Lasers and their biomedical applications

The text under the slides was written by

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LASERs

and their

biomedical applications

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Textbook pages:	Interconnection with other lectures:
126-131	Lect. 3. Fluorescence applications
134-137	Lect. 5. Scanning image formation in microscopy
141-144	Lect. 24. Flow cytometry, confocal laser scanning microscopy
533-539 !	Lect. 27. Modern microscopic techniques
541 !	

What do lasers give us?

What is a laser?

- A coherent monochromatic light source capable of delivering high photon energy into a defined small spot over a short time
- Light Amplification by Stimulated Emission of Radiation

What can we do with lasers?

- Biomedical research
- Laboratory diagnostics
- Clinical diagnostics
- Soft laser therapy
- Laser surgery
- Photodynamic therapy
- Cosmetology
- Other non-excelusively biomedical uses
  - data processing, transfer and storage (printers, holography, CD/DVD/Blu-Ray, fiberoptics)
  - measurement, localisation and aiming devices
  - industrial applications

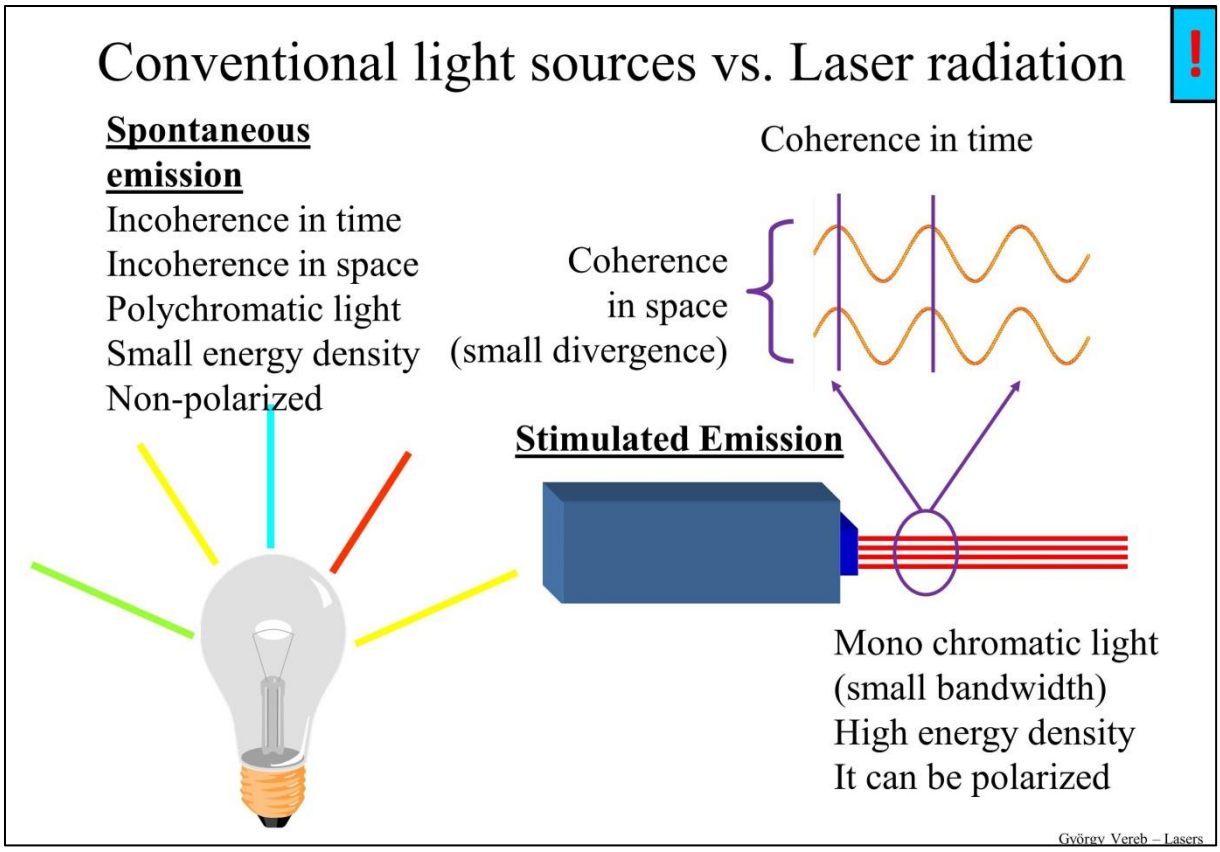
What do we learn today?

- The principles how lasers work
- The different types and characteristics of lasers
- How lasers interact with material
- What medical applications are based on these interactions

Aim: To understand

- how various lasers work and what kind of radiation they produce
- how (and why) different lasers can be used for different medical therapeutic interventions

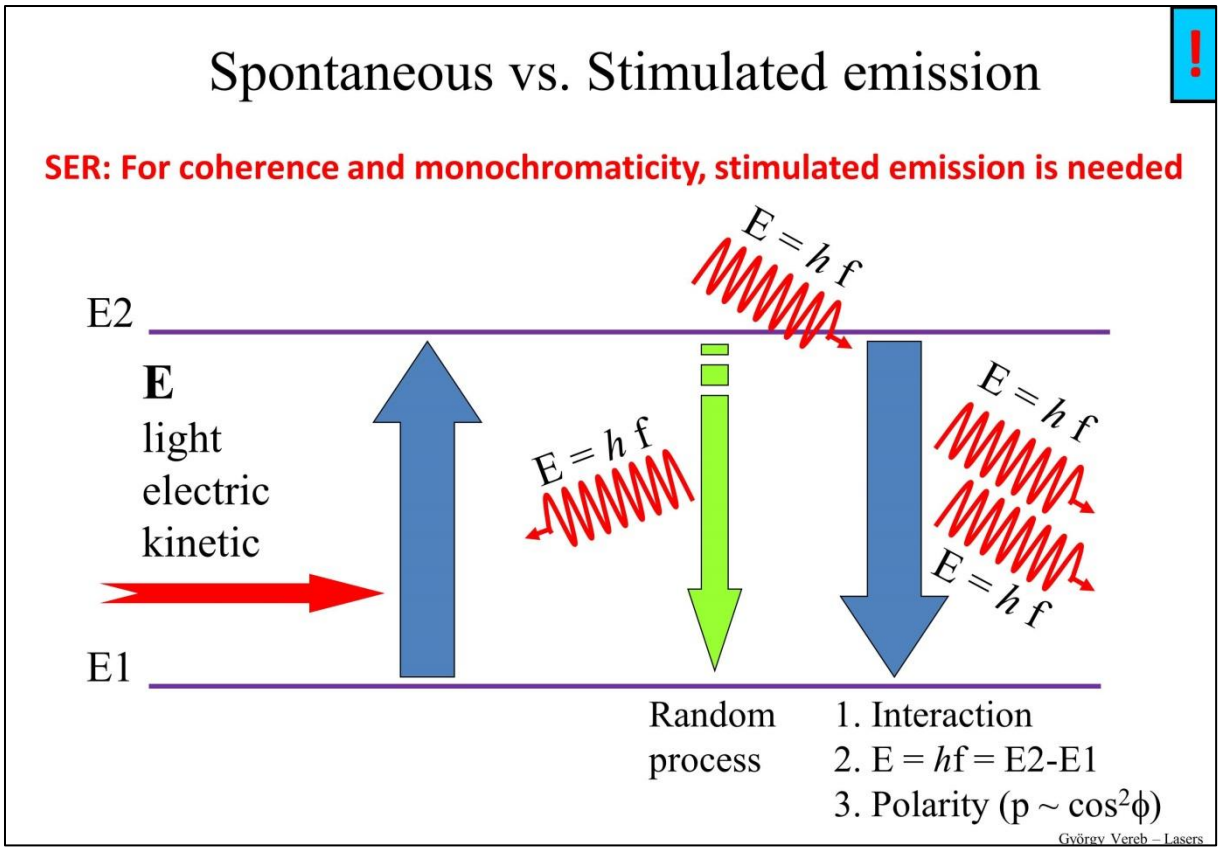
- The name LASER stands for Light Amplification by Stimulated Emission of Radiation
- In the first part of the presentation, we strive to understand how lasers work, why stimulated emission of radiation is needed and how light amplification can be produced. We also mention some examples of lasers used in biomedical applications
- In the second part we study how laser light can interact with material and learn some examples of medical applications that are based on these interactions



- Conventional light sources emit photons at random times unrelated to each other (incoherence in time) and in various directions (incoherence in space). Furthermore, the wavelength of emitted photons varies (polychromatic light). These all lead to destructive interference of photons arriving at the target spot. In general, the energy density is not very high either, and decreases with the square of the distance from the source. Overall, the energy that can be absorbed by a spot targeted by the light is very small compared to the energy emitted by the light source.
- Additionally, the light emitted from conventional light sources is usually not polarized (the angle between the electric field vector of the photons and a reference axis perpendicular to the direction of propagation varies from photon to photon).
- As opposed to spontaneous emission of photons from conventional light sources, laser light is characterized by coherence in space and time (photons going in the same direction and the peaks and troughs of their waves coinciding). Photons are also of (nearly) the same wavelength, so if they are coherent in time upon emission, they keep this coherence over a long distance. (The distance over which the first destructive interference can be observed is the coherence length. This can be very long, even in the km range, given that the differences in wavelength are very small – the range of wavelengths observed is called the bandwidth. The small differences are caused by the uncertainty principle which relates energy and time in the same manner as speed and distance, the product of their uncertainties being $\leq h/2\pi$.) As opposed to lasers, the

coherence length for photons emitted from conventional light sources can be a few ten centimeters only.

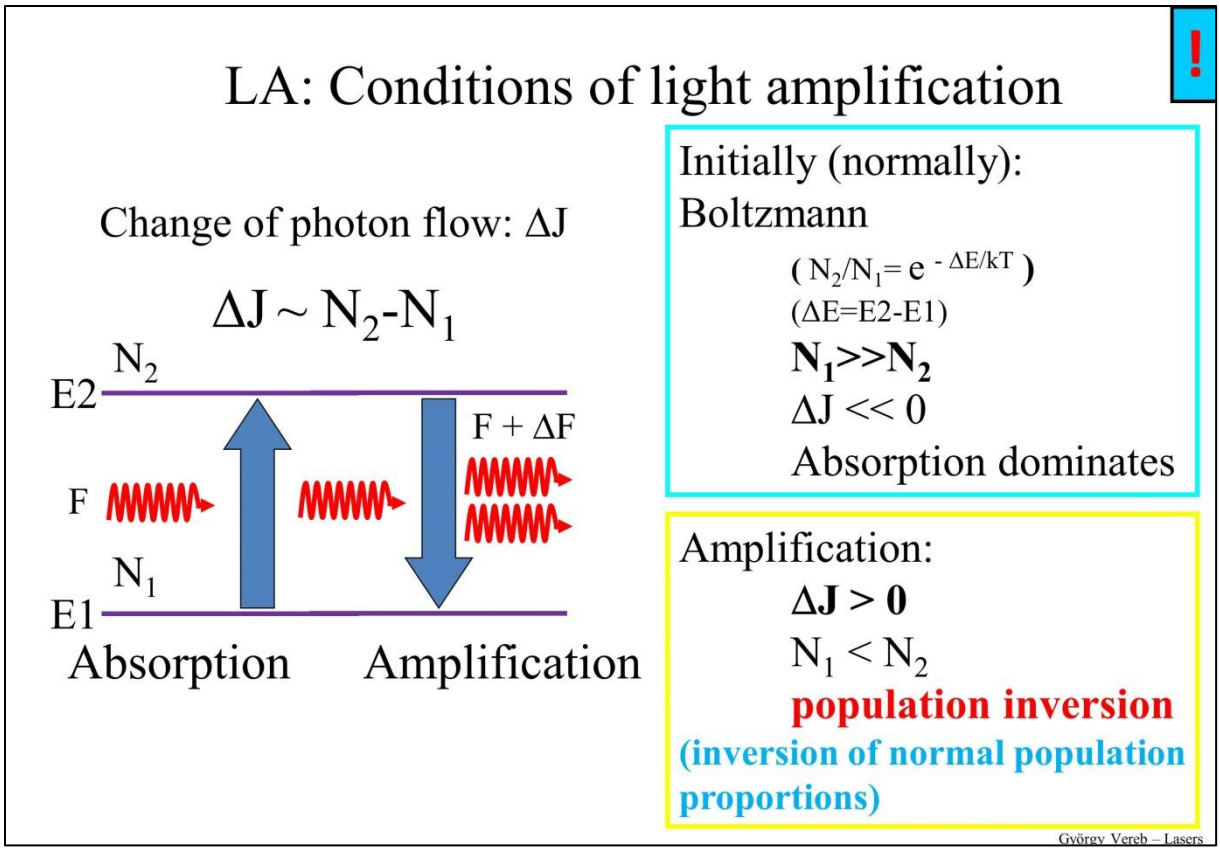
- These properties allow the delivery of a large fraction of the energy of emitted photons into a targeted spot.
- Depending on the technical solutions applied, polarized laser emission can easily be generated without excessive additional loss of energy. (A single photon is always polarized!)



- To understand how laser light can be generated, we need to first remind ourselves of what happens to an excited state that can relax by emitting electromagnetic radiation. After excitation by some form of energy of the particle in E1, the instability of the excited state E2 (striving to minimize energy) results in spontaneous emission of a photon by the particle. (Of note, these E1, E2 levels do not necessarily correspond to the S0 and S1 levels described in the Jablonski diagram – see fluorescence, but in many cases, they do.)
- The spontaneously emitted photon is emitted at a random time after excitation (these times distribute around the excited state lifetime, i.e. in a nanosecond range) and propagates in a direction defined by the orientation of the emitting particle (which in fluids and gases can freely rotate before spontaneous emission occurs). This gives rise to timewise and spatial incoherence of the bulk emission from the material. If there are more excited energy levels, the emission will also be polychromatic, with wavelengths corresponding to the various energy differences between levels.
- However, if a particle is still in excited state and is hit by a photon of appropriate properties, it will undergo stimulated emission. The photon hitting the particle is called a perturbing photon as it abruptly ends the temporary existence in excited state which otherwise could have lasted longer, until spontaneous emission would have happened. This photon needs to carry the same energy as the energy difference of E2 and E1, so it follows that the stimulated photon and the perturbing photon will be of the same energy, which is the key to monochromatic emission in lasers. The other conditions that must

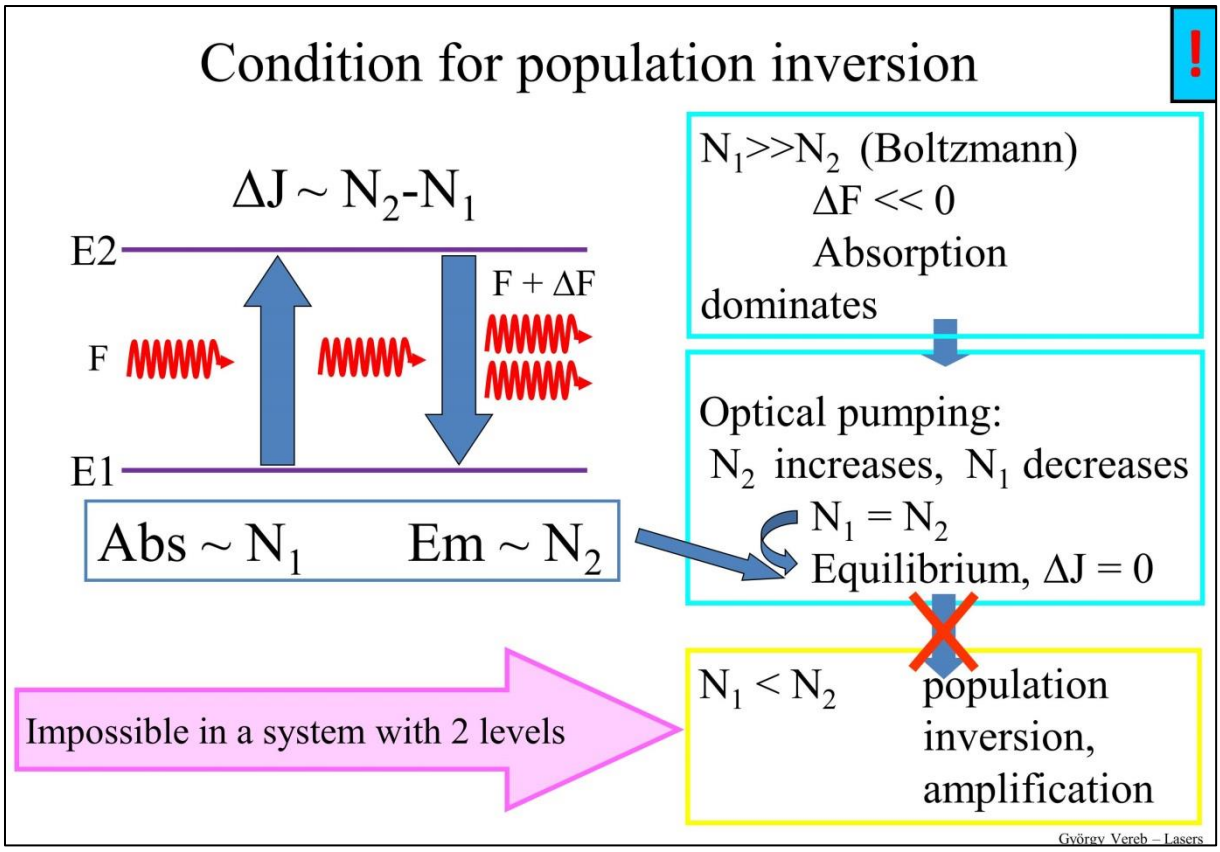
hold are the physical interaction of the excited state and the perturbing photon, and a polarity condition. The latter means that the emission dipole vector (the vector connecting the most positive and most negative points) of the excited particle and the electric field vector of the perturbing photon should be closely parallel (in more precise terms, the probability of stimulating the emission is proportional to the cosine^2 of the angle between the two vectors). This polarity condition allows the generation of polarized laser light.

- Finally, we must note that stimulated emission does not only yield one more photon (of the same wavelength) in addition to the perturbing photon, but this second, stimulated photon will propagate in the same direction and in the same phase as the perturbing photon – the keys to spatial and temporal coherence in lasers. The perturbing photon is not affected by the perturbation event in terms of either its direction of propagation or its energy or polarization.
- Summarily, we conclude that stimulated emission of radiation is the key to creating pairs of photons that are the same wavelength and coherent.



- So far, we have generated a coherent monochromatic group of photons made up of two members. We need more, so we need amplification – hence LA (light amplification) in the name of lasers.
- Examining the conditions for light amplification, we first observe that in a system with two levels, E1 and E2, there are only two routes a particle can take: if it is in E1, by absorbing a photon with energy corresponding to the difference of E2-E1, it will go to E2, that is, it will be excited. However if it is in E2, meeting the photon will stimulate emission and de-excite the particle. In the first case, a photon going through the laser material (emitted previously from one of the laser's particles) will be absorbed and lost. In the second case, it will stimulate emission and will be doubled.
- Since the probability of both events (quite unexpectedly) is the same provided the particle has encountered the photon, the expected fate of photons in the laser material depends on the proportion of E1 to E2 state particles. Mathematically this translates to the ΔJ change of photon flow (J: flux, number of photons per unit time) over a unit distance being proportional to N2-N1, the difference of the number of particles in E2 and E1.
- For materials in equilibrium, the proportion of N2/N1 is given by the Boltzmann formula. For materials at regular temperature, N2/N1 is extremely small, so N2-N1 is negative, which implies that (mostly spontaneous) photons emitted by the laser material will be preferentially absorbed, so no amplification can occur.

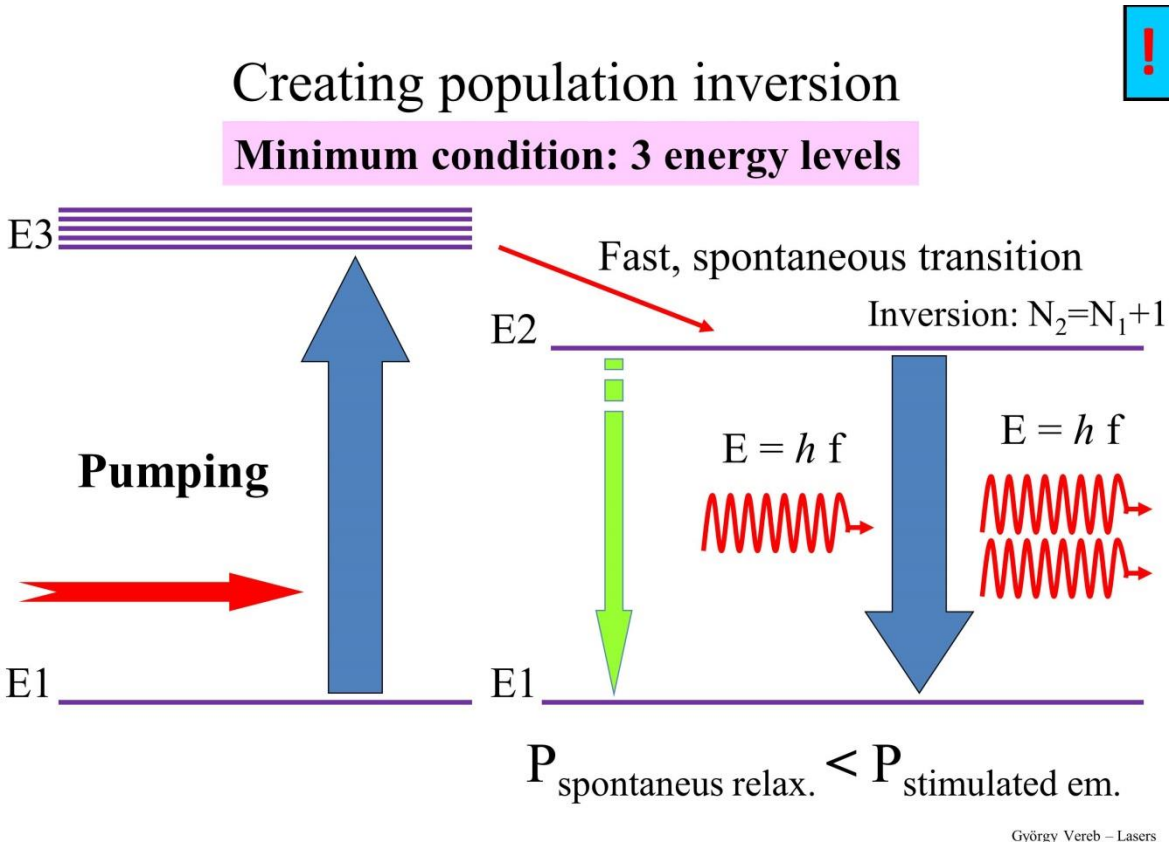
- For amplification to occur, this N2/N1 ratio of the two populations must be turned around (inverted), sot that N2>N1, and N2-N1>0. This turning around of normal population proportions is termed population inversion.



- For the sake of a thought experiment, let us try to invert the population in this two level system of E1 and E2. Inversion would mean exciting particles in E1 to go to E2 until there are more in E2 than in E1. For this, let us suppose that we can have unlimited access to photons of the proper energy and use these photons to excited particles in E1. This is called optical pumping.
- When we reach N1=N2, the chances of the next photon hitting E1 or E2 state particles are 50%-50%. At this point each photon will either get absorbed or double with equal chances, depending on whether it met an E1 or an E2 particle.
- This means that on average, out of two photons going through the material, one will be absorbed and one will be doubled, so if two go in, on average two got out. By extension of the idea, if 2000 photons go in, roughly 2000 come out, implying that there will be an equilibrium and no further loss of photons (as at the starting of the thought experiment when absorption dominated), but there will also be no population inversion and amplification, no matter how strong optical pumping is.
- Taking a somewhat philosophical approach, we can say that in a system with two levels it is not possible to reach inversion. The reason for this is that particles can only change their energy state in one way – from E1 going up and from E2 going down – and it is the very same device, the photon of the proper energy, which can cause this transition. It is as if we had a single straight rail track for a train between point A and B. The same train can only go from B to A if first it went from A to B. So on average the number of trips in

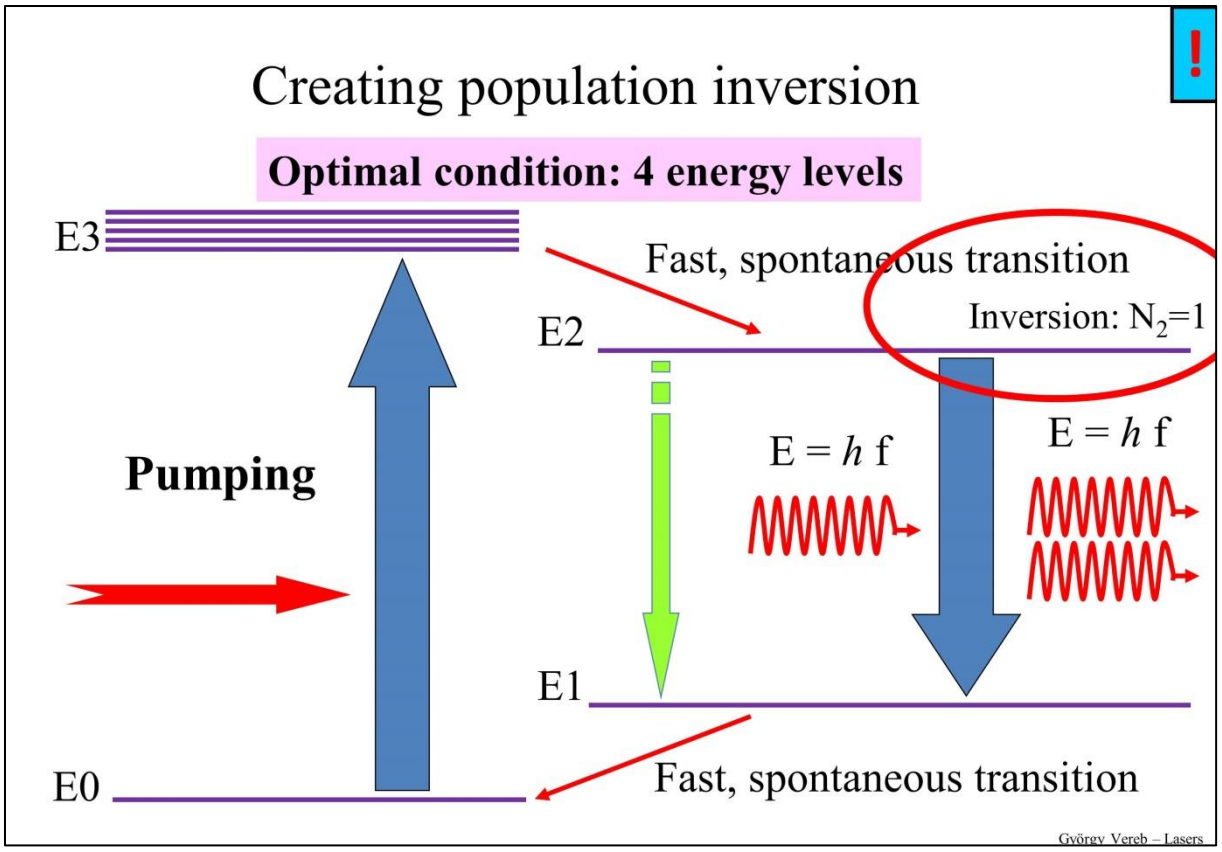
the two directions will be even, making the train appear in A and B equal times. However, for amplification and population inversion – by analogy – we wish to have the train always to start from B, and always travel from B to A on this track.

- Can we solve this train problem? Of course. We need to build a rail from A to a third point, C (off the straight rail between A and B), and continue the rail from C to B. Then the train can always come from B to A, and take the route back through the third point, C, without going in the "wrong" direction on the rail between A and B. Let us see how this can be implemented for a particle.



- Now we have an energy level system with 3 levels, E1 and E2 from the previous two level case, and E3 added, as an analogy to point C in the railway example. E2 is called the laser excited state, and E1 the laser ground state. Spontaneous and stimulated emissions occur in E2 and take the particle to E1.
- From E1, it takes a larger energy packet for pumping – exciting – to E3. The form of energy input can be various and should match the material. Since we use an energy packet size for pumping which is different from that of the photon arising in the E2-E1 transition, we have no crosstalk between driving the process of ”going up” and ”going down”.
- For having enough time for particles to gather up in E2, the lifetime of E2 must be relatively long (metastable level). This means that spontaneous emissions will occur less frequently, and most de-excitations can occur through stimulated emissions.
- Conversely, lifetime of E3 should be short, so that at any given moment only a few particles are in E3, and E3 is used to quickly fill E2.
- E3 is represented by a multitude of nearby lines, as the possibility to excite from E1 to one of many similar E3 levels increases the efficiency of pumping – the pumping energy packets do not have to be exactly the same size.
- Relaxation from E3 to E2 generates heat (during the fast, spontaneous transition). Some lasers need very intensive cooling to take this heat away, others, particularly diode lasers are more energy efficient and produce very little heat.

- E1 here is the absolute ground state and also the laser ground state, and is stable.
- In summary, we need minimally three energy levels for population inversion to occur.
- One needs to consider that population inversion only occurs if half of the total number of particles plus one is in E2 (so N2>N1, minimally N2=N1+1). This is not very economical, as the majority of all the particles needs to be pumped using a lot of energy for population inversion to occur.



- The previously mentioned issue of being economical can be solved by a 4 level system which is the optimal condition for creating population inversion.
- Here, we have one more level, E0, which is the absolute ground state, while E1 remains the laser ground state.
- E2, the laser excited state should be metastable also in the 4 level system. E3 also here needs to be short-lived.
- But also E1 must be short-lived, so particles that arrive to E1 while producing photons do not stay there, rather immediately relax to E0, which is stable. This relaxation usually produces heat, which needs to be dissipated.
- In this scenario E1 is always virtually empty, so pumping a single particle from E0 to E3 causes this particle to quickly end up in E2 and cause inversion relative to the empty E1. This makes the system far more sparing on pumping energy compared to a three level system.
- It is important to note that we cannot introduce the extra E3 and E4 levels into to the initially described system where the material had two energy levels. Materials that comply with the minimum and optimal requirements for inversion (and therefore amplification), including the number of levels and their relative lifetimes, must be identified among naturally occurring substances, generated artificially from more complex atomic/molecular systems.

So, to summarize.....

Which four basic properties distinguish lasers from conventional light sources?

- Coherence in space
- Coherence in time
- Monochromaticity
- Polarized

Which photophysical phenomenon provides for these properties?

- Stimulated emission

What are the condition(s) that make stimulated emission possible?

- Photon interacts with excited electron
- Energy of photon equals the energy liberated when this electron returns to a lower energy level
- Polarity of the photon is appropriate

Why do we need population inversion for a laser to operate?

- To achieve amplification

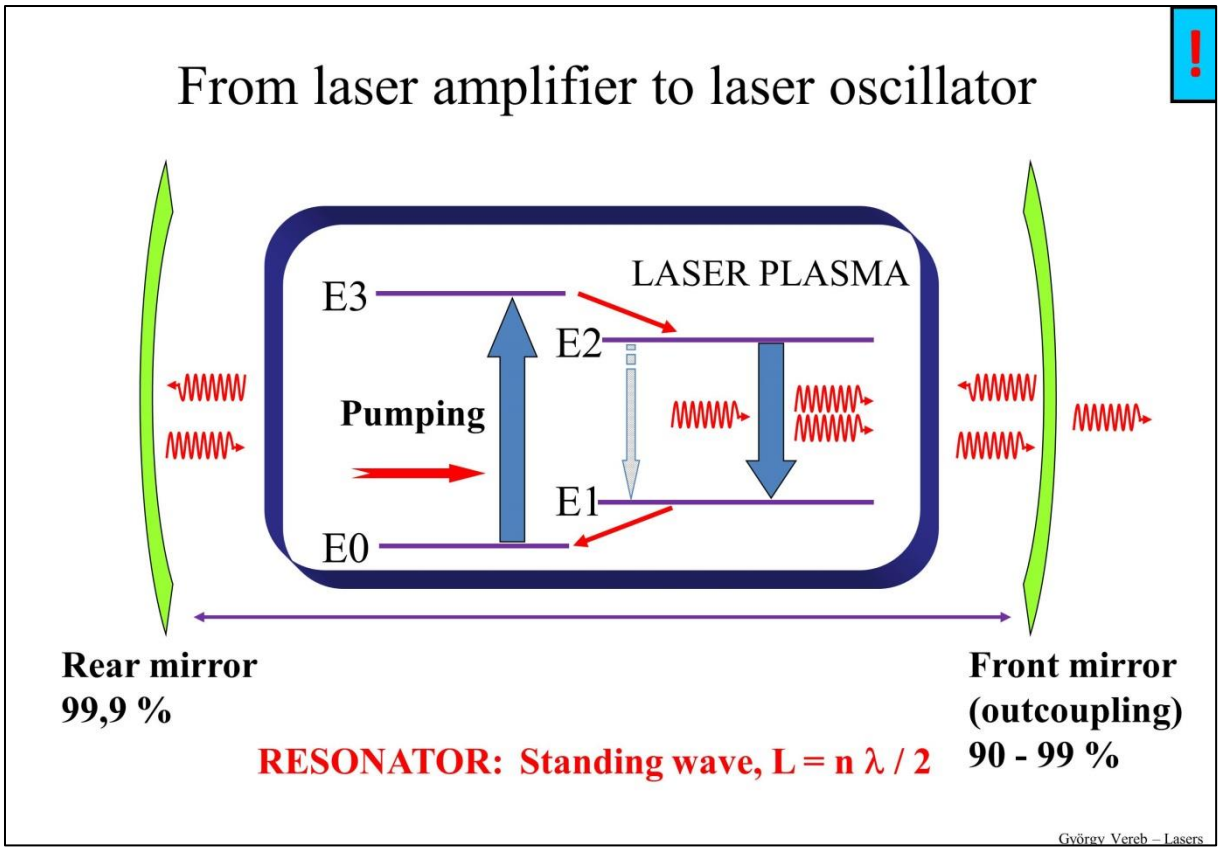
What's the minimal and what's the optimal condition for population inversion? (should also be able to draw the relevant figure)

- Minimal: 3-energy-level system
- Optimal: 4-energy-level system

What else is needed for population inversion, when at least the minimum condition holds?

- Pumping

- The slide summarizes the main ideas discussed so far.



- The principles discussed so far give the foundation for creating a laser amplifier. In a system where a laser material can be pumped to population inversion (usually creating plasma state in gaseous materials), and then spontaneously emitted photons colliding with excited state (E2) particles, which are in majority, generate, by stimulated emission, more photons coherent with them and of the same energy. Then these photons can again stimulate emissions and produce and amplification cascade until the coherent group of photons leaves the laser material.
- One must realize that each coherent monochromatic group of photons generated by a spontaneously emitted photon will propagate in the direction where the spontaneous photon was originally heading to. Since excited particles can occupy versatile spatial orientations in the laser material, spontaneous photons are emitted in all directions, and thus from a laser amplifier the coherent groups of monochromatic photons also propagate in all directions of space. This is not very useful for the targeted investment of energy by way of photons, so a laser oscillator is created to be able to select a single direction of light propagation.
- The laser material is placed between two mirrors that are placed at a distance, which allows the production of a standing wave and is therefore called a resonator. The distance between the mirrors should be the exact multiple of the half wavelength of the light emitted from the E2-E1 transition.

- The standing wave consists of photons coming and going between the two mirrors (hence the name oscillator), in constructive interference with each other. Consequently, the stimulated photons they give rise to in their path also join the standing wave since they propagate in the same direction as the perturbing photon and are in phase with it.
- Since this standing wave constantly amplifies, any other group of photons generated by spontaneous emissions that are not in phase with the standing wave is destroyed by destructive interference.
- In a simplified approach, we could say that groups of photons propagating at angles to the central axis between the mirrors do not return from the mirrors on the same path that they arrived on, so cannot form a standing wave. (In reality, it is possible to have more than a single standing wave along the central axis, such lasers have multiple „modes", which can either be suppressed, or separated into multiple beams.) Photons at extreme angles hit the wall of the laser device and not the mirrors, and thus do not give rise to standing waves.
- To be able to use the laser light, one of the mirrors needs to be imperfect – it should randomly let a certain fraction of photons through, rather than reflecting it. This mirror is called the outcoupling mirror.
- The transmittance of the outcoupling mirror has to match the gain factor of the laser material. In broad terms, if a photon coming and going between the two mirrors is able to stimulate in one round trip the emission of the second photon with, e.g., 1% chance, the outcoupling mirror should only let out that extra 1% and reflect the rest of the photons to replenish this loss in the next round.

Some types of lasers

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State	Material	pumping	λ (nm)	output	E (W)	t (ns)
gas	He-Ne	electric pulse	633	c.w.	0,1	
	Ar++	electric pulse	488, 514	c.w.	100	
	Kr++	electric pulse	657 752	c.w.	3	
	CO2	electric pulse	10600	c.w.	30	
	Excimer (ArF, XeCl)	electric pulse	193, 308	pulsed	10 MW	1-3
liquid	dye	laser light	various	pulsed/c.w.	3	
	dye (Rh 6G)	laser light	600	pulsed	10000	1 fs
solid	Ruby (Cr+++ & Al2O3)	flashlamp	694	pulsed	200 MW	100
	Nd-YAG	flashlamp	1065	pulsed	1 MW	10
	Nd-YAG / KTP	flashlamp	532.5	pulsed	2 MW	10
	Nd-YAG	Xe lamp	1065	c.w.	60	
	Er-YAG	flashlamp	2900	pulsed	1 MW	10
Diode	GaAs	current	840	c.w. / pulse	5	HF
	AlGaAs	current	760	c.w. / pulse	50	
	GaInAsP	current	1300	c.w. / pulse	20	

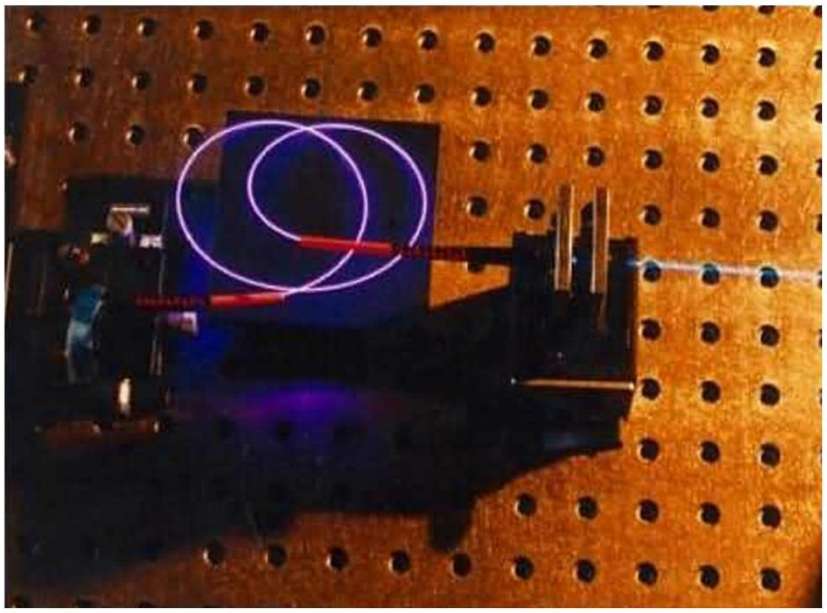
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- Most of the lasers used in medicine are gas and solid lasers, however, nowadays diode and solid state lasers gain popularity for their relatively easy handling and good power economy. For the same reason, liquid (dye) lasers have never been very popular, as their handling is cumbersome and they need another laser for pumping which makes that both complicated and uneconomical. (On a side note, many of the dyes used are carcinogenic.)
- In terms of pumping, the nature of the laser material defines the optimal or only possible mode.
- The emitted wavelength is a major factor that defines the range of possible applications (see more later). In addition, some laser materials can emit more than a single wavelength, which implies that they have more than one level with properties of the E2 laser excited state.
- Laser output may be a continuous electromagnetic wave (c.w.), or pulsed. In this latter case, the pulse length and the repetition rate affect the applicability (fs: femtosecond, HF: high frequency).
- The total power output can be vastly different for various types of lasers. The table shows the high end powers, rather than the generally used ones.
- It should be considered that the momentary intensity of a pulsed laser that lases for only 1 ns in every 10 ms is 10 million times greater than that of a c.w. laser with the same total output power.
- Laser energies should not be confused with the *hf* per photon energies.

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Guiding laser light

Visible laser: mirrors, fiberoptics (coupling with lenses)

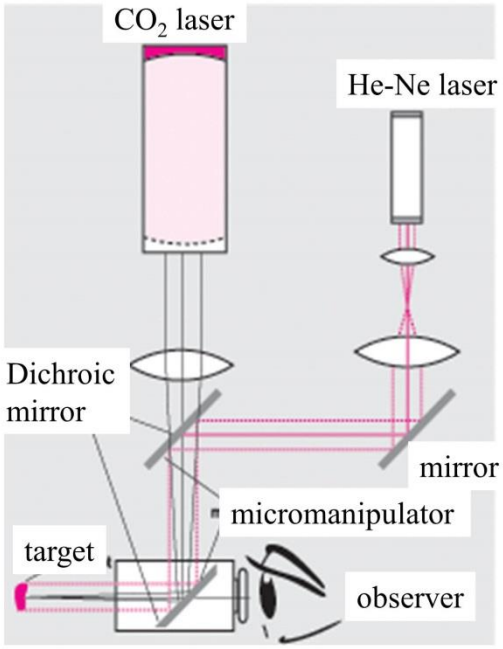


- Once the laser emission is generated, it needs to be directed to the spot, which is to be targeted by the radiation.
- Visible and ultraviolet laser light is usually directed by fiberoptics, although mirrors or the direct positioning of the laser source can also be used.
- However, in medical applications the flexibility and easier positioning provided for by fiberoptics is preferred. The advantage is more obvious in the case of lasers where the apparatus generating the laser is bulky.
- Fiberoptics are made of two different types of glass, one with a higher refractive index forming the central core, and a low refractive index glass sheath (called the cladding) around it. If light impinges on the outer edge of the core from the inside (when the glass fiber is bent), it suffers total internal reflection owed to the lower index of refraction of the cladding (see also in the lecture on Optics).
- The light from the laser is focused with a lens onto the center of the glass core, positioned meticulously to avoid hitting the cladding (called coupling in), and is guided along the core exploiting total internal reflection.
- At the end of the fiber, another lens is used to form a required beam shape (collimated, diverging or focused).

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Guiding laser light

Infrared (eg. CO_2 laser):
Mirrors
Targeting laser in the visible range (eg. He-Ne, diode)



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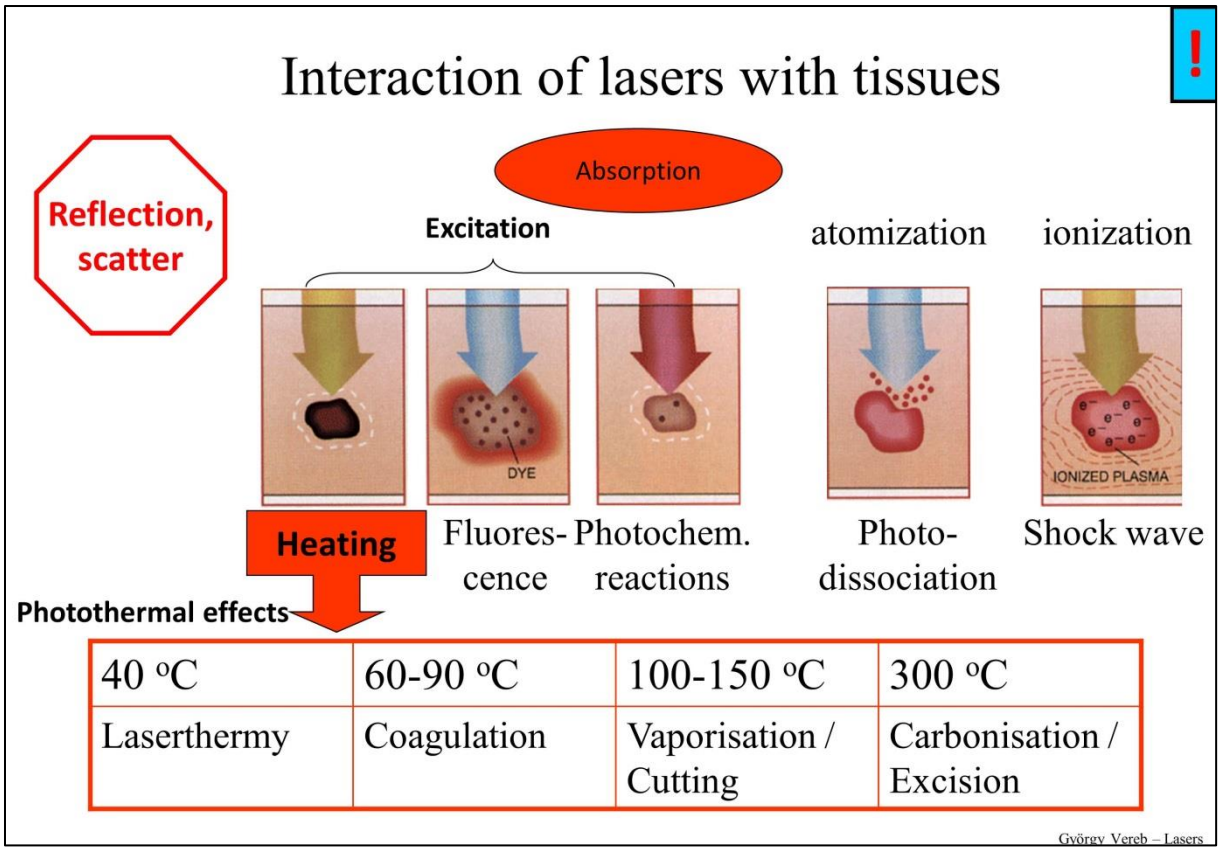
- In the case of infrared emission, such as that of the CO_2 fiberoptics cannot be used for laser guiding, only mirrors. This makes application somewhat cumbersome, nevertheless, owed to the high absorption coefficient of water around 10 micrometer wavelength (1000 1/cm), the CO_2 laser is extensively used in medicine.
- Since infrared is not visible, a visible (usually red), low intensity laser source (usually He-Ne or diode) is applied for proper targeting in such a manner that its light beam follows the same path as that of the infrared photons.

Medical applications of lasers

<table>
<tr><th colspan="2">LOW POWER</th><th rowspan="2">diagnostics</th><th colspan="2">HIGH POWER</th></tr>
<tr><td rowspan="4">lab diagnostics</td><td>flow cytometry</td><td colspan="2" rowspan="4"></td></tr>
<tr><td>laser nephelometry</td></tr>
<tr><td>correlation spectosc.</td></tr>
<tr><td>microscopies, tweezer</td></tr>
<tr><td rowspan="3">clinical diagnostics</td><td>endoscopy</td><td rowspan="3"></td></tr>
<tr><td>laser doppler</td></tr>
<tr><td>fotodynamic diag.</td></tr>
<tr><td rowspan="2">soft laser therapy</td><td>hyperemisation</td><td rowspan="3">therapy</td><td rowspan="3">laser surgery</td><td>coagulation (60-90 C)</td></tr>
<tr><td>laserthermy</td><td>vaporization (100-150 C)</td></tr>
<tr><td colspan="2"></td><td>carbonization (300 C)</td></tr>
<tr><td colspan="3"></td><td colspan="2">photodynamic therapy</td></tr>
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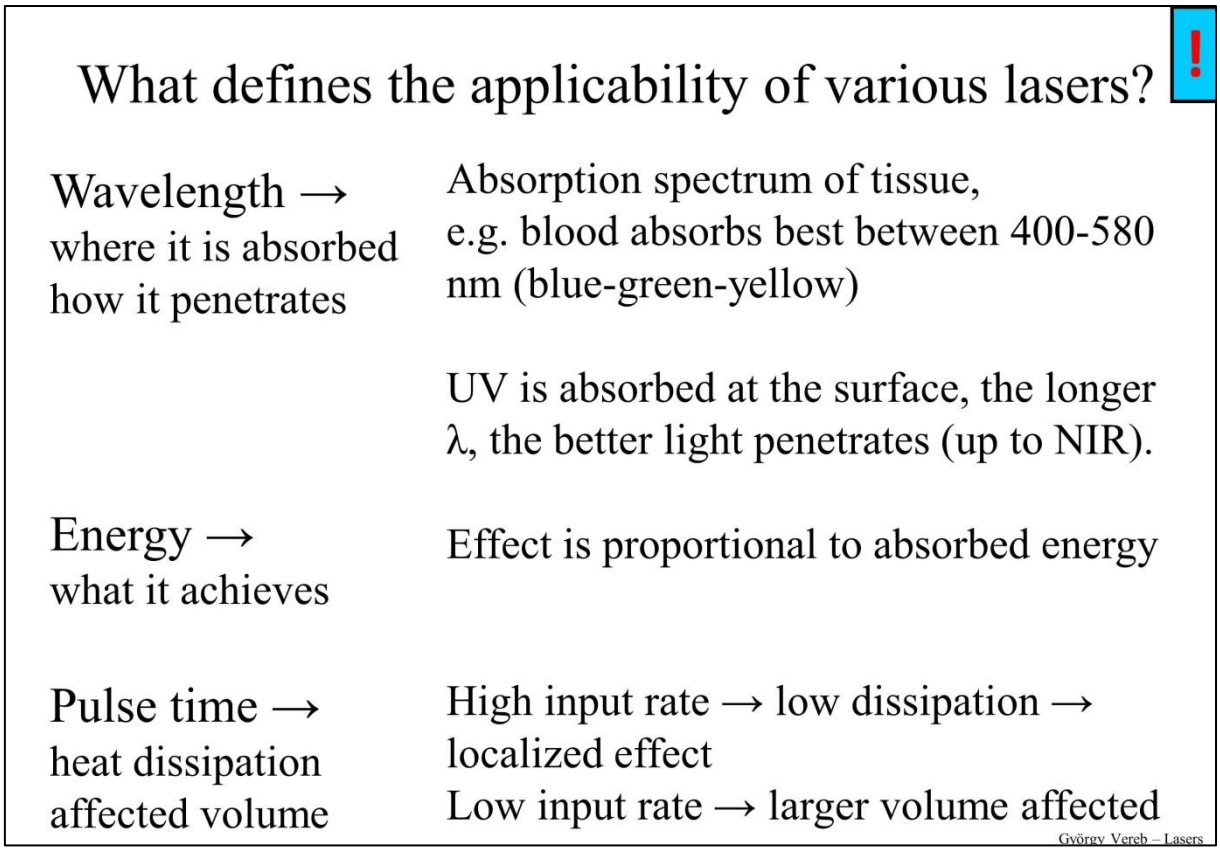
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- The table summarizes the main biomedical applications of lasers. Regarding diagnostic applications, the reader is referred to the other relevant lecture materials.
- In the next part of this presentation we consider therapeutic applications, based on both low and high power lasers.
- In addition to photodynamic therapy and the thermal effects of lasers mentioned here for therapeutic applications, some other effects used in medicine will also be discussed.



- Photons arriving at a tissue either pass through it unaltered, or after being scattered, or they get absorbed. This figure categorizes the effects of absorbed laser photons from the therapeutic (and biophysical) perspective.
- Absorption of photons causes excitation of the absorbing material, followed by relaxation, during which heat can be generated. In general, this is what we call photothermal effect.
- Different effects can be evoked depending on the temperature of the target volume. Raising the temperature to approximately 40 °C is called laserthermy. At this temperature, there is no tissue damage in the short-term; rather there is an acceleration of diffusion and metabolism (including increased mitochondrial activity), and increased (membrane) permeability. Collectively, these phenomena are called bio-stimulation and are used to accelerate wound healing. Good results have been achieved in the therapy of skin ulcers and other open wounds, muscle strains and bruises, sinew/tendon and nerve injuries, as well as the attenuation of chronic pain in the muscle-skeletal system.
- If the targeted volume is heated up to 60-90 °C, protein coagulation occurs which necessarily entails cell destruction.
- Heating to 100 °C leads to boiling of water in the tissue, and consequently to the rapid expansion of its volume (corresponding to a small explosion). This process is called vaporisation. It is suitable for cutting tissues.

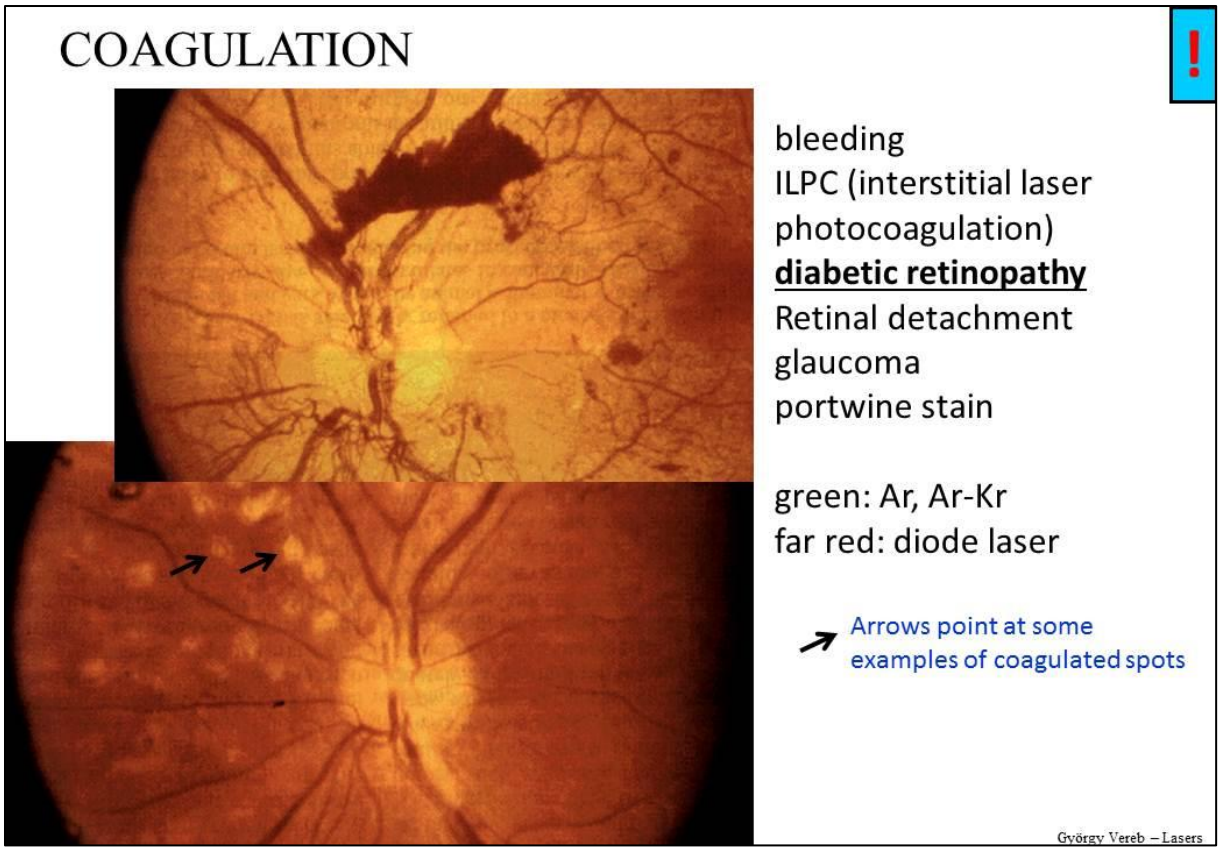
- Over 300 °C, tissues become charred in a phenomenon called carbonisation. It is ideal for eliminating unwanted tissues.
- Some excited molecules can relax to produce fluorescence. In addition, in the excited state they can undergo photochemical reactions. These phenomena are exploited in photodynamic diagnosis and therapy.
- If the photon has enough energy to break up molecular bonds, as for example in the case of excimer lasers (ArF, XeF) radiating in the ultraviolet range, the phenomenon of photo-dissociation can be observed. This process results in atomization, i.e. deconstruction of the targeted volume into its component atoms within a short time.
- The energy of a single photon in the visible 400-700 nm range is not sufficient for causing ionization - please recall that X-ray and gamma radiations with photon energies over 100 times greater than that of visible photons were mentioned as electromagnetic radiation with ionizing properties. However, when the energy of several visible photons are added up, the total energy reaches the ionization threshold this is called multiphoton ionization because many coherent photons in constructive interference must hit the target electron at the same time, which can only be provided by the high photon density in a focused laser beam. The generated ionized plasma rapidly expands and produces a shockwave.



- Before giving more details about the discussed interactions and their medical applications, some general considerations must be given to the applicability of various lasers (see also the text to the table about various lasers and their properties!).
- Wavelength defines both absorption and penetration. When blood vessels need to be coagulated without harming tissues around them, it is practical to choose a laser which is absorbed best by haemoglobin (420-570 nm range). Melanin containing tissues have a rather flat absorption spectra, so using red lasers selects melanocytes against RBCs.
- The lasers used must have the appropriate wavelength for optimal absorption in the target tissue and optimal transmission through tissues that need not be affected but are located along the beam path.
- Since UV photons are capable of atomizing, they do not penetrate deep, rather, are absorbed on the surface.
- Visible photons penetrate deeper with increasing wavelength, since the number of non-specific interaction cycles of the material with the electromagnetic field over unit distance decreases with decreasing frequency (=increasing wavelength).
- In the far infrared (e.g. CO_2 laser), penetration in water containing materials is low again, because water absorbs this wavelength specifically and with great efficiency.
- In addition to choosing specific photon energies for specific tasks (e.g. UV for atomization, far infrared for vaporization and carbonization), the total energy conveyed to the tissue

also determines the outcome. Absorbing more energy increases the temperature more when the photothermal modes are used.

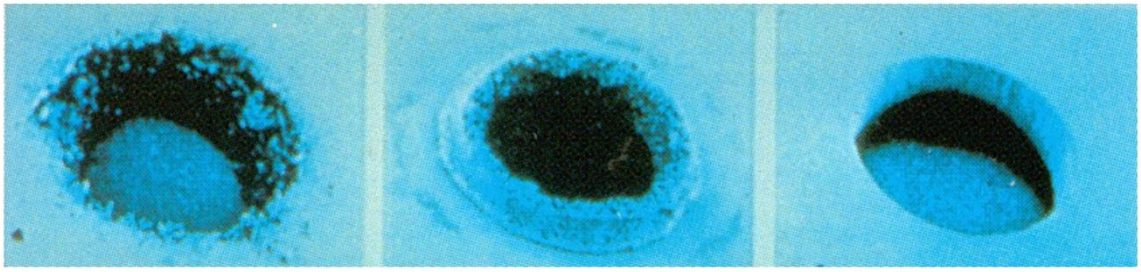
- The time over which the given amount of energy is absorbed is also important. A low rate of input allows time for the heat to dissipate further, and a larger volume is affected. A quick pulse can restrict the full effect to the volume actually hit by the laser. For multiphoton ionization to occur, a large number of coherent photons need to be jammed into the same small volume at the same time for their energy to add up, so large output powers with very short (femtosecond) pulses need to be used.



- Heating to 60-90 °C causes coagulation. If the coagulate occurs in capillaries or smaller blood vessels, the blood circulation ceases in the given area, which can serve to staunch bleeding during surgery, or to counter the pathological effect of hyper-proliferated blood vessels (such as in the case of diabetic retinopathy and congenital port-wine stains).
- The coagulated areas become scar tissue in the long term, so the volume and position of coagulated tissue must be carefully considered.
- Interstitial laser photocoagulation (ILPC) is an endoscopic procedure in which the fiberoptic is lead through an endoscope tube into the center of the tissue area that needs to be treated (e.g. a tumor which cannot be removed surgically, or only at high risk), and the laser emitted from the fiberoptic is adjusted to coagulate the target tissue in situ. This later becomes a scar.
- Scars produced by photocoagulation can also be used to keep tissues together, for example in the case of retinal detachment.

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TISSUE REMOVAL USING VARIOUS LASER EFFECTS

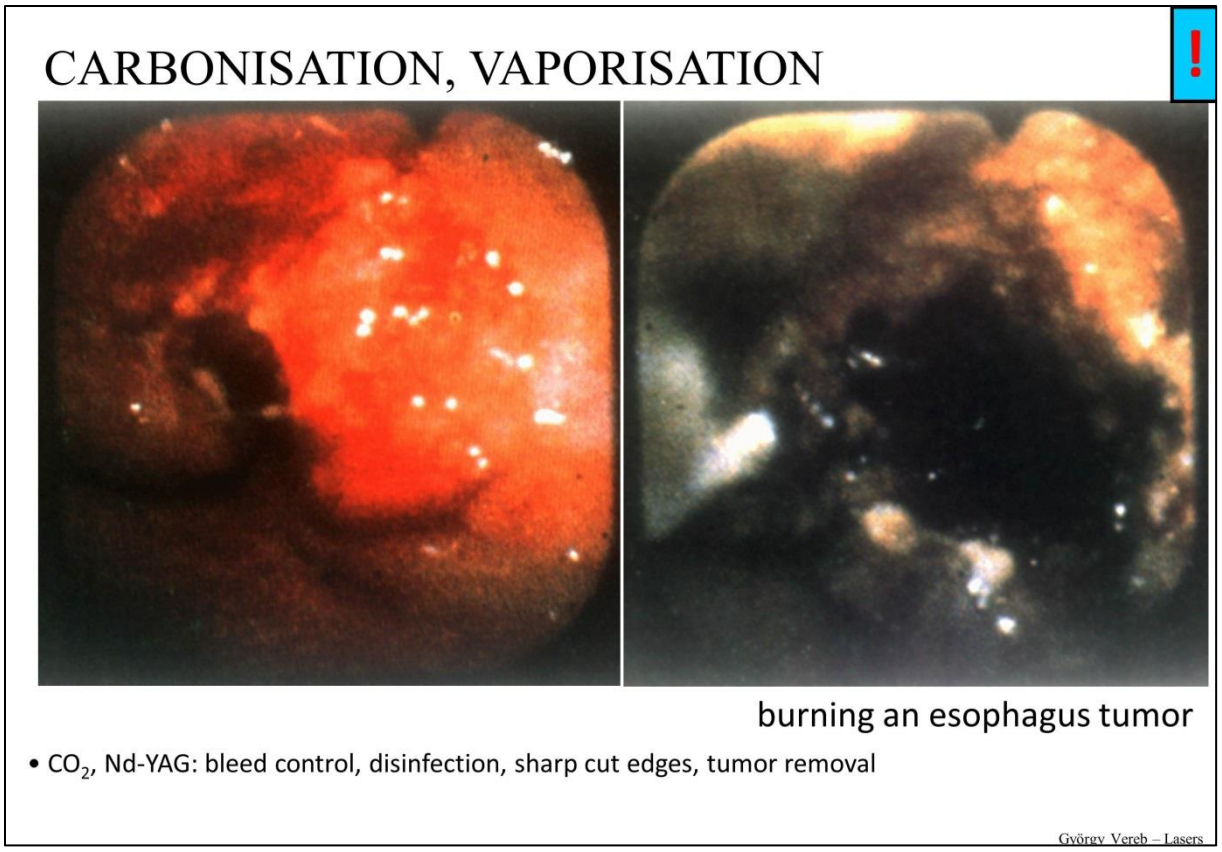


Nd-YAG	CO_2	Excimer (ArF)
vaporisation	carbonisation	atomisation

György Vereb – Lasers

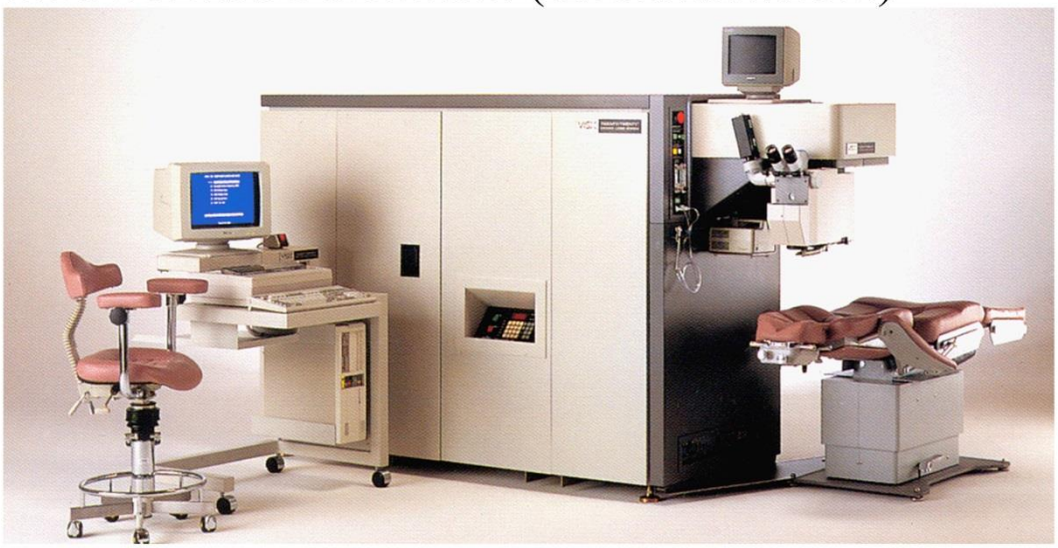
- The small diameter and the high power density make the laser beam an ideal surgical knife. By focusing the almost parallel beam, the irradiated area can be reduced to a micrometer sized diameter thus further increasing the power density. The sharp, cutting (excision) effects of lasers based on vaporization, carbonization or atomization can be applied both for simpler operations and for complicated interventions involving inner organs, and hyperaemic tissues, also in body cavities such as the mouth, larynx, rectum, and ear. For this purpose the most widely used lasers are the CO_2 and the Neodymium:YAG lasers. These emit in the far- and near infrared region, and the penetration depth ranges between 0.03 - 4 mm.
- Vaporisation involves raising the tissue temperature above 100 °C. One liter of water is 55.55 moles, and each mole of water vapor occupies 24 liters at normal temperature and pressure. This is an overall 55.55*24=1333 times expansion. If this happens over a short time (depending on the rate of energy absorption), it qualifies as an explosion. However, since the volume affected can be made extremely small (mm^3 range and below) by focusing the laser light, a spatially well controlled tissue destruction can be implemented. As demonstrated on model tissues, the surface of the remaining tissue is not perfectly smooth owed to the nature of explosion.
- After carbonization, there also are minor surface irregularities around the destroyed tissue. Depending on the rate of energy input, there can also be a ring of coagulated tissue around the charred part.

- During the course of atomization a highly confined tissue loss occurs, and many modern laser cutting devices are based on this effect. Since the absorption of UV-photons in all kinds of tissues is high, this radiation is suitable only for surface or near-surface treatment. It is important to note that the prevalence of DNA breakages and subsequent mutation of surrounding non-atomised tissues has not been investigated in long term follow-up studies.



- Carbonization is one of the most commonly applied methods of eliminating unwanted tissues, such as tumors. The process can be employed even in areas rich in blood vessels, because with proper rate of energy input, enough heat can be conducted to a ring of tissue around the carbonized area to cause coagulation and mitigate bleeding.

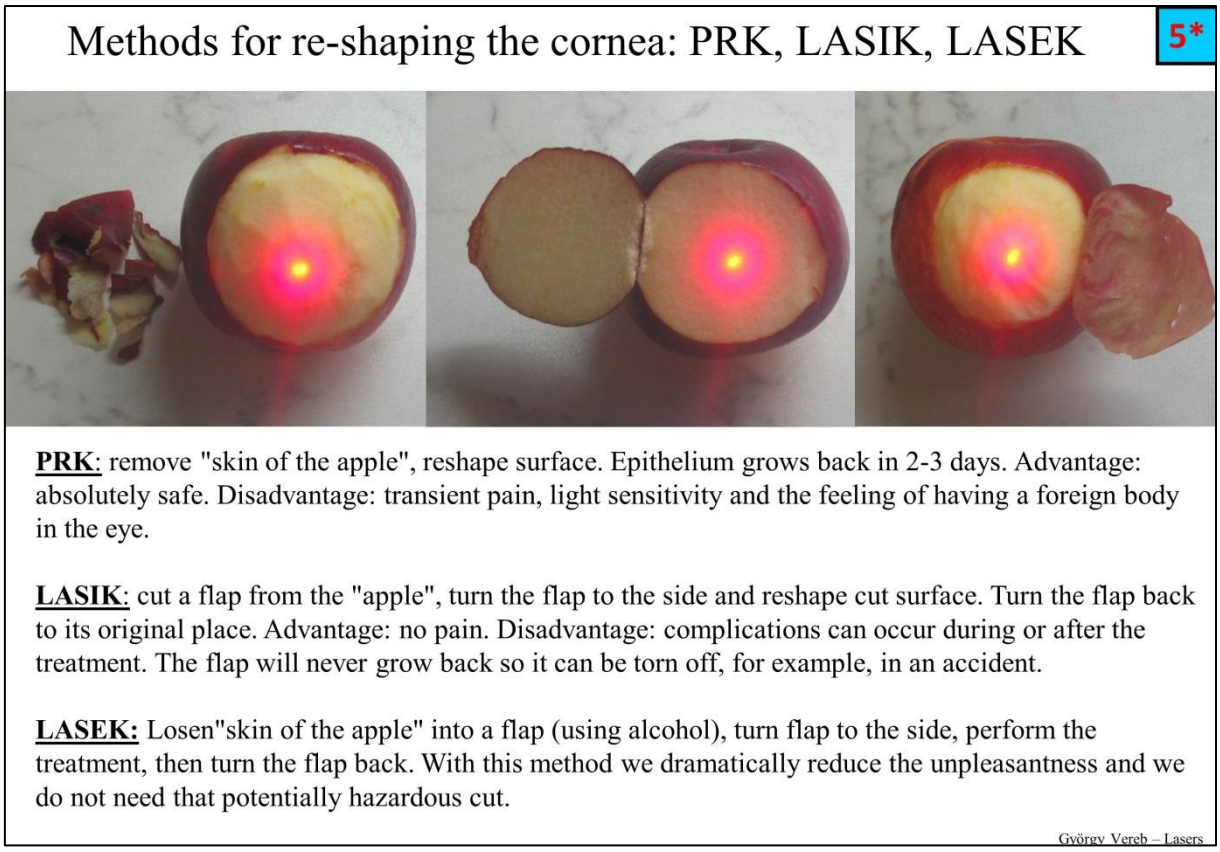
PHOTODISSOCIATION (ATOMISATION)



- Shaping the cornea – an alternative to spectacles (PRK = Photorefractive keratectomy)
- Laser angioplasty
- Excimer lasers (UV)

György Vereb – Lasers

- A special field of laser therapy is the application of lasers to refractive surgery of the eye. In case of nearsightedness, (myopia), the dioptric power of the eye is larger than necessary, and in addition to using concave lenses, this can also be compensated for by reducing the curvature of the cornea by thinning the central region. In the case of farsightedness (hyperopia), the dioptric power has to be increased, so a circular ditch is created on the circumference to increase curvature. It is also possible to make more complex refractive corrections to the eye e.g. in the case of astigmatism.
- Initially, vaporization by CO_2-lasers was used to remodel the cornea and later Nd:YAG lasers which allowed a more controlled milling away of tissues. Atomization with excimer lasers now allow a more precise tissue sculpting with a sharper border (see „Tissue removal using various laser effects" above). Excimer lasers can be used in one of 3 techniques: PRK, LASIK, or LASEK (see below).
- Fiberoptic transmission of the UV-emission of excimer lasers – especially in the case of high energy pulses – presents a serious technical challenge. However, the development of monomodal fiberoptics makes it possible to transmit 1 MW impulses through a glass fiber of less than 1 mm diameter with relatively little loss. This feature enables the atomization in blood vessels of atherosclerotic plaques that are resistant to or unsuitable for balloon angioplasty. This so-called laser angioplasty, is gaining more widespread use in both the treatment of sclerotic coronary arteries as well as in the arteriosclerosis of other organs.



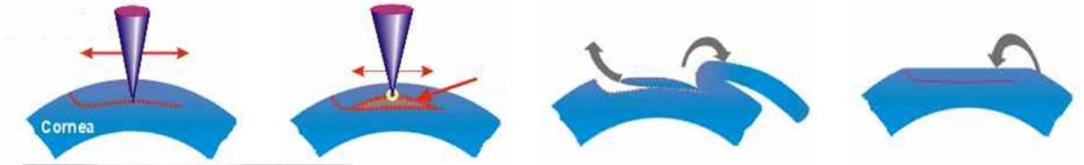
- The outer structure of the cornea can be compared to that of an apple: the skin of the apple is analogous with the surface epithelium of the cornea and the flesh of the apple beneath with the stroma of the cornea.
- During photorefractive keratectomy (PRK), the corneal epithelium i.e. the skin of the apple is scraped away and discarded, and the treatment is performed on the clean surface of the underlying stroma. The epithelium then requires a few days to regrow. The advantage of the procedure is that it is completely safe. Its primary disadvantage is that until the epithelium regrows there is a level of discomfort resulting from light sensitivity and the sensation of a foreign-body in the eye. In addition, the basal membrane of the original epithelium is destroyed in the process.
- Laser assisted in situ keratomileusis (LASIK) avoids these problems by cutting a thin flap of epithelium parallel to the surface of the cornea. The flap is then lifted, the reshaping is performed on the underlying stroma, and then the flap is folded back. The advantage is that there is no temporary discomfort. The disadvantage is that since the flap never reattaches completely (the cornea is not vascularized, no scar is formed – thankfully, since scar tissue is not transparent), it can be dislocated in a car-accident or sports injury. Moreover, the resultant surface curvature can be determined less precisely than with PRK.
- Laser epithelial keratomileusis (LASEK) attempts to incorporate the advantages of both methods. A thin protective flap is created from the epithelium after denaturing with

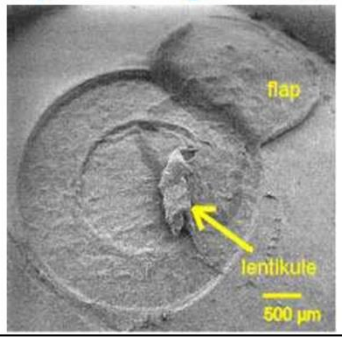
alcohol. This flap is folded back and replaced after reshaping the stroma. Since restults are comparable to that of PRK, in current practice, PRK finished with placement of a protective contact lens is preferred over this method.

MULTIPHOTON IONISATION

Basis: in the focus of the laser multiphoton and cascade ionisation takes places owed to the high photon density (10^{12}W/cm^2), plasma is formed (10^{18}/cm^3 electrons) and shock wave with GPa pressure creates a tiny discontinuity in the focus. Femtosecond pulsed lasers (Nd-YAG) can be used.

Femtosecond LASIK

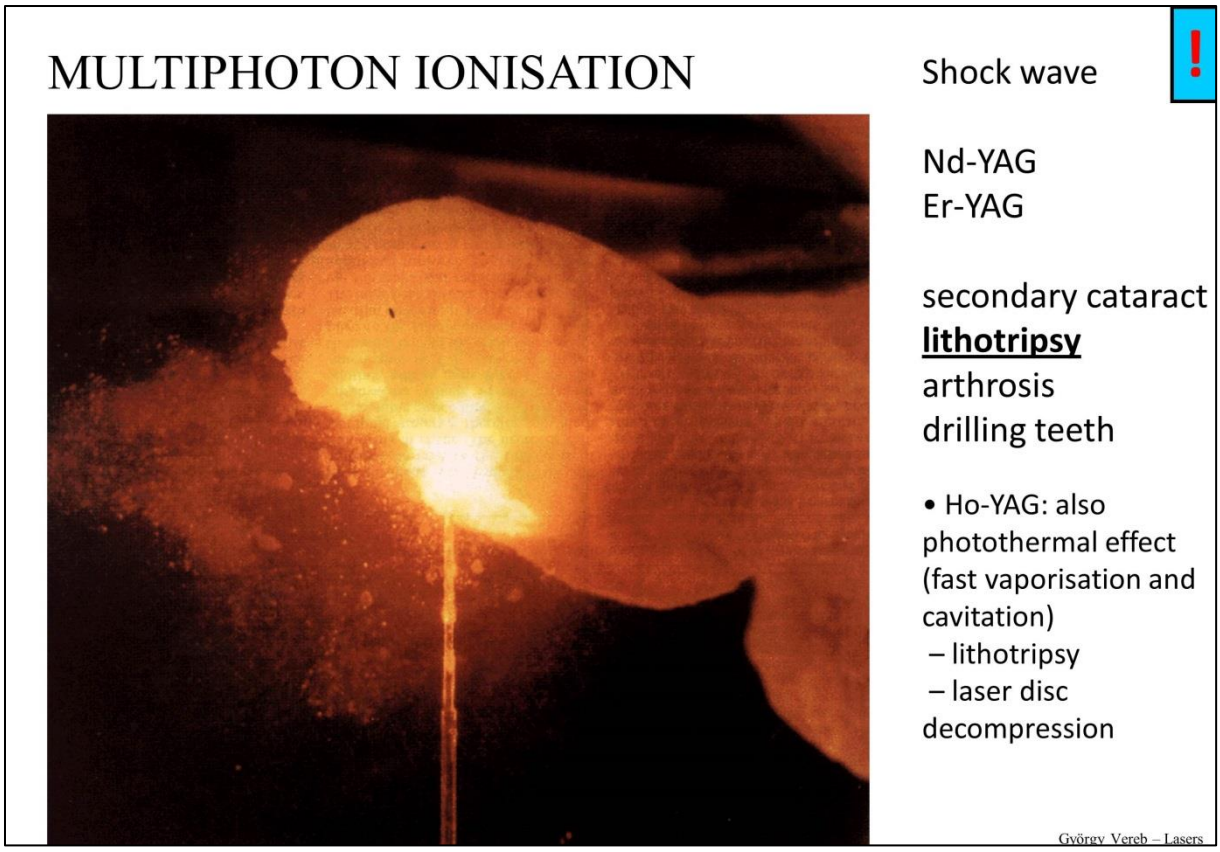




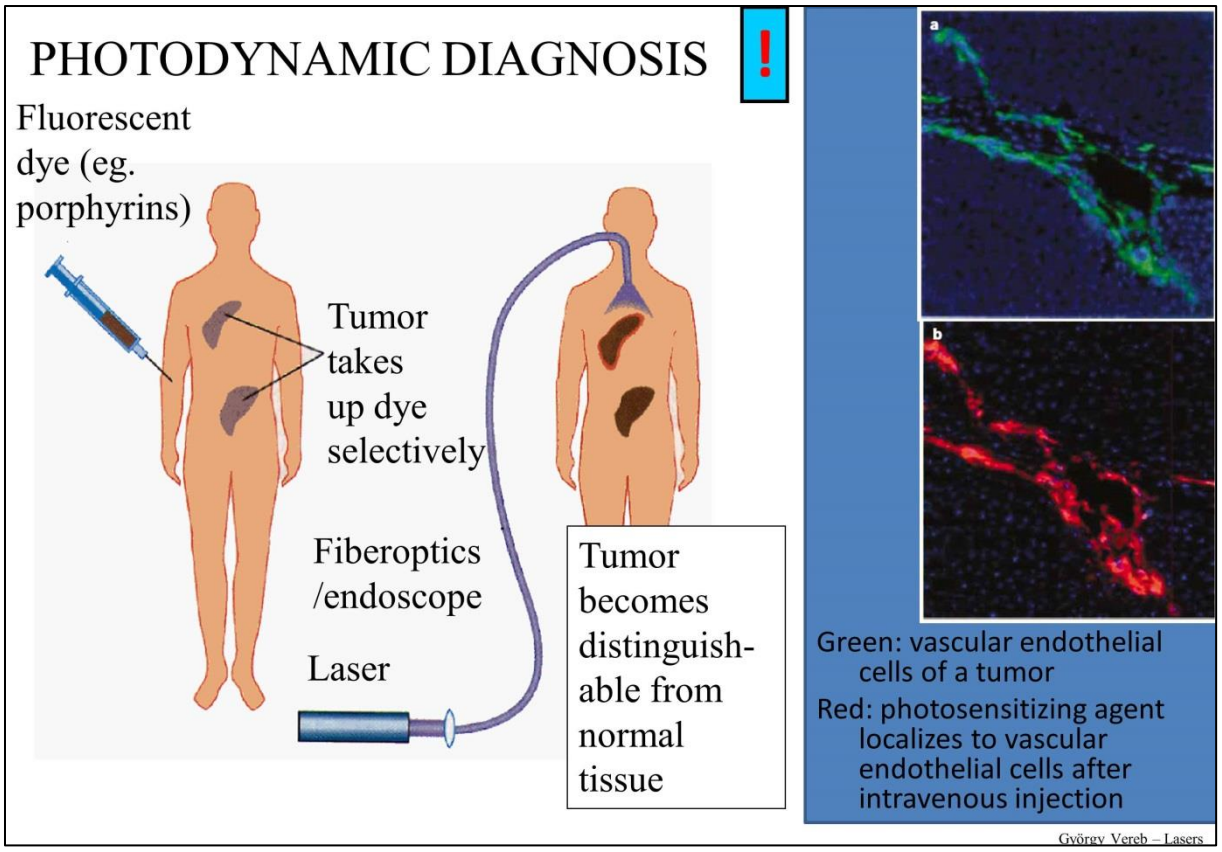
The laser can be used to make a perforation around the unnecessary piece of cornea, which is then removed.

György Vereb – Lasers

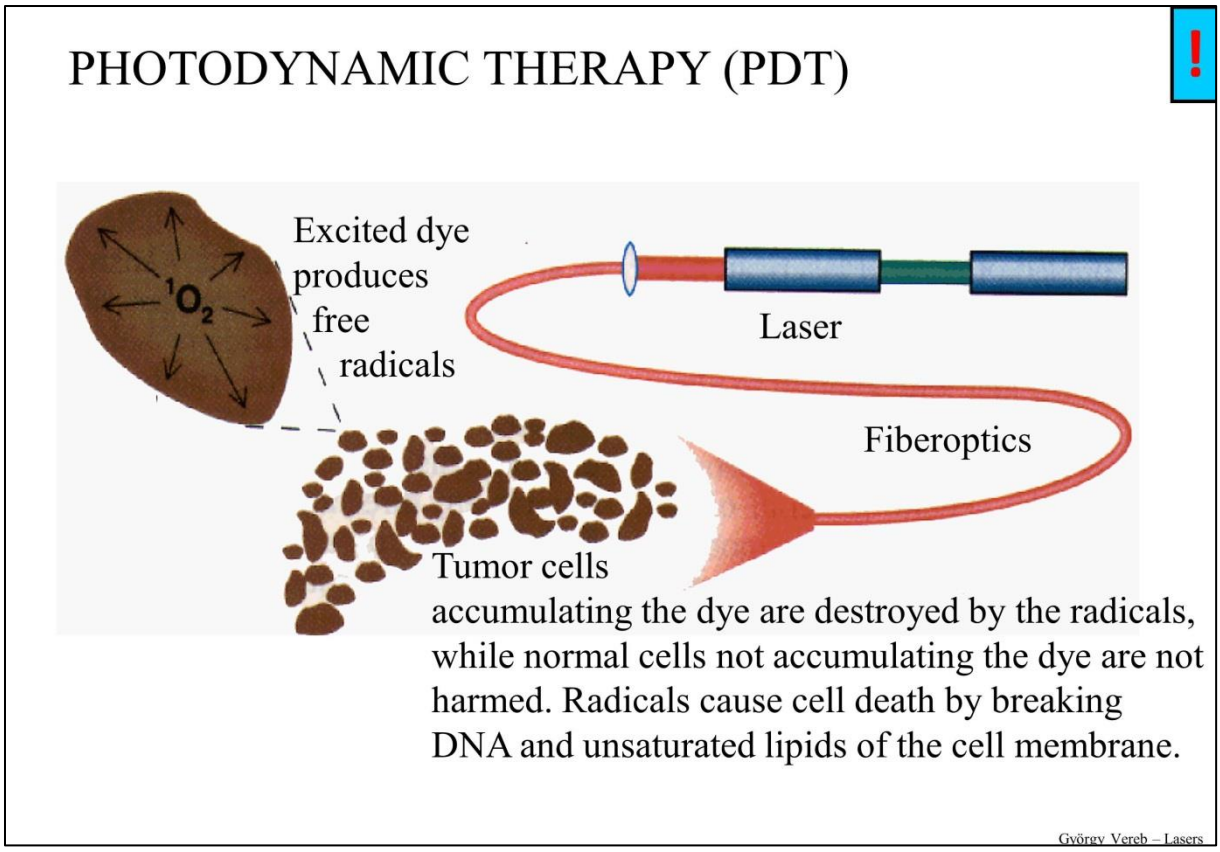
- Photons in the red or near infrared range penetrate relatively deeply into most of human tissues. If the photon density reaches a critical value (~ 1 TW/cm2) non-linear effects: multiphoton effects and cascade-ionization can take place. Such photon energy densities can be attained by a short pulse of a high energy laser beam focused on a small spot, affecting a sub-femtoliter sized (below 10^{-15} liter – 1 cubic micrometer) tissue volume. If the density of free electrons that are generated during the ionization reaches 10^{18} /cm^3, ionized plasma is produced. This plasma expands rapidly and triggers a mechanical shock wave of GPa amplitude. The particles moving away from the center at high speed create cavitation, which results in a cyclic expanding and collapsing of a bubble. At the end of this process, a microscopic gas bubble remains in the place of the targeted volume, which is then absorbed within a few minutes. The ionization effect can be used to general tissue loss in small and precisely localized volume, whereas the shock wave and cavitation induced by the ionization can be used to destroy harder (calcified) tissues and gall or bladder stones.
- Owed to the high precision, this method can be used to remove a well defined part from the corneal stroma, adjusting the refractive power with extreme precision (eagle's vision) and at the same time avoiding the destruction of the basal membrane and the epithelium. Please not that in the image above, the flap is made so that the place of the removed tissue (lenticle, yellow arrow) can be well observed. In clinical femtosecond LASIK applications only a small incision is made to remove the excess stroma, not a complete flap.



- Multiphoton ionization can be used to generate small, well defined shock waves that can be used to remove tiny pieces of tissue. Examples include the removal of fibrous deposits on the lens capsule (secondary cataract) after a complicated cataract surgery, milling away calcified deposits from arthrotic joints, breaking up kidney or gall stones (lithotripsy, as shown in the image) and destroying part of the nucleus pulposus of the vertebral disc to decompress the nerves in the case of disc herniation.
- Often the generation of plasma state material causes very rapid vaporisation in the nearby environment (plasma is really hot), which causes further shock waves and tissue destruction. This is most useful in the laser ablation of stones that contain some water, such as bladder stones with crystal water.
- The lasers used are usually Nd:YAG or Ho:YAG operated in femtosecond pulse mode.
- In the case of drilling teeth with this method, the lack of need for anaesthesia is a major advantage. In this case, the removal of very tiny volumes of tissue at a time requires a very small change of momemtum, so the tooth itself practically does not move (its mass is so much larger than that the material removed in one pulse). Therefore, there is no shaking of the dental pulp that would be causing the pain during conventional tooth drilling.



- In photodynamic diagnosis, the fluorophore excited by the laser can be endogenous (a molecule produced by the targeted tissue, e.g. porphyrins), or a substance introduced into the body from outside, e.g. by venous injection, which selectively accumulates in certain organs or in tumor tissues. An endoscope can be used to guide the laser through fiberoptics into body cavities, such as the lungs or the gut. Another fiber bundle is used to carry the fluorescent photons back and the source of fluorescence can be identified in the image. Usually the regions that fluoresce have undergone pathological changes (tumors or precancerous lesions). These tissues can be then removed surgically, or treated exploiting the presence of the fluorescent substance in them using PDT, as discussed on the next page.

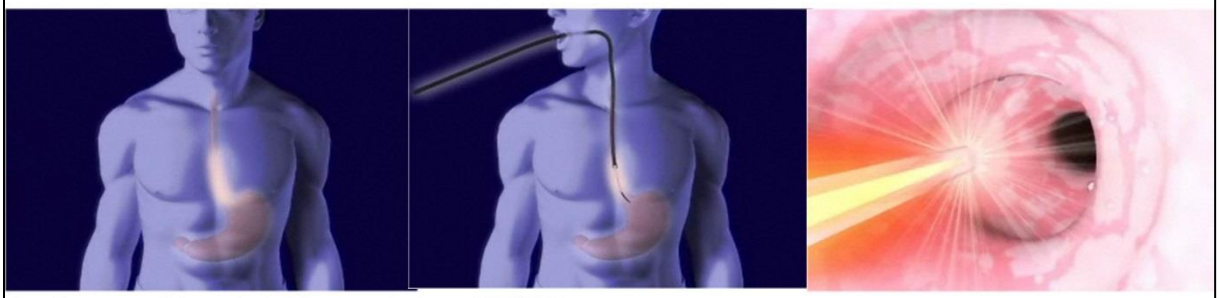


- The excited fluorophore can enter into a photochemical reaction, during which free radicals are generated. Photodynamic therapy (PDT) exploits the cytotoxic effects of the induced free radicals (molecules, atoms or ions with unpaired electrons).
- Upon illuminating the tissue with laser light, the radicals destroy tumor cells that have selectively accumulated the dye, while normal cells not accumulating the dye are not harmed. Radicals cause cell death by breaking DNA and unsaturated lipids of the cell membrane (see radiation biology).
- Usually various synthetic porphyrin derivatives or other structurally related compounds are used for PDT. In spite of the fact that their absorption is lowest in the red range, therapeutic practice typically employs red light to excite porphyrins because of its greatest possible penetrating depth. The application of coherent monochromatic light is also useful because transmission via fiberoptics is possible with little attenuation of intensity and the radiation dose can be estimated more precisely. Monochromatic light of a suitable intensity is easily provided via laser light.
- All cells take up and release porphyrins and other photosensitizers, but at a different rate. So a time window must be found for each dye when there is still sufficient amount in tumor cells but hardly any in normal cells. Dye development efforts strive to optimize the length of the time window, the ratio of tumor vs. normal tissue concentration, the efficacy in producing free radicals and the stability of the dyes.

PDT in Cancer Treatment

- **Minimally invasive**
- **Less damage to surrounding healthy cells**
- **PDT best suited for:**
  - Early stage tumors
  - Inoperable for various reasons
- Limited success due to lack of specificity and potency of photosensitizing agents

PDT for cancer of the esophagus



http://www.mayoclinic.com/health/photodynamic-therapy/MM00719

György Vereb – Lasers

- Since PDT is minimally invasive as opposed to regular surgery, its application is recommended when
- (1) there is no risk in a failed therapy, such as with early stage pre-cancerous lesions, which can be followed up and re-treated or operated on, and to start their treatment with surgery would cause disproportional damage to the body. So a simple polyp of the colon is best removed by endoscopic surgery, because its removal is not traumatizing and does not cause large scars or dysfunction. On the other hand, a large leukoplakia of the oral cavity is better first treated with PDT, giving the pre-cancerous cells a chance to dye and the normal ones to live on, without forming a huge scar (which would distort the tissues and possibly cause dysfunction).
- (2) the tumor cannot be removed by surgery without risking life or rendering life quality unacceptable. In this case treatment is aimed a prolonging life expectance with minimized adverse effects.
- Although PDT has been in development for many decades, its application is still quite limited. Developing new photosensitizers along the principles mentioned afore is expected to improve its applicability.

Take-home message

Ask yourself:

- In what aspects is laser light different from light from conventional sources?
- What are the mechanisms and conditions that make the generation of laser possible?
- In what ways do lasers interact with tissues and which properties define the type and place of interaction?
- What are the medical applications of lasers, what kind of lasers are used for each and what type of laser-tissue interaction(s) is each based on?
- As an MD (DMD):
  - Is there a consequence of using a laser in a given treatment in terms of:
    - therapeutic outcome/success
    - patient comfort/quality of life
    - financial aspects