Swept-wavelength lasers based on GaSb gain-chip technology for non-invasive biomedical sensing applications in the 1.7–2.5 μm wavelength range

AUGUSTINAS VIZBARAS,1,* IEVA ŠIMONYTĖ,1 ARŪNAS MIASOJEDOVAS,1 AUGUSTINAS TRINKŪNAS,1 TADAS BUČIŪNAS,1 MINDAUGAS GREIBUS,1 GRETA NAUJOKAITĖ,1 NICOLAS TORCHEBOEUF,2 SERGE DROZ,2 DMITRI BOIKO,2 ŽILVINAS DAMBRAUSKAS,3 ANTANAS GULBINAS,3 AND KRISTIJONAS VIZBARAS1

1UAB Brolis Semiconductors, Molėtų pl. 73, LT-14259 Vilnius, Lithuania
2Centre Suisse d’Electronique et de Microtechnique SA (CSEM), CH-2002 Neuchâtel, Switzerland
3Institute for Digestive Research, Medical Academy, Lithuanian University of Health Sciences, Eivenių g. 4, LT-50161, Kaunas, Lithuania
*augustinas.vizbaras@brolis-semicon.com

Abstract: The infrared spectral region beyond 1.7 μm is of utmost interest for biomedical applications due to strong overtone and combination absorption bands in a variety of important biomolecules such as lactates, urea, glucose, albumin, etc. In this article, we report on recent progress in widely tunable swept-wavelength lasers based on type-I GaSb gain-chip technology, setting a new state-of-the-art in the 1.7 – 2.5 μm range laser sources. We provide an application example for the spectroscopic sensing of several biomolecules in a cuvette as well as an experimental demonstration of a non-invasive in-vivo sensing of human serum albumin through the skin.

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1. Introduction

The spectral region 1.7 – 2.5 μm contains a number of important spectral features for various sensor applications including strong overtone and combination molecular absorption bands in the gas molecules such as CO, CO₂, CH₄, NH₃ etc [1], in liquid phase biomolecules such as glucose, lactate, albumin, urea, ammonia [2], as well as the atmospheric transmission window (2 - 2.3 μm) for LIDAR and remote sensing applications [3]. All mentioned application fields would greatly benefit from the availability of a high-brightness, compact, low-power consumption and low-cost tunable wavelength source. Semiconductor laser source is the ideal candidate due to the nature of the technology offering unmatched Size, Weight and Power, Cost (SWaP-C) and manufacturing scale advantages. A widespread semiconductor laser design for spectroscopic applications is based on distributed feedback grating (DFB) technology which allows emission of highly coherent single mode light and ability to continuously tune the emission wavelength across 2-3 nm by changing the drive current. This is sufficient for sensing applications, where the target substance has spectrally narrow absorption lines as compared to the laser tuning bandwidth, for example in molecular gas sensing [1,4]. However, for biomedical sensing applications in liquids such as blood, interstitial fluids, saliva etc., a much wider tuning range is required because the molecular ro-vibrational absorption spectra in liquid phase are spectrally very broad due to collisions. Therefore, a tuning range of > 100 nm is required to enable scanning across an absorption peak of a molecule of interest [5]. Such performance is not available for DFB lasers. It can either be achieved using DFB laser arrays, monolithic widely tunable lasers based on Vernier-
effect [6,7] or external cavity lasers, which have been demonstrated as table-top sources [8]. Most of the mentioned widely tunable laser technologies are well matured for the wavelengths below 1700 nm, while their implementation in the spectral region above 1.7 μm is scarce, the performance is quite limited or the emission is not in a single-mode regime [9–11]. These limitations are caused mainly by the lack of a high-quality gain-material. Thus the gain chip utilizing standard material platforms such as InP experiences a significant performance droop at the wavelengths above 1.7 μm, while limited efforts have been invested worldwide in alternative narrow-gap materials, such as GaSb with the spectral coverage up to almost 4 μm on a direct bandgap optical transition [12, 13]. In this work based on our early results on broadband superluminescent diodes used as gain-chips for widely tunable external cavity lasers [14], we go further and demonstrate the full potential of GaSb type-I quantum well based light source technology with the emphasis on the GaSb gain-chip devices as a gain medium for widely tunable coherent radiation sources rather than broadband incoherent sources. Furthermore, we discuss the application scenario of such sources for biomedical sensing of some critical biomolecules and demonstrate a spectroscopic sensor concept with an experimental sensing validation of a number of critical biomolecules including a non-invasive measurement of human serum albumin absorbance spectrum recorded from a human wrist.

2. Materials and methods

In this work we present results on swept-wavelength lasers based on the GaSb gain-chips operating in the external-cavity Metcalf-Littman configuration and tunable with a high-speed MEMS mirror. The gain-chips are the key enabling components of such widely tunable lasers, because they define the tuning range and the output power. For the best performance, the direct type-I quantum well technology based on GaSb alloys was chosen.

The device wafers were epitaxially grown on 3-inch Te doped n + GaSb substrates using an industrial solid-source multi-wafer molecular beam epitaxy machine, equipped with Al, Ga, In, As, Sb as elemental source materials and Si, GaTe and Be as dopant sources. The device layer sequence was started with a 50 nm n-doped GaSb buffer followed by a 60 nm thick AlxGa1-xAsySb1-y linearly graded layer, nominally doped at 1 x 10^{18} cm\(^{-3}\) density and compositionally graded from 0 to 50% on Al content and As concentration adjusted so as to maintain the lattice matching to the substrate. The grading was followed by a 2.2 μm thick lower Al0.5Ga0.5As0.04S0.96 cladding, in which first 1500 nm were nominally doped to 3 x 10^{17} cm\(^{-3}\) and the following 700 nm were doped to 7 x 10^{17} cm\(^{-3}\) in order to reduce the free-carrier induced losses of the optical mode. The cladding layer was followed by an undoped AlxGa1-xAsySb1-y waveguide and a barrier layer, in which two compressively strained quantum wells (QWs) were embedded. QW emission wavelength was tuned by changing the alloy composition in the quantum well. Thus for 1.7 μm wavelength, AlGaInSb QWs were used in the active region. For 1.9 and 2.1 μm emission wavelengths, GaInSb QW material was used. For longer wavelengths, quaternary GaInAsSb QWs were used. QW and waveguide thicknesses were adjusted for a 1% transverse vertical optical confinement factor per QW. For the optical mode symmetry, both waveguide layers on the n and p sides were left nominally undoped. The p - side waveguide was followed by 2.2 μm thick Al0.25Ga0.75As0.02Sb0.98 cladding doped with Be. The first 700 nm of the layer were doped at 1 x 10^{18} cm\(^{-3}\), followed by a 500 nm thick slice doped to 1 x 10^{18} cm\(^{-3}\), while the last 1000 nm of the cladding were doped to 5 x 10^{18} cm\(^{-3}\). Cladding was followed by 60 nm p\(^{+}\) AlxGa1-xAs0.08Sb0.92 cladding grading and topped with 200 nm of a heavily Be-doped (1 x 10^{19} cm\(^{-3}\)) GaSb p-contact layer.

The wafers were processed as quasi-index guided single-angled facet (SAF) gain-chip devices. For a single spatial mode output, the 4 μm-wide and ~1.5 μm-deep ridge waveguides were defined by UV photolithography and Cl-based ICP RIE etching, followed by sputtering of a ~330 nm thick SiO\(_2\) insulation. A contact window on the top of the ridge was defined by lithography and opened by means of CF\(_3\)/O\(_2\) based ICP-RIE dry etching. Ti/Pt/Au was used as
a top ohmic contact followed by a ~2 µm thick Au plated heatsink. The wafers were thinned down to ~120 µm to facilitate cleaving. As the last step, the back side Ti/Pt/Au contact was evaporated. The wafers were cleaved into bars of 1 mm and 0.7 mm cavity length and the bar facets were coated. The output facet was anti-reflection coated to have the reflectivity < 0.1% and the back facet got a high reflectivity coating with the reflectivity > 95%. Each bar contained 18 angled gain-chips and 2 straight ridge Fabry-Perot (FP) laser chips used as a reference for facet reflectivity measurements and basic laser parameters extraction for comparison and evaluation of the gain-chip performance in the external cavity configuration.

3. Results

The main results are presented in the three subsections below, we discuss, respectively, the gain-chip performance, the widely tunable laser operation and the model experiment using this laser as a spectroscopic instrument (a sensor). In this paper we would like to address the versatility of the GaSb gain-chip technology and its perspectives as a widely tunable laser platform enabling biomedical sensing applications of a high potential impact. A detailed technical report on the design of our widely tunable laser and its characteristic properties such as a linewidth, mode-hopping, stability, etc., falls outside the scope of this article and will be published elsewhere.

3.1 Gain-chips

An optical microscope image of the processed angled-facet gain-chip is shown in Fig. 1. An extremely low output facet reflectivity is essential for reaching the widest tunability in the external cavity laser configuration as it affects the laser stability, mode-hopping, wavelength selectivity and tuning as well as the ability to fully exploit the material gain bandwidth. For a sufficiently low reflectivity of the output facet, the device does not lase but emits in amplified spontaneous emission (ASE) regime. A small amount of optical feedback can initiate lasing and cause a collapse of a broad ASE spectrum to a narrow lasing spectrum. Our angled waveguide design combined with the deposition of an AR facet coating allows us to routinely reach the modal facet reflectivity in the $10^{-4} - 10^{-5}$ range [15, 16]. A good indication for low modal reflectivity is a complete quenching of the self-lasing effect in the stand-alone gain-chip after the deposition of the AR/HR coatings. This is indicated by infinite lasing threshold currents in all gain chips in Table 1, which summarizes the gain-chips used as light sources for widely tunable lasers at different wavelengths, their active region design, cavity length and main performance figures. It can be seen that very low modal reflectivity values are achieved in the entire 1700 – 2400 nm range. Detailed explanation of the methodology for evaluating experimental modal facet reflectivity for angled facet gain-chips that was used in this work can be found in our earlier work [15].
Fig. 1. (a) Optical microscope image of a processed angled facet gain-chip. The arrow mark at the bottom left corner indicates the output facet direction; (b) SEM image of the processed gain-chip displaying dry-etched ridge and the electroplated Au heatsink.

Table 1. Design and main performance parameter summary for the gain-chips used in this work.

| λ_{center} (nm) | 1730 | 1920 | 2100 | 2300 | 2380 |
|----------------|------|------|------|------|------|
| QW material    | AlGaInSb | GaInSb | GaInSb | GaInAsSb | GaInAsSb |
| No of QWs      | 2    | 2    | 2    | 2    | 2    |
| L_{cavity} (mm) | 0.7  | 0.7  | 0.7  | 0.7  | 1    |
| θ_{waveguide} (deg) | 5    | 5    | 6    | 7    | 7    |
| P_{ASE} (mW)^1 | 0.3  | 3.3  | 2.6  | 0.6  | 6    |
| P_{FPre} (mW)^2 | 14   | 66   | 53   | 28   | 40   |
| I_{thGC} (mA)^3 | ∞    | ∞    | ∞    | ∞    | ∞    |
| I_{thFPre} (mA)^4 | 205  | 160  | 150  | 220  | 100  |

1 P_{ASE} – maximum ASE output power measured in free-running mode; 2 P_{FPre} – maximum output power measured from the reference Fabry-Perot laser diode within the same bar; 3 I_{thGC} – self-lasing threshold of an angled waveguide chip; 4 I_{thFPre} – threshold current of a reference Fabry-Perot laser diode (AR/HR coated) within the same bar.

The normalized emission spectra of this family of GaSb gain-chips are shown in Fig. 2. The drive currents were fixed at two times above the corresponding threshold currents of the reference FP lasers in order to facilitate their comparison. It can be seen that the spectrum of the 1920 nm gain-chip is strongly affected by the absorption of an atmospheric water vapor, whereas the emission of a 2300 nm gain-chip has a strong dual band emission with peaks centered at 2300 nm and 2000 nm. The longer wavelength emission band corresponds to the optical transition between the ground levels of the quantum well e1 – hh1, whereas the shorter wavelength band originates from the transition between the first excited levels e2-hh2. The ASE emission on this transition can be reached due to the subband filling effect in the gain-chip with the high self-lasing threshold due to the combination of the low-AR facet coating and waveguide bending, as discussed in [17]. The subband filling effect is largely favored by the low-effective mass of the heavy holes in the compressively strained quantum well and by the weak electron-phonon scattering in the GaInAsSb material. In the present paper, the external cavity is adjusted to assist the laser operation between the ground states in the QW. However, it is possible to optimize the external cavity for lasing at any frequency within the...
gain curve of the two transitions, resulting thus in a very broad tuning range from a single chip. In our prototype shown in Fig. 3(a) we were limited by the MEMS mirror tilt angle range, admitting the frequency tuning across each of the two transitions separately, as discussed in the next section.

Fig. 2. Normalized amplified spontaneous emission (ASE) spectra for a family of the gain-chips CW driven in similar conditions – i.e. at pump currents being twice larger the corresponding reference FP laser threshold currents indicated in Table 1. The heatsink temperature was maintained at 20 °C. The ASE spectra from different gain-chips are indicated by different colors.

3.2 Swept-wavelength external cavity laser

In order to demonstrate the full potential of GaSb type-I QW gain-chip technology platform we have chosen to build external cavity laser based on the Metcalf-Littman configuration. In order to enhance the wavelength tuning speed, an electrically driven Au-coated tilt-tunable MEMS mirror was chosen with a mechanical resonance frequency of ~200 Hz, thus offering the sweep rates in excess of 100 Hz. For the external cavity setup we used a commercial off-the-shelf holographic diffraction grating with 600 grooves/mm and a blaze wavelength of 1200 nm. A commercial short-focal length and high NA aspheric lens was used for the beam collimation. A photographic picture of the external cavity assembly with indication of the main building blocks is shown in Fig. 3(a). However, for these preliminary experiments, we were not able to find off-the-shelf collimation lenses equally good suited for all studied wavelengths, as it can be seen from the higher operating currents in some of the gain chips in Fig. 3(b). The laser based on the gain-chip with emission centered at 2380 nm had an optimal mode profile for coupling with the collimation lens used, and its lasing threshold (measured in Fig. 3(b) with the MEMS mirror angle adjusted for 2420 nm) was substantially lower as compared to the lasers based on four other gain-chips. (In future work, we will improve the collimated beam quality by optimizing the gain-chip design to be better suited for available commercial collimation lenses.) Comparing the data in Table 2 and the $L-I-V$ performance curves in Fig. 3(b), one can spot that for a well collimated beam of the gain chip, the threshold current of the external cavity laser is comparable to that of the stand-alone reference Fabry-Perot laser. The experimentally recorded laser emission spectra at fixed MEMS mirror tilt angles are shown in Fig. 4. An inset shows one selected emission spectra plotted in the logarithmic scale to illustrate the single-mode lasing. The side-mode suppression ratio...
(SMSR) of better than 25-35 dB is routinely achieved in all lasers. The SMSR value indicated in the inset of Fig. 4 is mainly limited by the dynamic range of our FTIR spectrometer (~30 dB). A detailed study on the performance of this MEMS-tunable external cavity laser will be published elsewhere. The main performance parameters of the tunable lasers are summarized in Table 2.

Fig. 3. (a) A photograph of the prototype of widely tunable MEMS laser with indicated main building blocks. The red line illustrates the beam path in the cavity; (b) L-I-V performance data of MEMS based external cavity lasers operating in single wavelength mode. Experimental conditions were: heatsink temperature at 20 °C, operation mode continuous wave.

Fig. 4. Laser emission spectra from the different lasers recorded at fixed MEMS mirror positions, in a linear scale. The inset represents one selected spectrum in a log scale showing the side-mode suppression ratio of > 35 dB and indicating the single mode operation. The curve colors are used to indicate the link between the laser data and the respective gain-chip data in Fig. 2.
For a wide wavelength sweep across the spectral bandwidth of the gain-chip, the MEMS mirror was driven with a sine-wave signal changing the mirror tilt angle from $-5$ to $+5$ degrees. As can be seen from Fig. 5, this travel range was not sufficient to exploit the full bandwidths of the gain-chips, and thus laser tuning performances were limited by the MEMS mirrors rather than by the gain-chips. This is particularly visible in the 2300 nm and 2380 nm gain-chips. Nevertheless, all our swept-wavelength GaSb lasers demonstrate excellent performance, showing the maximum output powers up to 50 mW in the single-mode operation regime and the tuning bands of > 200 nm/chip while maintaining the CW output powers above 20 mW across the entire tuning bands. To the best of our knowledge, both in terms of the output power and the tuning bandwidth, these results are beyond the state-of-the-art tunable GaSb lasers in the 1.9–2.5 micron spectral range. The laser based on the gain-chip centered at 1700 nm has significantly lower output power and tuning range performance as compared to the long-wavelength counterparts. We attribute this to our premature GaSb gain-chip design used at such short wavelengths and expect to improve it in a future work. Nevertheless we note that the performance of our 1700 nm external cavity laser is still comparable to or better than commercial state-of-the-art widely tunable lasers available in the market. In addition, our implementation of a widely tunable laser based on a compact, lightweight MEMS mirror allowed us to significantly reduce its footprint as compared to the commercial competitors based on mechanical stages for grating or mirror rotation.

![Fig. 5. Laser tuning curves in five widely swept wavelength lasers recorded at 20 °C heatsink temperature, CW operation mode. The curve colors are used to indicate the link between the laser data and the respective gain-chip data in Fig. 2.](image)

For the fast wavelength sweeping, the MEMS mirror was tested up to 150 Hz driving frequency, recording 300 spectra per second (on the forward and backward travels of the mirror), resulting in the wavelength sweeping speed of 66 000 cm$^{-1}$/s. Tuning speed is limited by the mechanical resonance of MEMS mirror used in the experiment (~200 Hz). An illustration of the fast sweeping is shown in Fig. 6. While the MEMS mirror allows very fast wavelength sweeping, it also introduces a nonlinear response in the sweep signal which needs to be taken into account when converting the time-domain signal into the wavelength domain. Such performance is extremely attractive for building a spectroscopic laser sensor that could be applied for real-time biomedical sensor applications. For this purpose we have performed a model experiment, which is presented in Section 3.3. In our spectroscopic sensor experiment, we have introduced an additional wavelength control circuitry to take the nonlinear MEMS mirror response effect into account.
It can be seen from Table 2 that our widely tunable laser platform offers impressive performance such as the routinely achievable wavelength tuning bandwidth in excess of 380 cm\(^{-1}\) per chip, the output powers exceeding 20 mW in the entire 1.9-2.5 micron spectral band and the wavelength sweeping frequency in excess of 100 Hz. These results mark a new technological opportunity for such applications as optical coherence tomography (OCT) and real-time sensing for biomedical or LIDAR applications. In the next section we present a spectroscopic sensor demonstrator for biomolecule sensing applications based on our swept-wavelength external cavity laser prototype.

### 3.3 Swept-wavelength spectroscopic sensor

Encouraged by the wide spectral tuning performance of our swept-wavelength GaSb laser, we consider it as a key building block for a spectroscopic sensor in biomedical applications for detecting key biomolecules such as glucose, lactates, urea, albumin, etc. in a real-time manner and, potentially, non-invasively. While our current sensor prototype is implemented with discrete opto-mechanical elements such as MEMS mirrors, diffraction gratings, aspherical lenses, etc., our ultimate goal is to transfer this technology to a hybrid GaSb/Si platform, for which initial proof-of-concept solutions have already been demonstrated [18, 19]. Four molecules of interest were selected for the model experiment: urea, glucose, lactate and bovine serum albumin (BSA). BSA was used as a surrogate simulator of human serum albumin (HSA) due to their nearly identical molecular structures and molecular masses (BSA – 66.4 kDa, HSA – 66.5 kDa). The molecules were dissolved in Tris-Buffered-Saline (TBS) solution at different concentrations. Table 3 summarizes the target molecules, their physiological concentrations [20] and the relevant importance as biomarkers for healthcare applications. As a validation method we compared the spectra measured with our
spectroscopic sensor to the ones obtained with a table top FTIR spectrometer. The molecular spectra in the solutions were recorded in the transmission mode.

Table 3. Summary of the biomolecules used for the spectroscopic sensor experiment.

| Molecule          | Typ. physiological range (mmol/l) | Concentrations used in the experiment | Main absorption peaks (nm) | Relevance as a biomarker                                      |
|-------------------|-----------------------------------|--------------------------------------|---------------------------|-------------------------------------------------------------|
| Bovine serum albumin | 35-55 *                           | 30-50                                | 2174, 2255, 2285          | Main blood plasma protein, nutrition/hydration             |
| Urea              | 3.6-7.1                            | 2-30                                 | 2150, 2200                | Renal function                                              |
| Lactate           | 0.6-1.7                            | 5-50                                 | 2092, 2260, 2300          | Sepsis, trauma severity, athlete performance, Diabetes, metabolic disturbances |
| Glucose           | 4.2-6.4                            | 5-50                                 | 2140, 2270, 2330          | Diabetes, metabolic disturbances                            |

* Bovine serum albumin concentration is in [g/l].

In order to detect the molecules listed in Table 3, we have assembled a spectroscopic laser sensor consisting of three widely swept-wavelength lasers based on the gain-chips centered at 1920 nm, 2100 nm and 2300 nm as indicated in Fig. 7. The gain-chip at 1920 nm was added primarily to allow a coverage of the water molecule dominant absorption region for baseline and water displacement correction. Three collimated beams from the swept-wavelength lasers were combined into a solitary beam using free-space optics. After that they were transmitted through a 1 mm thick cuvette filled with the investigated molecular solution. The transmitted signal was collected and focused to a GaInAs photodiode with extended sensitivity range and a cut-off wavelength above 2.65 μm. The absorption spectra were extracted by taking the ratio between the transmission curves measured in the sample and in a reference TBS cuvette of the same thickness 1 mm.

![Fig. 7. Schematic diagram of a swept-wavelength laser (SWL) based spectroscopic sensor.](image)

The absorption spectra of the four main molecules extracted from the transmission measurements with the single GaSb-based swept-wavelength laser (SWL) are shown in Fig. 8 in comparison with the transmission measurements obtained with the tabletop FTIR spectrometer. It can be seen that the laser-based measurements nicely reveal the ro-vibrational absorption bands of the investigated molecules as affirmed by a good agreement with the FTIR measurements. The laser-based measurements allow recording of the entire absorption
bands due to the extremely broad tuning bandwidths (more than 200 nm) of our lasers. Note that the weak absorption features in glucose and urea molecules are more clearly pronounced in the laser-based measurements as compared to the FTIR spectra, indicating a better sensitivity of our sensor due to much higher brightness of the light source. This again indicates the potential of the laser-based spectroscopic sensor in low-concentration sensing. Figure 9 illustrates experimentally measured transmission spectra of urea in a broader range of concentrations, extending down to its physiological concentrations in a healthy human blood. The sensitivity and the ability to identify the underlying spectral features greatly increases with the wavelength sweeping bandwidth, allowing an easier baseline control and straightforward decoupling of the targeted molecular signatures from the entire complex.

The wide spectral coverage in our spectroscopic sensor is realized by combining three GaSb swept-wavelength lasers as indicated in Fig. 7. The molecular absorbance spectrum recorded with the spectroscopic sensor in a very broad spectral range is shown in Fig. 10. It can be seen that the wide-range scanning nicely captures the entire absorption fingerprint of the BSA molecule including the weak spectral features at 2060 nm, 2270 nm and 2350 nm. It must be noted that the entire spectrum was recorded in less than a second, thus offering opportunity for real-time sensing.

![Fig. 8. Absorbance spectra of (a) 50 g/l BSA solution, (b) 30 mmol/l urea, (c) 50 mmol/l glucose and (d) 50 mmol/l lactate molecules recorded in transmission mode using a swept-wavelength laser (blue line) and a tabletop FTIR spectrometer (orange line). Solutions were kept at room-temperature, nominally 21 °C.](image-url)
For non-invasive in-vivo sensing application, the spectroscopic sensor was reconfigured for measurements of diffuse reflectance from a sample as shown in Fig. 11. We used a dual core ultra-dry fused silica fiber probe with very low OH content (0.25 ppm) and a NA of 0.22. The two fiber cores were identical, with a diameter of 600 microns each and a cladding thickness of 60 microns. The distance between the center of the emission core and the center of the collection core was 720 microns and the edge to edge gap was 120 microns. The combined SWL beam was coupled into one core of the fiber probe, which was put in a direct contact with the human wrist. The second core was used to collect the diffuse reflection signal from the underlying tissue and the collected light signal was then focused on a GaInAs photodiode.
Initially, in order to evaluate the feasibility of such a non-invasive measurement with a commercially available fiber probe, we performed 3D Monte-Carlo simulations of the light-tissue interaction and evaluate the light penetration depth and propagation path. The Monte-Carlo model was adapted after [21], and the simulation parameters were used based on the literature data found in [22, 23]. The 2D cross-sections of the statistical distributions for propagation path of the collected photons and the photon absorption are plotted in Figs. 12(a) and 12(b) respectively. The simulations predicted that the light penetration depth in the skin is almost 1 mm, in reasonable agreement with the literature data [24]. At the same time, our simulations showed that the majority of photons collected by particular probe was scattered within the first 0.5 mm thick skin underlying tissue. Furthermore, the absorption was strongest in the 200-300 μm thick region below the skin surface. This depth coincides with the approximate location of the papillary dermis layer, containing a dense network of capillary blood vessels, the primary target for our non-invasive optical probe. Our simulations showed that the selected off-the-shelf dual-core fiber probe is far from the most optimal one, collecting only 0.041% of the incident light from the launch fiber, with only 22% of the collected light being scattered from the papillary dermis layer. The poor collection efficiency of the commercially available fiber probe was compensated for by the high output power in the entire tuning bandwidth of our swept-wavelength lasers. In our setup, the typical output power out of the fiber was ~10-15 mW in the entire tuning band of all three lasers, yielding the diffuse reflection signal of 4 – 6 μW magnitude and containing about 1-1.5 μW power scattered from the papillary dermis layer. This signal can be detected with commercial GaInAs photodiodes operating at room-temperature and showing sensitivities down to several tens of pW. We thus concluded that non-invasive sensing of biomolecules in the human skin tissue is feasible with the considered spectroscopic sensor and the fiber probe geometry.
For the non-invasive sensing experiment, an informed consent was obtained from two patients volunteered to perform the study. Human subjects were white Caucasian skin type 34 years old male individuals. All reported testing conform to the ethical requirements as defined the Lithuanian biomedical research ethics law No.VIII-1679.

For the proof-of-concept experiment, the fiber probe was put in a gentle contact with the skin of two patients using approximately the same locations on the wrists. A few experimentally measured diffuse reflectance spectra are shown in Fig. 13(a). The measurements showed good repeatability, each time revealing a fairly strong spectral dip seen around 2170 nm in the raw data, where the human serum albumin has a strong absorption, as demonstrated in the previous section (see Fig. 8(a)).

The raw measured data were then processed, accounting for the silica fiber dispersion and background water absorption. The silica fiber exhibits a strong absorption cut-off at the wavelengths > 2100 nm, which can be appreciated from the measured fiber transmission in Fig. 13(b).
The background signal originates primarily from the water absorption and, like the fiber transmission cut-off, it needs to be taken into account in the baseline normalization of the measured diffuse reflectance spectra. For this purpose, we used the product of experimentally measured fiber transmission function and TBS transmission spectrum in a cuvette. The resulting transmission spectrum was scaled to fit the background at the edges of measured diffuse reflectance spectra from the wrist as indicated in Fig. 14(a). Using it as a baseline, we removed the TBS contribution and revealed the underlying molecular absorption spectrum of the tissue. The extracted absorbance spectra of the underlying tissue are shown in Fig. 14(b). For comparison, we have also plotted the absorbance spectrum of the bovine serum albumin. The dominating human serum albumin absorption is clearly visible, in agreement with the consideration that the HSA is the most abundant protein in the human blood plasma, constituting about 50% of the total serum proteins.

The measured in-vivo diffuse reflectance spectra also contain information about other molecules such as lactate, glucose, urea, etc. These can be revealed by a spectral decomposition of the extracted HSA spectrum, taking into account the specific signatures in the absorption spectra of these molecules, as discussed in the previous section. While this is by far not a simple task, we believe we provided a clear path and experimental evidence for non-invasive in-vivo absorption spectroscopy of blood constituents based on widely tunable swept-wavelength laser diodes. The most striking feature of our sensor is the ability to record in-vivo the diffuse transmittance spectrum from a patient skin in a wide wavelength range and within a fraction of a second. To the best of our knowledge, this is the first report about a non-invasive in-vivo recording of the entire spectral fingerprint of a human blood protein absorption obtained using a swept-wavelength laser.

Fig. 14. (a) Experimental diffuse reflectance measurements plotted together with a fitted TBS absorbance spectrum (violet); (b) Molecular absorbance spectra recorded from a non-invasive measurement normalized with regard to TBS from two different persons labeled in the figure with letters “A” (blue and orange curves) and “B” (red and green curves). The bovine serum albumin absorbance spectrum (violet curve) recorded with a table top FTIR instrument is plotted as a reference.

4. Discussion

In this work we have revisited the possibility to perform spectroscopic sensing for biomedical applications in the “sweet” spectral region beyond 1.7 microns, which is attractive due to a
sufficiently low water absorption up to 2.5 micron wavelength and stronger combination band absorption of molecules as compared to their absorption in the near-infrared range. At the same time, this spectral range is accessible for commercially available room-temperature extended GaInAs photodiodes, which offers high sensitivities, ease-of-use and high-speed operation. The short wavelength infrared (SWIR) spectral region was not well exploited in the past, primarily due to unavailability or immaturity of the light sources. In this work we demonstrate a significant progress in performance of the light-sources based on GaSb type-I QW gain-chip technology, the key building block for the new widely tunable swept-wavelength laser platform. We demonstrate swept-wavelength lasers operating in single-wavelength mode in the entire 1.7-2.5 $\mu$m range, with the peak output power as high as 50 mW and routinely obtained wavelength tuning band of > 200 nm (or > 400 cm$^{-1}$) per chip at 10 mW or greater output power. Such performance is extremely attractive for building spectroscopic laser sensors. In this work, we present a SWL-based spectroscopic sensor for biomedical applications and we demonstrate its potential with several key biomolecules: bovine serum albumin, urea, glucose and lactates, uncovering the individual spectral signatures of each molecule and recording the molecular absorption spectra for concentrations as low as 2 mmol/l, which correspond to a physiological range. As a final milestone, we demonstrate the non-invasive in-vivo fast spectroscopic measurement through the human skin, uncovering molecular absorbance spectrum of the underlying blood and tissue. A clear spectroscopic signature from the most abundant molecule in blood plasma - human serum albumin - is demonstrated with two different persons. We hope the same technique will allow us to uncover the underlying spectra of other critical blood constituents such as lactates, glucose, urea, demonstrating a clear pathway towards a non-invasive in-vivo blood-analysis sensor for healthcare applications that would have a major impact to the healthcare system and life quality. The future work will be to implement the swept-wavelength laser and the spectroscopic sensor concept in a hybrid GaSb/Si technology introduced in the earlier work [9,10] and, at the same time, to perform the preclinical testing of the table top spectroscopic sensor discussed here.

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