Wigner 121
Scientific Symposium

Wigner Research Centre for Physics
Institute for Solid State Physics and Optics
Department of Applied and Nonlinear Optics
Femtosecond Lasers for Nonlinear MicroscopyResearch Group

Introduction

The activity of our research group focuses on **research and development of ultrafast (ps, or fs) pulse solid state or optical fiber lasers for applications in *in vivo* 3D nonlinear microscopy.** Our aim is to develop laser systems that improve the quality of imaging (e.g. imaging depth, resolution), support easier handling (held-held imaging systems, fiber integration) or minimize the risk of thermal or photochemical damage of the living tissue. Main R&D results of the group include the **development of a long cavity, sub-ps pulse, tunable Ti-sapphire laser operating at ~22 MHz repetition rate utilizing a piezo controlled GTI for intracavity dispersion control**, an all-fiber Yb-fiber oscillator and amplifier laser operating at ~2 MHz repetition rate and delivering ~0.5 ps pulses and a two-wavelength sub-ps pulse laser system for CARS imaging applications. The research group also involved in **development and applications of different label free imaging techniques (2PEF, SHG, CARS, FLIM)** in the fields of dermatology, neurology and metabolic research with its partners at **Semmelweis University** (SE), **Szeged University** (SZTE) and **University of Sports Science** (TF), respectively.

Method

Piezo controlled GTI mirror comprising an UBCM

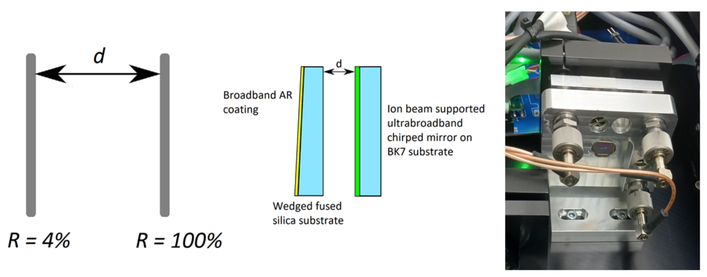


Fig. 1 Theoretical model *(left)*, physical layout (*middle)* and photo *(right)* of our piezo controlled GTI interferometer for dispersion compensation over the high reflectivity range of UBCM mirror (680-1040 nm).

Computed group delay and GDD of our GTI mirror (*d* = 15 µm)

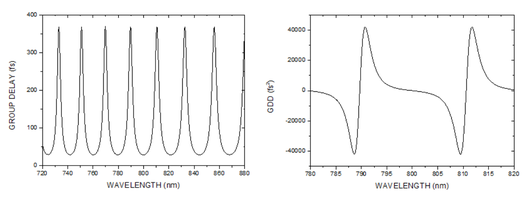


Fig. 2 Computed group delay *(left)* and GDD *(right)* vs. wavelength function of GTI mirror with mirror spacing of *d* = 15 µm.

Publications of the group

[1] Cserép C, Pósfai B, Lénárt N, Fekete R, László ZI, Lele Z, Orsolits B, Molnár G, Heindl S, Schwarcz AD, Ujvári K, Környei Z, Tóth K, Szabadits E, Sperlágh B, Baranyi M, Csiba L, Hortobágyi T, Maglóczky Z, Martinecz B, Szabó G, Erdélyi F, **Szipőcs R**, Tamkun MM, Gesierich B, Duering M, Katona I, Liesz A, Tamás G, Dénes Á. *Microglia monitor and protect neuronal function through specialized somatic purinergic junctions*. **Science**. 367(6477):528-537. (2020).

[2] **L. Fésűs, Á. Kropp**, G. Molnár, N. Kiss, G. Tamás, and **R. Szipőcs**, "*A 20 MHz, sub ps, Tunable Ti:sapphire Laser System for Real Time, Stain Free, High Contrast Histology of the Skin,*" in **Biophotonics Congress: Biomedical Optics 2020**, OSA Technical Digest (Optica Publishing Group, 2020), paper MTh3A.4. (2020).

[3] **Á. Kropp, L. Fésűs, G. Szipőcs, N. Wikonkál, and R. Szipőcs**, "*Fiber coupled, 20 MHz Repetition Rate, sub ps Ti:sapphire Laser for in vivo Nonlinear Microscopy of the Skin*," in **Biophotonics Congress 2021**, OSA Technical Digest (Optical Society of America, 2021), paper DF2A.5. (2021).

[4] **L. Fésűs, N. Wikonkál, and R. Szipőcs**, "*Numerical Analysis on ex vivo Second Harmonic Generation Images of Collagen Structure of Unstained Basal Cell Carcinoma Sections*," in **European Conferences on Biomedical Optics 2021** (ECBO), OSA Technical Digest (Optical Society of America, 2021), paper EW4A.9. (2021).

[5] **L. Fésűs**, D. Plázár, **A. Kolonics**, L. Martin, **N. Wikonkál**, M. Medvecz, and **R. Szipőcs**, "*Low concentration Phloxine B staining for high chemical contrast, nonlinear microscope mosaic imaging of skin alterations in pseudoxanthoma elasticum*," **Biomed. Opt. Express** 13, 252-261 (2022).

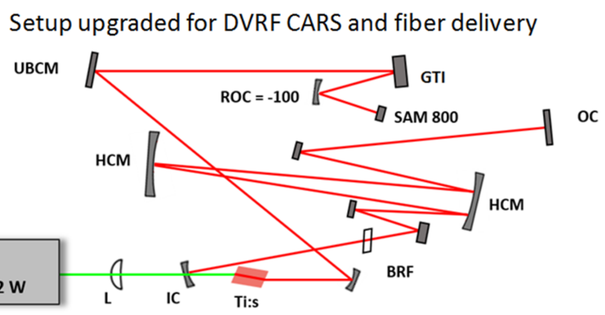
[6] **A. Kolonics**, T. Kawamura, **R. Szipőcs**, Zs. Radák, „*Accelerated epigenetic changes may contribute to the development of metabolic syndrome revealed by NADH FLIM*", 13th MiPschool, Obergurgl, Austria,(2023).

[7] **G. Szipőcs, Á. Kropp**, S. P. Chong, P. Török, and **R. Szipőcs**, "**Low Reflection Loss Dispersion Compensation Scheme for Broadly Tunable sub-ps Solid State Lasers**," in **CLEO 2023**, Technical Digest Series (Optica Publishing Group, 2023), paper JTh2A.121. (2023).

[8] **L. Fésűs, Á. Kropp, G. Szipőcs**, F. Meznerics, A. Bánvölgyi, N. Wikonkál and **R. Szipőcs**, „*Nonlinear microscopy for bedside diagnosis of basal cell carcinoma*", submitted to **J. Clinical Medicine** (2023).

Results

20 MHz, tunable, sub-ps Ti:sapphire laser

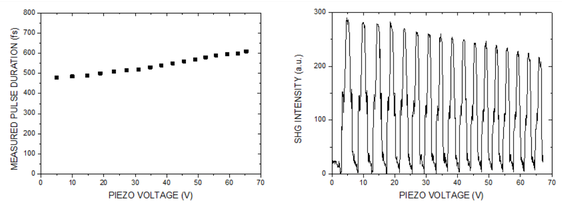


- Prism pair is replaced by GTI mirrors
- SESAM for mode-locking instead of hard aperture Kerr-lens mode-locking
- Ultrabroadband chirped mirrors

- Pump power at 532 nm: ~ 2.1 W
- Repetition rate: ~ 20 MHz
- Pulse duration: 0.6 – 1.0 ps (adjustable)
- Spectral bandwidth: < 2 nm

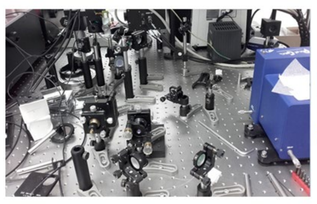
P. Antal, R. Szipőcs, "Tunable, low-repetition-rate, cost-efficient fs Ti:S laser for nonlinear microscopy," Appl. Phys. B**107**, 17-22 (2012)

Measured pulse duration and SHG signal vs. piezo control voltage

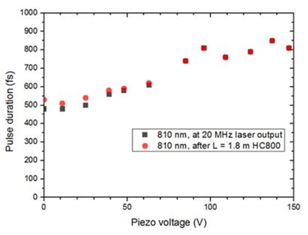


A fiber coupled, 20 MHz, sub-ps Ti:sapphire laser for nonlinear microscopy of the skin

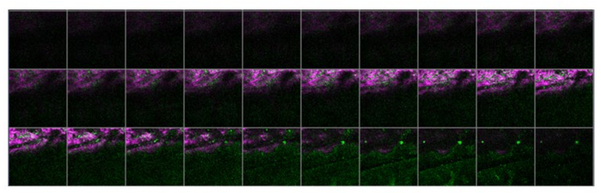
Fiber coupling to a 1.8 m long HC800-2 fiber



Laser pulse duration before (●) and after (●) a 1.8 m long HC800-2 fiber

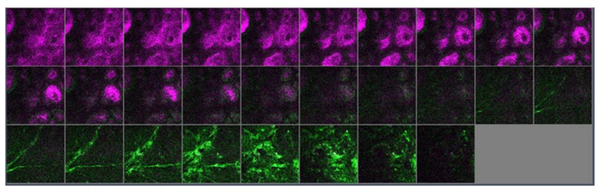


Z-stack imaging of basal cell carcinoma (BCC) biopsy



In case of BCC, we could **detect the border of the tumor** highlighted by a **strong contrast of AF (cells with basal cell morphology)** and **SHG (collagen fibers around tumor nest).**

Z-stack imaging of hemangioma biopsy



Hemangioma and **angiokeratoma** are vascular proliferations. **Hemangiomas** can be either congenital or acquired, spontaneously evolving with age. These **do not require further treatment. Angiokeratomas (AK) can not be distinguished from hemangiomas macroscopically,** and even though these have dermatoscopic features, **dermatoscopic differentiation is often challenging**. The distinguishing between hemangiomas and AK is important as **AK may indicate the presence of other severe diseases**. It is the most characteristic sign of **Fabry-disease** leading to **severe heart, lung and kidney damage**. **Early diagnosis** could be promote by the **recognition of AKs**. AKs can be a sign of other storage diseases.

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