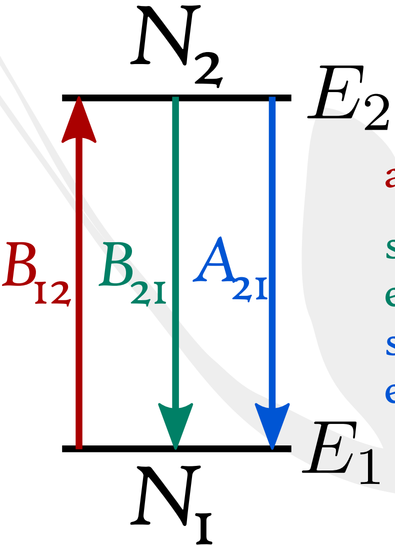


$$E_2 - E_1 = \Delta E = h\nu$$

Laser properties

- the emitted photon has the same direction $\Rightarrow$ low divergence
- the emitted photon has the same frequency $\Rightarrow$ small bandwidth
- the emitted photon has the same phase $\Rightarrow$ coherence

Einstein coefficients



absorption

stimulated emission

spontaneous emission

Einstein coefficients

- to each transition process, we can assign an **Einstein coefficient**
  - absorption: B_{12}
  - stimulated emission: B_{21}
  - spontaneous emission: A_{21}
- Einstein coefficients characterise the **probability of transition between two given levels** of an atom or molecule (they are different for different atoms and for different energy level pairs within atoms)

Populations: number densities

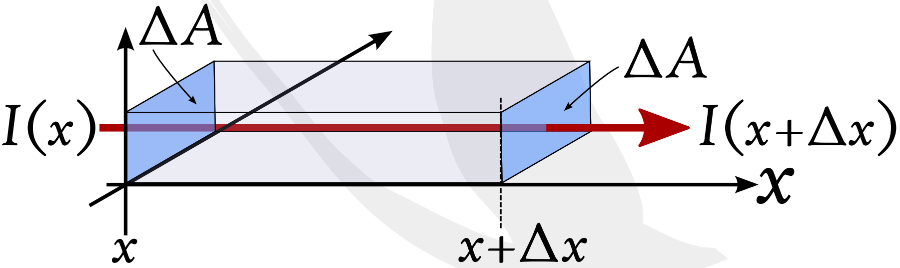
- the transition rate depends on the **number density of atoms** in the given atomic level, which is defined by the number of atoms in unit volume which are in the given state:

$$N_1 := \frac{\text{number of atoms in ground state}}{\text{volume}}$$

$$N_2 := \frac{\text{number of atoms in excited state}}{\text{volume}}$$

Light propagating in a medium

Let us assume that monochromatic light with frequency f propagates along the x direction in a medium in which both absorption and emission can take place. We shall examine the intensity changes due to these processes.



Light propagating in a selected volume of a medium.

Intensity changes I

- the intensity of light is given by the power of light incident on a unit surface perpendicular to the direction of propagation:

$$I = \frac{\Delta P}{\Delta A} = \frac{\Delta E}{\Delta A \Delta t},$$

  where P is power, E is energy, A is surface are and t is time

- as light travels through the medium, the intensity will change

$$\Delta I = I(x + \Delta x) - I(x)$$

Intensity changes II

- the causes of the change:
  - ground-state atoms or molecules may absorb photons, decreasing the intensity (ΔI_a)
  - excited-state atoms or molecules may emit photons through the process of stimulated emission, increasing the intensity (ΔI_st)
  - Why did we neglect spontaneous emission? $\Leftarrow$ In spontaneous emission, photons are emitted in random directions, so only a negligible portion of them will travel in the x direction.

Intensity–depth relation

- the intensity changes with depth x in the medium according to an equation that is identical in form to the Beer–Lambert law:

$$\frac{\mathrm{d}I}{\mathrm{d}x} = -k(f)I(x),$$

- where $k(f)$ is a combined absorption–emission coefficient defined as

$$k(f) := B_{21}\left(N_1 - N_2\right)\frac{n}{c}hf$$

- with h denoting Planck's constant, n the refractive index of the medium and c the speed of light in vacuum

The potential of amplification I

- the solution of this differential equation is

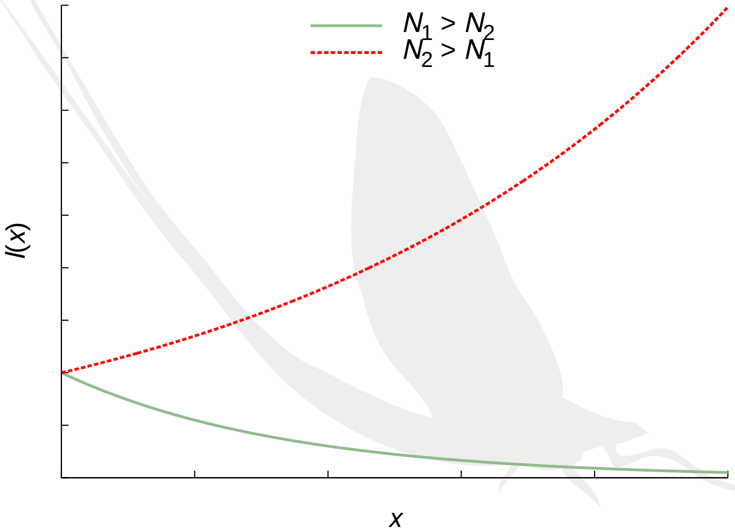
$$I(x) = I_0 \mathrm{e}^{-k(f)x}$$

- usually, when absorption is the dominant process, the intensity decreases in the medium
- but this formula may describe an exponential amplification if $k(f) < 0$
- the sign of $k(f)$ depends on the relative populations of the ground state and the excited state

The potential of amplification II

- if $N_1 > N_2$ (the ground state is more populated), $k(f)$ will be positive and the intensity will decrease in the medium — this is the case when absorption dominates
- if $N_1 < N_2$ (the excited state is more populated), $k(f)$ will be negative and the intensity will increase in the medium ☛ optical gain — this is the basis of laser operation

Optical gain



Population inversion I

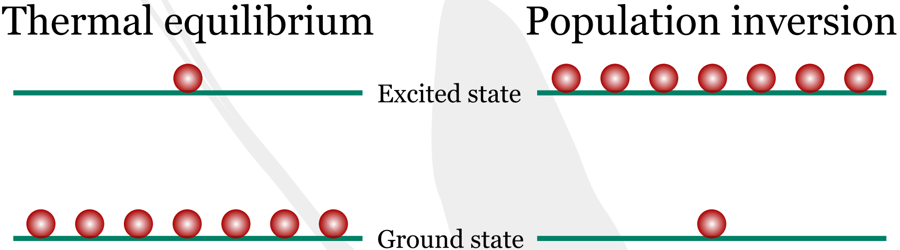
- population inversion: a state of a medium in which more atoms or molecules are in excited state than in ground state
- population inversion is a prerequisite of laser operation
- in thermal equilibrium, the ground state is much more populated than the excited state — from the Boltzmann distribution, it can be shown that

$$\frac{N_2}{N_1} \approx 10^{-35}$$

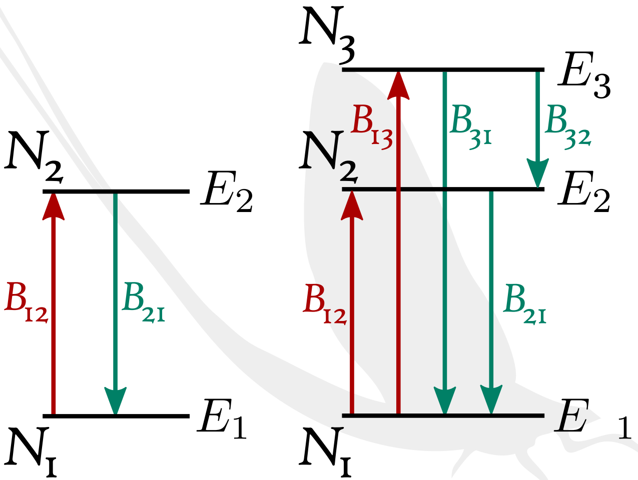
Population inversion II

- to reach population inversion, we must get the majority of the atoms or molecules into excited state, which requires an investment of energy — this is called **pumping**
- during the operation of lasers, the laser system returns some of the invested energy in the form of coherent, collimated laser light
- **active medium** or **gain medium** the medium in the state of population inversion in which stimulated emission takes place — the basis of laser operation

Population inversion



Population inversion problems I



Population inversion problems II

- in **two-level systems,** population inversion **cannot be established**
- $B_{21} = B_{12}$ — the Einstein coefficients are equal, so the more populated the excited state gets, the higher the rate of stimulated emission will be; once the populations of the two levels have become equal, the rate of stimulated emission will be equal to the rate of absorption, so the population cannot be increased further
- in **three- or more-level systems, population inversion is possible,** as the population of the middle state is increased by relaxation from higher levels as well as excitation from lower levels

Pumping types

Optical pumping

the source of energy is a **flash lamp** or **another laser**

Electric pumping

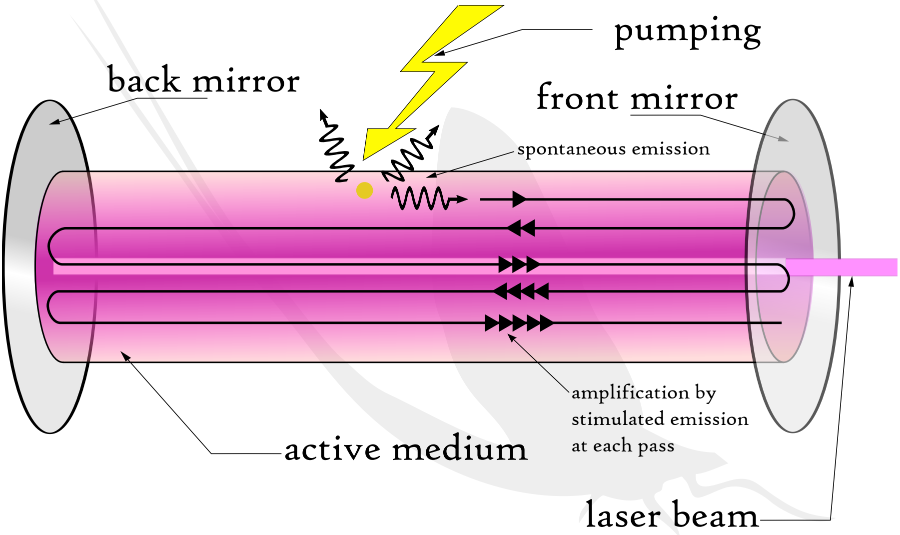
the source of energy is electricity

- electric discharge (in gas lasers)
- electric current (in semiconductor lasers)

Chemical pumping

the basis of pumping is a chemical reaction

Laser oscillator



Laser oscillator I

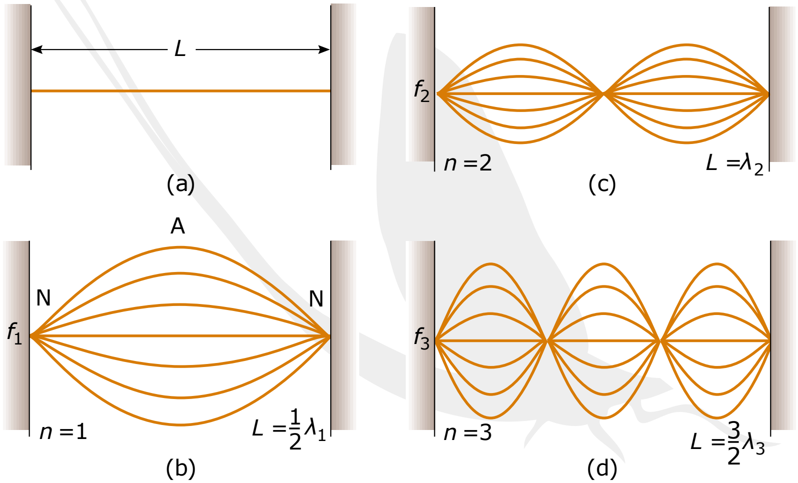
- laser oscillator or laser resonator: the arrangement in which the gain medium is between two mirrors, providing the necessary conditions for laser operation
- the active medium is pumped and it reaches the state of population inversion
- all throughout the medium, spontaneous emission may happen
- the light from spontaneous emission is amplified by the gain medium through stimulated emission

Laser oscillator II

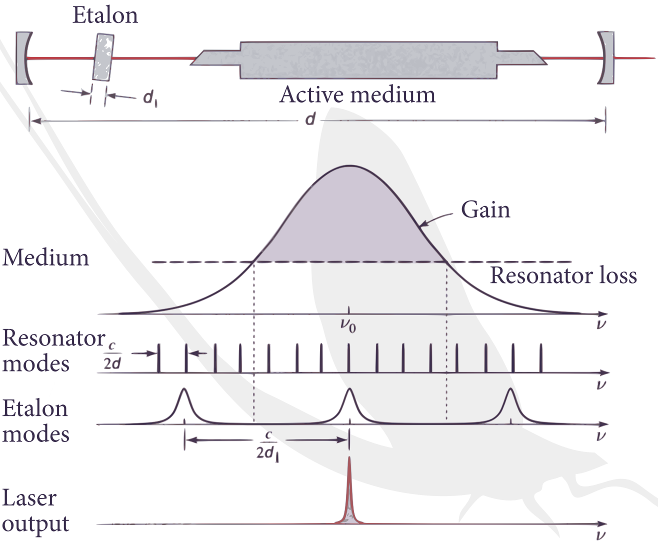
- when the amplified beam reaches one of the mirrors, it is reflected back to the medium, so it is amplified further by stimulated emission in the medium
- the laser beam 'bounces' back and forth between the mirrors, getting amplified in each pass
- one of the mirrors is totally reflective, but the other lets some of the laser beam out — **output coupler**
- **beams off the axis of the resonator will leave the resonator** sooner or later, so only beams exactly in the axis will be amplified significantly ☛ **very low divergence of laser beams**

Resonator modes

The resonator also selects certain frequencies:



Laser modes; tunability



Tuning a laser

- in broadband active media, there may exist several sets of levels in which population inversion can be built up and thus several wavelengths | frequencies at which optical gain is possible
- the laser oscillator selects certain frequencies depending on the distance between mirrors
- an **etalon** is used to select the desired output frequency out of these resonator modes
- tuning a laser: setting the output wavelength | frequency

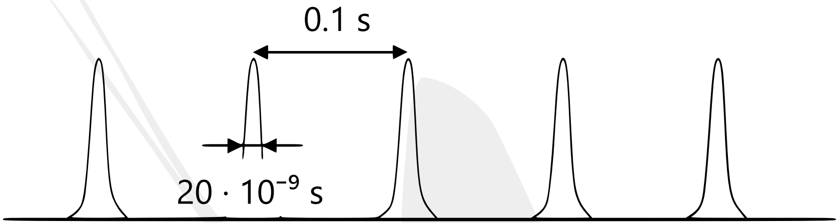
Continuous v pulsed operation I

- in **continuous mode,** laser output is relatively constant in time
- without further arrangements, laser operation will be continuous
- laser operation can be made **pulsed-mode,** in which laser power is concentrated in short pulses, whereas the rest of the time there is no significant laser output

Continuous v pulsed operation II

- ways to achieve pulsed operation:
  1. **mode-locking:** a fixed phase relationship is established between the modes of the laser cavity; pico-, femto- or even attosecond pulses can be produced
  2. **Q-switching:** laser operation is blocked until maximum population inversion is built up, then suddenly released ☛ high peak powers
  3. **pulsed pumping:** the pumping itself is pulsed, so population inversion will exist only part of the time and laser operation will be pulsed

Pulsed operation



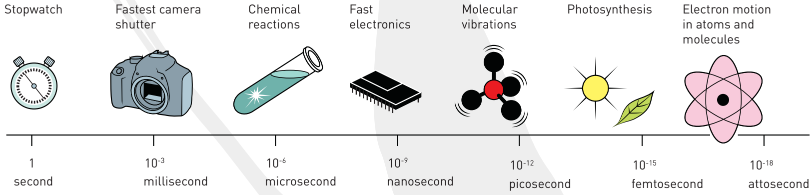
EG Nd-YAG laser with repetition rate $f = 10\,\mathrm{Hz}$, pulse energy $E = 2\,\mathrm{J}$, pulse duration $\tau = 20\,\mathrm{ns}$

Peak power: $P_{\max} = \frac{E}{\tau} = 10^8\,\mathrm{W}$

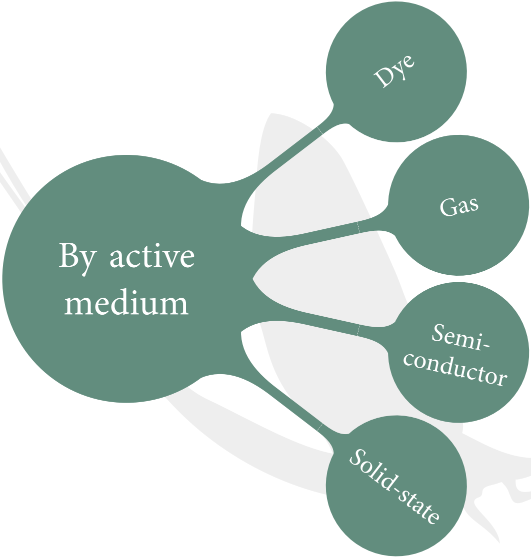
Average power: $P_{\mathrm{avg}} = \frac{E}{1/f} = 20\,\mathrm{W}$

(Paks nuclear power plant in Hungary: $1.86 \cdot 10^9\,\mathrm{W}$)

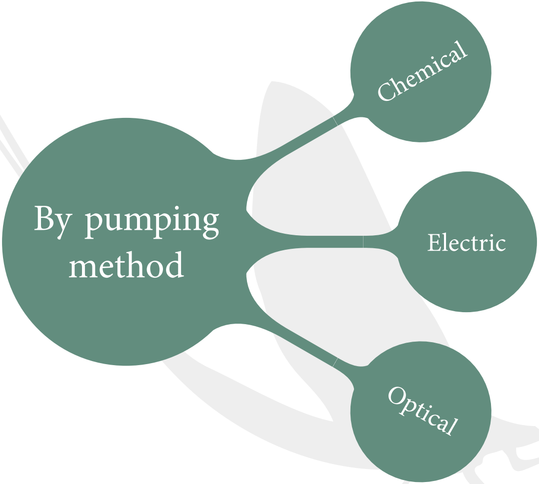
Timescales


Stopwatch
Fastest camera shutter
Chemical reactions
Fast electronics
Molecular vibrations
Photosynthesis
Electron motion in atoms and molecules
1 second
10^{-3} millisecond
10^{-6} microsecond
10^{-9} nanosecond
10^{-12} picosecond
10^{-15} femtosecond
10^{-18} attosecond

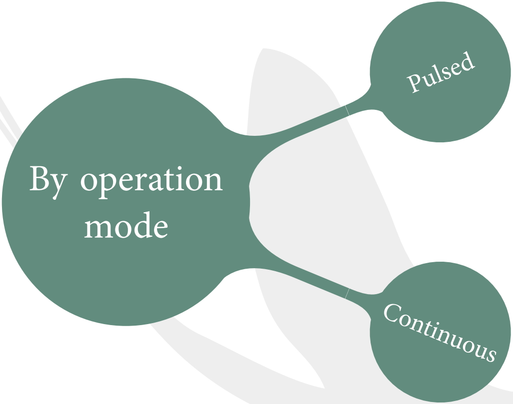
Laser types



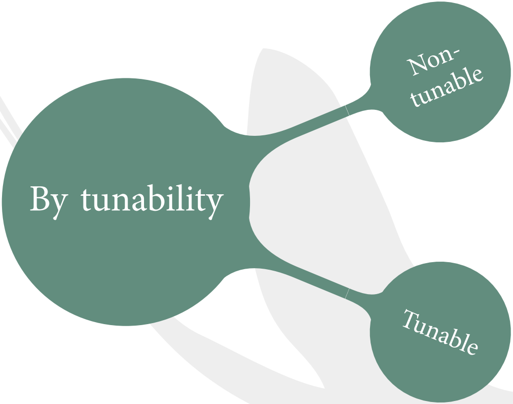
Laser types



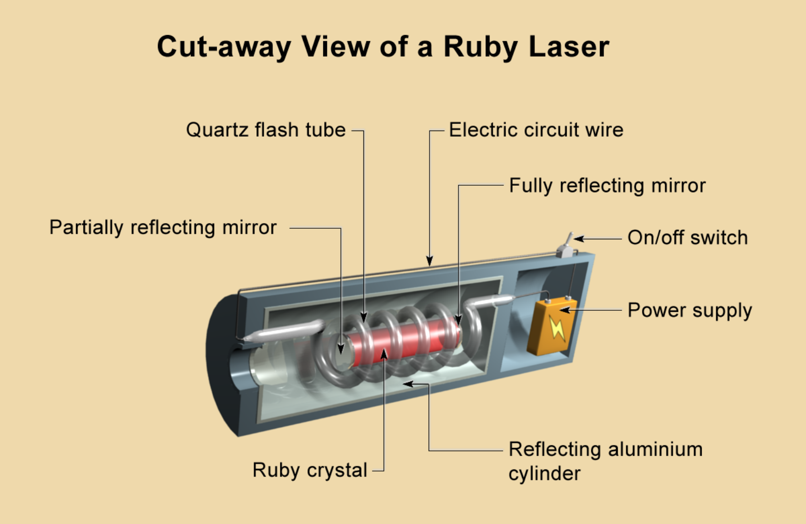
Laser types



Laser types



Solid-state lasers (ruby laser)



Solid-state lasers

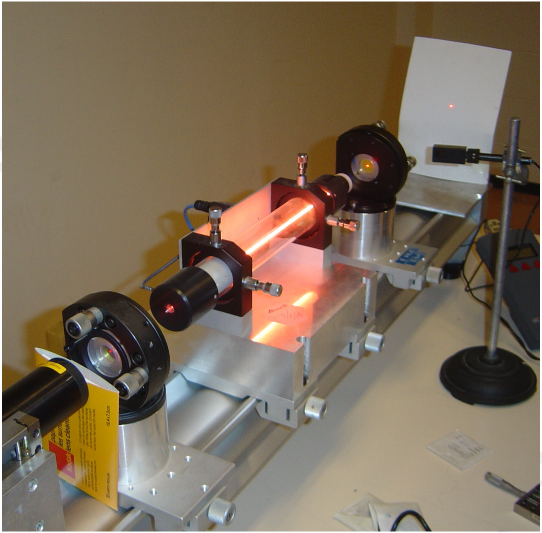
- example: ruby laser, Neodymium-YAG laser (Yttrium Aluminium Garnet)
- active medium: crystals or glasses doped with metal ions
- pumping: optical (flash lamps)
- operation: continuous or pulsed
- usually not tunable
- wavelength range: 600–1000 nm
- uses: in industry, for cutting and welding; medical applications include resurfacing of joints, vaporising kidney and gall stones, removing the rot from tooth cavities

Semiconductor lasers (diode laser)

Semiconductor lasers

- example: GaAs
- active medium: semiconducting crystal
- pumping: electrical current
- wavelength range: 375–1800 nm or even longer
- uses: CD/DVD players, laser printers, laser pointers; high-power variants can also be used for cutting and welding

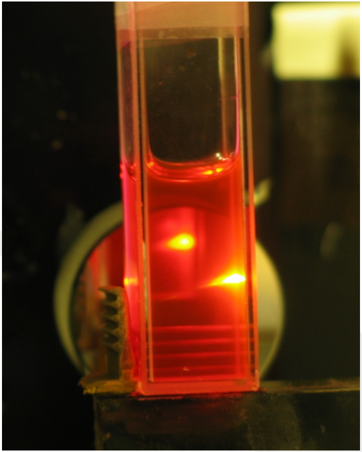
Gas lasers (He-Ne)



Gas lasers

- example: He-Ne, krypton, argon, CO_2 lasers
- active medium: gas or gas mixture
- pumping: electric discharge or chemical reaction
- wavelength range: 600 nm–10 μm
- **excimer** (← **exci**ted di**mer**) lasers: chemical reaction in which the product is only stable in excited state — having emitted a photon, it will dissociate ☛ depopulation of lower-energy state
- uses: industry (cutting and welding); medicine (tumour removal, laser scalpel)

Dye lasers



Dye lasers

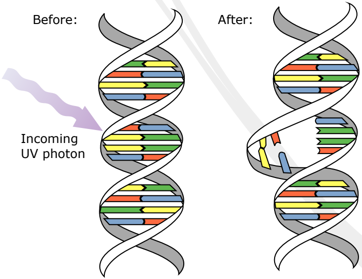
- example: rhodamine 6G
- active medium: organic dye
- pumping: optical (usually by another laser)
- operation: continuous or pulsed
- wavelength range: 400–600 nm
- almost continuously tunable (a few dyes can cover almost the whole visible spectrum)
- uses: gastroenterology, opthalmology

Mechanisms

- **scattering:** the electric field causes electrons in matter to oscillate ☛ they will also radiate; Rayleigh: $P_{\text{scattered}} \propto \lambda^{-4}$; important in plethysmography and flowmetry
- **absorption:** the energy of the photon gets absorbed by the particle; an electron gets in excited state
  - nucleic acids, aromatic amino acids absorb in UV
  - haemoglobin, melanin, carotin, bilirubin: absorb in the visible range
- **relaxation:** after absorption, absorbed energy is released

Biological effects of light

Mechanisms of relaxation



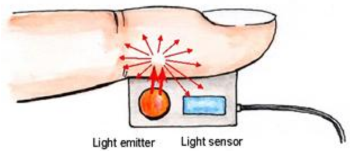
- emission of light ☛ spectroscopy (fluorescence, phosphorescence)
- transformation into thermal energy ☛ vaporisation, carbonisation
- photochemical reaction: eg, dimerisation of thymine by UV light ☛ DNA point mutation

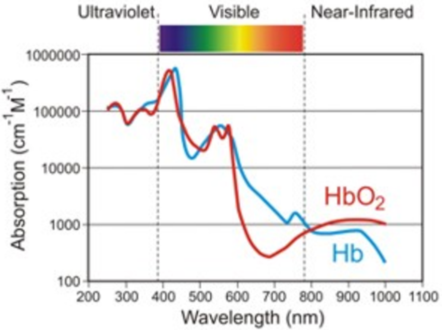
Laser spectroscopy

- small divergence ☛ focusability ☛ increased spatial resolution
- tunability & narrow bandwidth ☛ increased spectral resolution
- short pulses ($< 10^{-12}$ s) ☛ increased temporal resolution

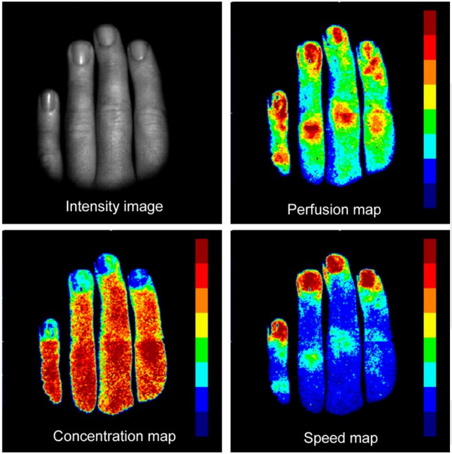
Plethysmography

light absorption depends on blood volume and oxygenation



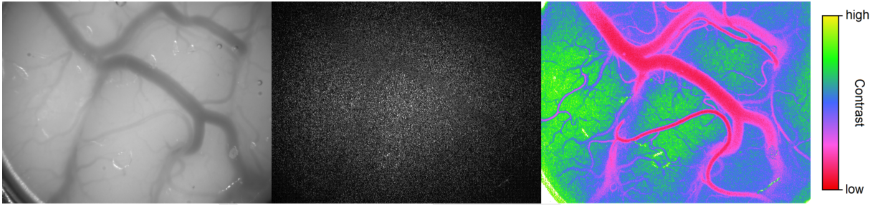


Laser flowmetry



- Doppler effect: the frequency of the wave reflected from a moving particle (eg, red blood cell) is shifted with an amount proportional to the relative speed
- narrow bandwidth of lasers ☛ the shift can be more accurately determined

Laser speckle flowmetry



- laser light is coherent ☛ interference pattern in scattered light (speckle)
- light scattered from moving particles ☛ the speckle gets blurred ☛ the blurring is proportional to the speed of the particles

Mechanisms 1

- absorption of laser photons
- followed by relaxation
  - radiative
  - non-radiative: heat
- types of effects:
  - *laserthermia:* < 40°C; no tissue damage; acceleration of diffusion and metabolism
  - *coagulation:* 60–90°C; cell destruction; stopping blood circulation
  - *vaporisation:* 100–150°C; boiling of water; rapid volume expansion
  - *carbonisation:* > 300°C; most often used in cutting and eliminating unwanted tissue

Mechanisms 2

- molecules excited by light can be involved in *photochemical reactions* ☛ photodynamic therapy
- photon energy high enough to break molecular bonds: *photo-dissociation*; breaking down molecules into atoms: *atomisation* ☛ laser cutting largely based on this
- non-linear effects above $\approx 1\,\mathrm{TW/cm^2}$: multi-photon effects, cascade ionisation
- strong ionisation: plasma is generated – this expands rapidly and might trigger a mechanical shock wave of GPa amplitude ☛ *photo-mechanical effect*

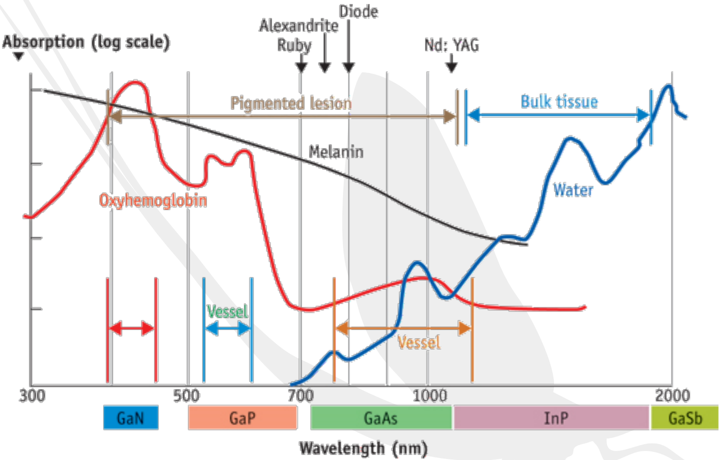
Applications

- *laserthermia:* ulcers, open wounds, muscle strains, nerve injuries
- *coagulation:* staunch bleeding, cure blood vessel proliferation
- *vaporisation:* tissue lesion, cutting, ablation of stones — but not for tumours as cells may spread
- *carbonisation:* cutting tissue and coagulating blood vessels around

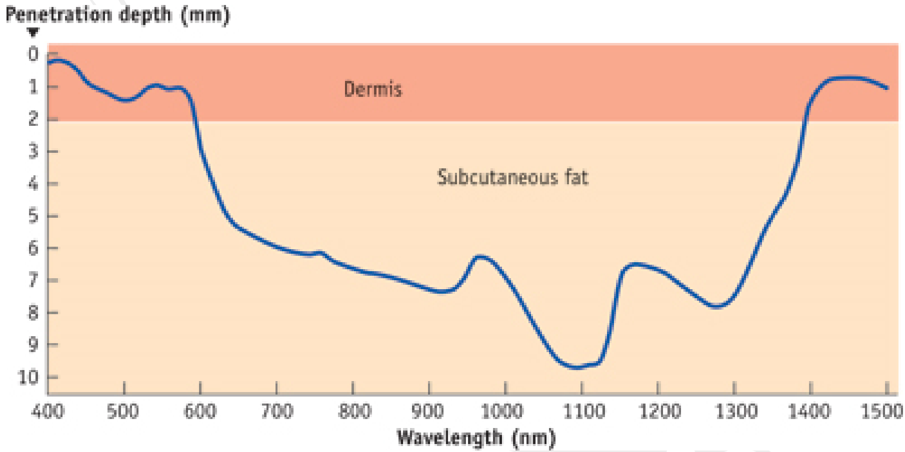
Factors to consider

- target chromophore: which light absorbent in the tissue we target
- main chromophores: haemoglobin, melanin and water
- laser wavelength (and thus laser type) must be chosen according to the target
- penetration depth: wavelength-dependent
  - UV: shallow penetration; suitable for surface or near-surface treatment
  - red, near-infrared: deeper penetration

Main chromophores



Penetration depth



Advantages of surgical lasers

- can be directed with high precision
- no touch ☛ reduced risk of infections; also sterilises
- coagulation ☛ closing up blood vessels ☛ reduced bleeding
- sharp wound edges
- easier, faster and more aesthetically acceptable healing
- blood clotting in neighbouring vessels ☛ reduced risk of tumour cell scattering

Surgery of inner organs I

- using a rigid or flexible endoscope (the former with lenses, the latter with fibre optics)
- invisible lasers (eg, infra-red): a targeting visible laser alongside
- collimation, targeting: computer-controlled micromanipulators
- primary mechanisms: vaporisation or carbonisation
- treatment of bleeding gastric ulcers: with coagulation
- interstitial laser-photocoagulation (ILPC): laser light is directed into the tumours of parenchymal organs (eg, liver)

Surgery of inner organs II

- kidney or gall bladder stones: laser ablation, photomechanical scattering
- treatment of herniated discs: percutaneous laser disc decompression – fibre optics through a thick syringe; Nd:YAG or Ho:YAG laser to ablate the protruding part

Lasers in opthalmology 1

- retinopathy
  - hypoxic tissues produce angiogenetic factors ☛ vessel proliferation
  - treatment: coagulate proliferated vessels and hypoxic tissues with laser
- retinal detachment: generate scars to stabilise the retina
- glaucoma
  - high intraocular pressure
  - the laser coagulates the trabecular meshwork at the base of the cornea ☛ increased fluid outflow ☛ reduced intraocular pressure
- these are mainly based on the coagulation effect
- cataract surgery

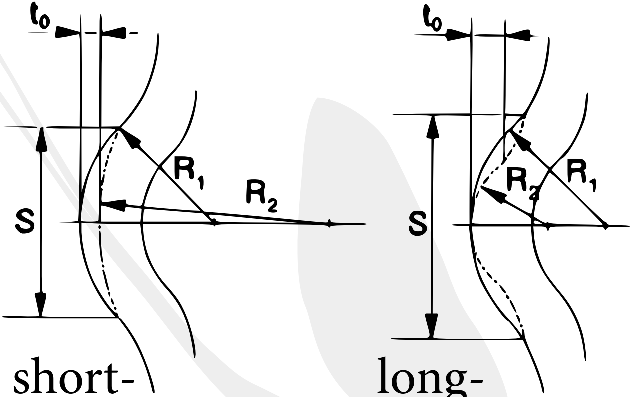
Refractive surgery

- cornea: $^2/_3$ of refractive power (P)
- short-sightedness: P too high
- how to reduce it? $\leftarrow$ lensmaker's equation ☛ reduce the curvature

$$P = \frac{1}{f} = (n-1)\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

- lasers to flatten the middle region
- long-sightedness: P too low ☛ ditch around the periphery ☛ increased curvature ☛ increased P

Refractive surgery



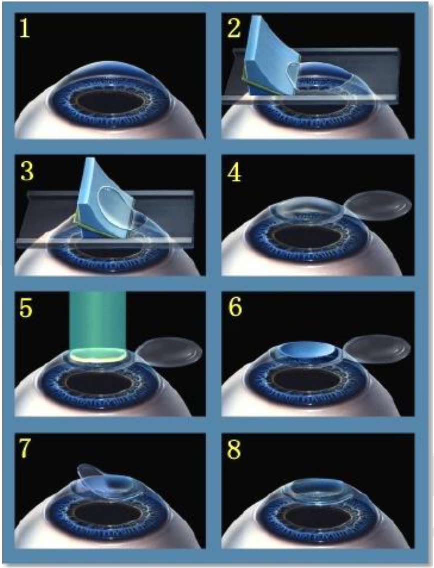
short-sightedness long-sightedness

CORRECTION

PRK, LASIK and LASEK

- cornea: stroma beneath the epithelium
- photorefractive keratectomy (PRK): epithelium removed, stroma shaped; the epithelium later regrows
- laser-assisted *in-situ* keratomileusis (LASIK): the epithelium is flapped back (using a mechanical device or a laser), the stroma underneath is shaped by the laser, then the epithelium is folded back
- laser epithelial keratomileusis (LASEK): like LASIK, but the flap is much thinner
- first CO_2 lasers, then Nd:YAG, then excimer lasers
- primary mechanism: atomisation

LASIK



Lasers in dermatology

- treatment of shingles, herpes simplex, ulcers, psoriasis
- blood vessel treatment; 'spider's vein' treatment by closing the feeding vein
- epilation
- wrinkle reduction
- tattoo removal

Haemangiomas

- result of excess capillary formation
- treatment: coagulating the capillaries

Lasers in dentistry

- mechanical drills cause vibration in the whole tooth ☛ pain
- use lasers (eg, Er:YAG) to ablate decayed regions
- problem: heat generation also causes pain ☛ advantage of pulsed lasers: less time for heat generation and dissipation
- tooth whitening: bleaching agent activated by lasers, 3-4 shades of whitening
- seal tubules that are responsible for hot and cold sensitivity

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