SCIENTIFIC REPORT OF SHORT TIME SCIENTIFIC MISSION

STSM title: IR AND THZ SENSOR TECHNOLOGY FOR BIOMEDICAL IMAGING
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CONTENTS

1. Analysis of world research activities "Terahertz for skin cancer and biomedics"

1.1. Introduction

The COST Action BM1205 joins together the experts from the physics and laser technology fields with the professionals of the medical background. One important goal of the BM1205 is to enhance the knowledge about possibilities of using the "difficult" terahertz frequency range (0.1 – 1 – 10 THz, respectively 3 mm – 300 μm – 30 μm) for the human skin tissue characterization in order to develop new methodologies for the skin cancer detection. The other frequency ranges like visible EM radiation, near and mid IR and from other side the millimeter-waves are relatively well known and covered with powerful sources and detectors. Contrary to that, the terahertz "gap" needs special attention and efforts for the design of the compact and effective source-detector systems.

Although the terahertz technologies have been developed now already 50 years with the initial driving force in radio astronomy stimulated by the discovery of the cosmic background radiation (2.725 K, λ_{peak}=1.063 mm) in 1964, the practical use of THz radiation in biomedical applications is still in the rather beginning stage. Reason for that is the lack of convenient and efficient compact (solid-state) sources, somewhat also still existing problems with the availability of cheap, compact and efficient detectors that could be arranged in the form of focal plane arrays for imaging.

The situation has improved remarkably during the last 10 years. Important step forward was the design of the first THz range quantum cascade laser (QCL) in 2002[1]. Our earlier analysis[2] showed that after approximately year 2004 followed the boost of terahertz research so that presently around 2000 papers per year is published under that topic. It can be shown (see figures in Chapter 2) that approximately in year 2004 started also fast progress in the THz detector side with the introduction of the FET transistor based focal plane arrays capable to work at room temperatures. But serious work is needed also in source side as the THz QCLs need still cryogenic cooling (while mid IR QCLs can work at room temperature).

However, what should be emphasized - the transfer of THz technology to the biomedical field has not shown the proper progress as the number of respective publications is rather low (in the range of 20 per year). We will confirm this below by the analysis of the statistics from the Reuters Web of Science database. The COST BM1205 Action has here possibility to give here remarkable positive impact and also improve the position of Europe in worldwide competition in this high-tech field.

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1 *Nature* **417**, 156-159 (9 May 2002) Terahertz semiconductor-heterostructure laser. Rüdeger Köhler1, Alessandro Tredicucci1, Fabio Beltram1, Harvey E. Beere2, Edmund H. Linfield2, A. Giles Davies2, David A. Ritchie2, Rita C. Iotti3 & Fausto Rossi3

1. NEST-INFM and Scuola Normale Superiore, Piazza dei Cavalieri 7, 56126 Pisa, Italy
2. Cavendish Laboratory, University of Cambridge, Madingley Road, Cambridge CB3 0HE, UK
3. INFM and Dipartimento di Fisica, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy

2 R. Reeder, E. Velmre & A. Udal: Avances in terahertz technology with emphasis on quantum cascade lasers, Electronics and electrical engineering, 2010, N8(104), pp. 47-50.

1.2. Monitoring of research activity in the field of biomedical terahertz technology

Summary of publication activity is presented in Table 1.1 and in Fig. 1.1 below.

Table 1.1 Research activity (publications per year) results corresponding to the theme “Terahertz technologies for skin cancer detection, for skin and tissue research and for biomedical applications”. Statistics is obtained from the analysis of the inquiries from the Web of Science database.

Year	**“THz”** AND **”skin”** AND **“cancer”** (clear application for human skin cancer)	**“THz”** AND **”cancer”** NOT **“skin”** (other cancer types than skin cancer)	**“THz”** AND **”skin”** NOT **“cancer”** (skin research without focus on cancer)	**“THz”** AND **”tissue”** NOT **“skin”** NOT **“cancer”** (tissue research without focus on skin or cancer)	**“THz”** AND **”biomedical”** NOT **“skin”** NOT **“cancer”** (general biomedical applications without focus on skin or cancer)	**Sum of columns** (using terahertz radiation for any cancer or any tissue or biomedical applications in general)
2013	0	5	6	8	4	23
2012	2	4	5	0	7	18
2011	1	5	3	6	1	16
2010	2	2	7	2	3	16
2009	1	3	3	3	1	11
2008	1	1	5	5	4	16
2007	1	4	2	2	2	11
2006	1	2	0	0	2	5
2005	2	1	1	4	2	10
2004	1	1	1	2	4	9
2003	2			3	1	6
2002	1		1	2	8	12
2001			1	3	1	5
2000				1	1	2
1999						
1998						
1997				1		1
Sum	15	28	35	42	41	161

Remarks. All searches were made for topics=“Terahertz” that gave also positive answers if this keyword or abbreviation “THz” was mentioned in abstract. Other keywords were checked from title to be sure that only clearly relevant studies had been included. Additionally many irrelevant cases were excluded by content analysis (e.g. if electrical skin-effect was considered). Publications that considered animal tissues without possibility of generalization were excluded. Note that the table columns may be summarised to see total activity as generally the columns do not refer to same publication multiple times (with one exception “... biomedical tissue” from year 2001).

It must be mentioned that the presented statistics may somewhat underestimate the number of publications as it may omit the cases if the authors have used in titles the keywords with slightly shifted meaning, e.g. “carcinoma” instead “cancer” or “biological matter” instead of “tissue”.

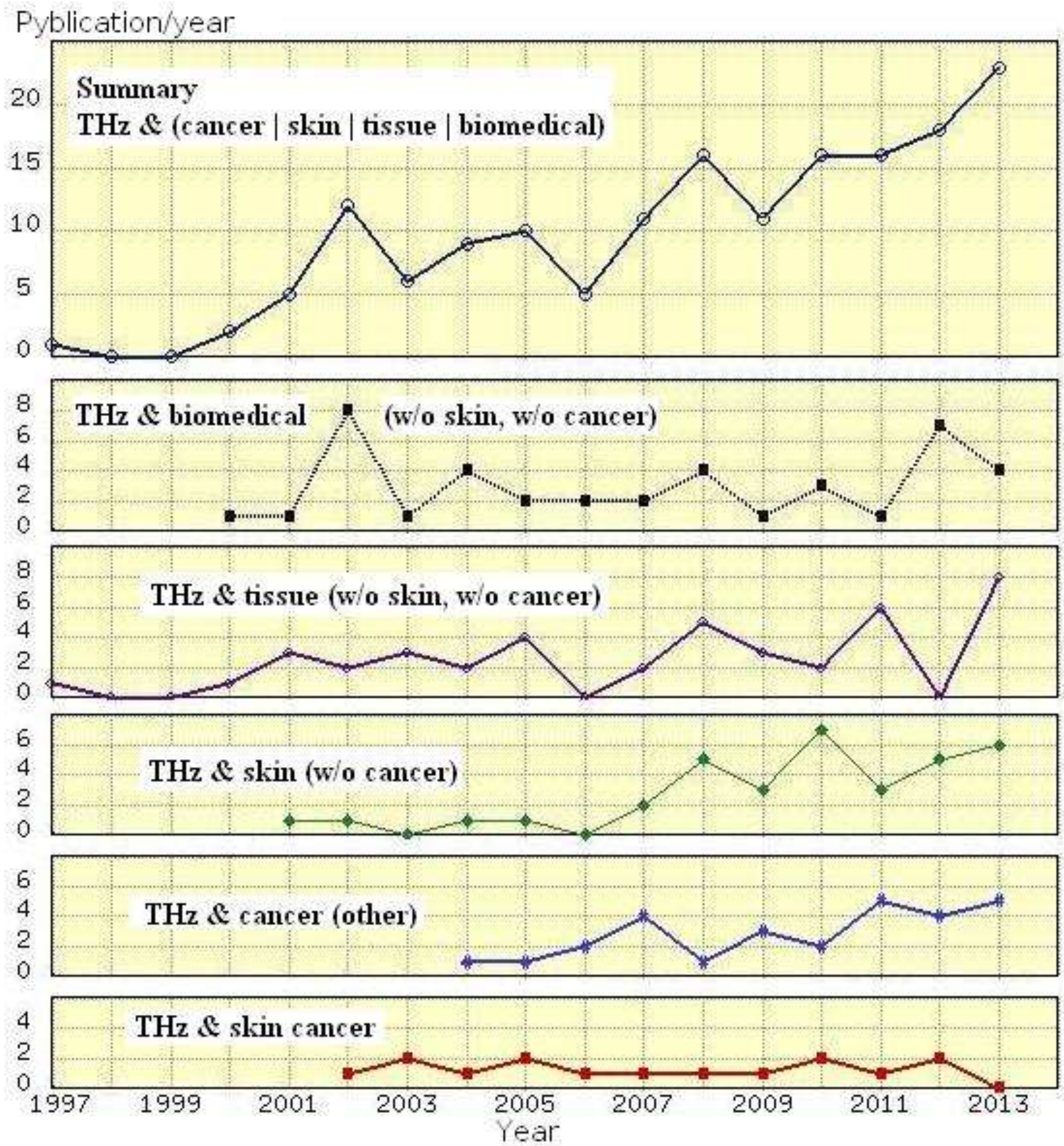

Fig. 1.1 Summary of publication activity under the theme “Terahertz technologies for skin cancer detection, for skin and tissue research and for biomedical applications”. Results correspond to the Table 1.1 and are obtained from the analysis of the inquiries from the Web of Science database.

1.3. Summary of the most influential publications and groups

The most influential publications in the subfields of THz biomedics are collected to the table 1.2.

Table 1.2 Summary of the most cited publications in the subfields of THz biomedics

Subtheme	Year	Authors	Affiliation	Publication	Cited
THz & skin cancer	2002	R. Woodward, B. Cole, V. Wallace et al.	Cambridge Univ. UK, TeraView Ltd.	Terahertz pulsed imaging in reflection geometry of human skin cancer and skin tissue, PHYS. IN MED. AND BIOLOGY, vol. 47, N21, p. 3853, (11 pages)	**218**
	2003	R. Woodward, V. Wallace, D.Arnone et al.	ibid.	Terahertz pulsed imaging of skin cancer in the time and frequency domain, JOURNAL OF BIOL. PHYSICS, vol. 29, N2-3, p. 257 (5 pages)	**101**
	2003	R. Woodward, V. Wallace, R. Pye et al.	ibid.	Terahertz pulse imaging of ex vivo basal cell carcinoma, JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 120, N1, p. 72 (7 pages)	**168**
	2007	M. Mogensen, G. Jemec	Copenhagen Univ.	Diagnosis of nonmelanoma skin cancer ..., DERMATOLOGIC SURGERY, vol.33, N10, P. 1158 (17 pages)	**56**
	2011	C. Joseph, A. Yaroslavsky et al.	Univ. Massachusetts USA	Continuous wave terahertz transmission imaging of nonmelanoma skin cancer, LASERS IN SURGERY AND MEDICINE, vol.43, N6, P. 457 (8 pages)	9
THz & cancer (focus on other cancers not skin)	2007	S. Nakajima, H. Hoshima et al.	Riken res. institute, JAP	Terahertz imaging diagnostics of cancer tissues with a chemometrics technique, APPL. PHYS. LETT., vol. 90, N4, 3 pages	40
	2009	S.J. Oh, J. Kang et al.	Univ. of Seoul, Yonsei Univ., KOREA	Nanoparticle-enabled terahertz imaging for cancer diagnosis, OPTICS EXPRESS, vol. 17, N5, p. 3469 (7 pages)	**59**
	2009	P. Ashworth et al.	Cambridge Univ. UK and partners	Terahertz pulsed spectroscopy of freshly excised human breast cancer, OPTICS EXPRESS, vol. 17, N15, p. 12444 (11 pages)	**81**
	2010	M-A. Brun, F. Formanek et A. Yasuda al.	Tokyo Medical and Dental Univ., JAP	Terahertz imaging applied to cancer diagnosis, PHYSICS IN MEDICINE AND BIOLOGY, vol. 55, N16, p. 4615 (9 pages)	18
	2012	C. Yu, S. Fan, Y. Sun, E. Pickwell-Mcpherson	Hong Kong Univ. of Science and Technology	The potential of terahertz imaging for cancer diagnosis: a review of investigations to date, QUANTITATIVE IMAGING IN MEDICINE AND SURGERY, Vol. 2, N1, p. 33 (13 pages)	12
THz & skin (focus on skin research not on cancer)	2001	B. Cole, R. Woodward, D. Crawley et al.	Toshiba Res. Europe Ltd., Cambridge UK and partners	Terahertz imaging and spectroscopy of human skin, in-vivo, SPIE book series: COMMERCIAL AND BIOMEDICAL APPLICATION OF ULTRASHORT PULSE LASERS ..., Vol. 4276, pp. 1-10 (11 pages)	41
	2004	E. Pickwell, B. Cole, A. Fitzgerald	Cambridge Univ. UK & Teraview Ltd.	In Vivo study of human skin using the pulsed terahertz radiation, PHYSICS IN MEDICINE AND BIOLOGY, vol. 49, N9, p. 1595 (13 pages)	**136**
	2008	Y. Feldman, Al. Puzenko, P. Ben Ishai et al.	The Hebrew Univ. of Jerusalem, IL	Human skin arrays as helical antennas in the millimeter and submillimeter wave range, PHYS. REV. LETT., vol.100, N12	16
	2009	Y. Feldman, Al. Puzenko, P. Ben Ishai et al.	ibid.	The electromagnetic response of human skin in the millimetre and submillimetre wave range, PHYS, IN MED. AND BIOLOGY, vol.54, N11, p. 3341 (23 p.)	18
	2009	J. Suen, P. Tewari, Z. Taylor et al.	Univ. of California L.A. USA	Towards medical terahertz sensing of skin hydration, Book series: Studies in health Technology and Informatics MEDICINE MEETS VIRTUAL REALITY ... , vol.142, p.364 (5 pages)	13
	2011	D. Bennett, W. Li, Z. Taylor et al.	ibid.	Stratified media model for terahertz reflectometry of the skin, IEEE SENSORS JOURNAL, vol.11, N5, p. 1253 (10 pages)	8

Table 1.2 (continuation) Summary of the most cited publications “THz and tissue”

Subtheme	Year	Authors	Affiliation	Publication	Cited
THz & tissue (no primary focus on skin or cancer)	2000	P. Han, G. Cho, X. Zhang	Rensselaer Polytechnic Inst., NY, USA	Time-domain transillumination of biological tissues with terahertz pulses, OPTICS LETTERS, vol. 25, N4. p. 242 (3 pages)	**152**
	2001	S. Smye, J. Chamberlain, A. Fitzgerald et al.	Leeds Teaching Hospitals, UK	The interaction between Terahertz radiation and biological tissue, PHYSICS IN MEDICINE AND BIOLOGY, vol. 46, N9, p. R101, (12 pages)	**90**
	2001	T. Loffler, T. Bauer, K. Siebert et al.	Frankfurt Univ. Giessen Univ. GE, Leeds Univ. GB	Terahertz dark-field imaging of biomedical tissue, OPTICS EXPRESS, vol.9, N12, p. 616 (6 pages)	**109**
	2001	B. Ferguson, B. Wang, S. Gray et al.	Rensselaer PI, NY, USA & Adelaide Univ., AU	Identification of biological tissue using chirped probe THz imaging, MICROELECTRONICS JOURNAL, vol. 33, N12, p. 1043 (19 pages)	**45**
	2003	A. Fitzgerald, E. Berry, N. Zinov'ev et al.	Leeds Univ. UK, Leeds Teaching Hospitals, UK	Catalogue of human tissue optical properties at terahertz frequencies, JOURNAL OF BIOLOGICAL PHYSICS, vol. 29, N2-39, p. 123, (6 pages) (0.5-2.5 THz)	**36**
	2005	J. Nishizawa, T. Sasaki, K. Suto et al.	Semic. Res. Inst., Sendai, JAP, Tohoku Univ, JAP and partners	THz imaging of nucleobases and cancerous tissue using GaP THz wave generator, OPTICS COMMUNICATIONS, vol. 244, N1-6, p. 469 (6 pages) (tested e.g. 0.835, 1.465, 2.86 THz)	**51**
	2008	M. Nazarov, A. Shkurinov, E. Kuleshov V. Tuchin	Moscow State Univ. and Saratov State Univ. RU	Terahertz time-domain spectroscopy of biological tissues, QUANTUM ELECTRONICS, vol. 38, N7, p. 647 (8 pages) (studied 0.1 - 3.5 THz)	**21**
	2008	G. Png, J. Choi, B. Ng et al.	Adelaide Univ. AU & Rensselaer PI, NY, USA	The impact of hydration changes in fresh bio-tissue on THz spectroscopic measurements, PHYSICS IN MEDICINE AND BIOLOGY, vol. 53, N13, p. 3501 (17 pages)	**40**
	2009	S. Huang, Y. Wang, D. Yeung et al.	Chinese Univ. Hong Kong	Tissue characterization using terahertz pulsed imaging in reflection geometry, PHYSICS IN MED. AND BIOLOGY, vol. 54, N1, p. 149 (12 pages)	**27**
	2009	H. Hoshina, A. Hayashi, N. Miyoshi et al.	Riken research inst., Fukui Univ. and partners, JAP	Terahertz pulsed imaging of frozen biological tissues, APPLIED PHYSICS LETTERS, vol. 94, N12	**28**
	2009	J-H. Son	Univ. of Seoul, KOREA	Terahertz electromagnetic interactions with biological matter and their applications, JOURNAL OF APPLIED PHYSICS, vol.105, N10	**37**
	2011	G. Wilmink, B. Ibey, T. Tongue et al.	Air Force Res. Lab. and partners, TX, USA	Development of a compact terahertz time-domain spectrometer for the measurement of the optical properties of the biological tissues, J. OF BIOMEDICAL OPTICS, vol.16, N4 (tested range 0.1-1.6 THz)	**11**
	2011	D. Bennett, Z. Taylor, P. Tewari et al.	Univ. of California L.A. USA	Terahertz sensing of corneal tissues, J. OF BIOMEDICAL OPTICS, vol.16, N5 (tested range 0.2-1 THz)	**14**

Table 1.2 (continuation) Summary of the most cited publications "THz and biomedical"

Subtheme	Year	Authors	Affiliation	Publication	Cited
THz & biomedical (no primary focus on skin or cancer)	2000	C. Ciesla, D. Arnone, A. Corchia et al.	Univ. of Cambridge, UK	Biomedical applications of terahertz pulse imaging, COMMERCIAL AND BIOMEDICAL APPLICATIONS OF ULTRAFAST LASERS, Book Series of SPIE, vol. 3934, p. 73 (9 pages)	34
	2002	T. Loffler, K. Siebert, S. Czasch et al.	Frankfurt Univ. and Giessen Univ. GE, Leeds Univ. GB,	Visualization and classification inbiomedical terahertz pulsed imaging, PHYSICS IN MEDICINE AND BIOLOGY, vol.47, N21, p.3847 (6 pages)	40
	2002	K. Siebert, T. Loffler, H. Quast et al.	ibid.	All-optoelectronic continuous wave THz imaging for biomedical applications, PHYSICS IN MEDICINE AND BIOLOGY, vol.47, N21, p.3743 (6 pages)	48
	2002	M. Beard, G. Turner, C. Schmuttenmaer	Yale University, CT, USA	Progress towards two-dimensional biomedical imaging with THz spectrometry, PHYSICS IN MEDICINE AND BIOLOGY, vol.47, N21, p.3841 (6 pages)	20
	2004	P. Siegel, R. Dengler	Caltech, CA, USA	Terahertz heterodyne imager for biomedical applications, TERAHERTZ AND GIGAHERTZ ELECTRONICS AND PHOTONICS, Book series: Proc. of SPIE, vol. 5354, p.1 (9 pages)	10
	2004	V. Wallace, P. Taday, A. Fitzgerald et al.	TeraView Ltd., Cambridge UK	Terahertz pulsed imaging and spectroscopy for biomedical and pharmaceutical applications, FARADAY DISCUSSIONS, vol.126, p.255 (9 pages)	**61**
	2006	S. Kim, F. Hatami, J. Harris et al.	Stanford Univ. and Univ. of California, USA & Univ. of Neuchatel, Switzerland	Biomedical terahertz imaging with a quantum cascade laser, APPL. PHYS. LETT., vol. 88, N15 (used 3.7 THz)	**56**
	2006	E. Pickwell, V. Wallace	TeraView Ltd., Cambridge UK	Biomedical applications of terahertz technology, JOURNAL OF PHYSICS D - APPLIED PHYSICS, vol. 39, N17, p.R301 (10 pages)	**147**
	2010	M. Schirmer, M. Fujio, M. Minami et al.	Osaka Univ. and Tokushima Univ. JAP	Biomedical applications of a real-time terahertz color scanner, BIOMEDICAL OPTICS EXPRESS, vol. 1, N2, p. 354 (13 pages)	12

Remarks. Table 1.2 reveals also the activity of the research groups. The founding leader in this area seems to be the Cambridge group (R. Woodward, V. Wallace, E. Pickwell, A. Fitzgerald, B. Cole, D. Arnone et al.) that worked actively around the Cambridge University and the TeraView Ltd. company in Cambridge Science Park in years 2002-2006. Later V. Wallace moved to the Western Australia University and E.Pickwell to the Hong Kong.

1.4. Conclusion

1. The activity of the using THz radiation for the biomedical applications has been surprisingly low (in the range of 15-20 publications per year during recent 6 years). This is only 1% of all publications related to usage of THz radiation!
2. Only couple of papers per year have been dedicated directly to the skin cancer detection!
3. It seems that the most influential publications belong to the time period of 8-12 years old. So the recent boost of development of new efficient detectors (FETs and others) and sources (QCLs and others) has not touched the biomedical applications field.

2. Analysis of world research activities “Terahertz and transistors or other devices”

2.1. Introduction

In this chapter we analyse briefly the rise of the terahertz research in general. The main motivation here was to observe the influences of the appearance of the efficient room temperature focal plane detectors based on the field effect transistors (FETs) during the last years.

Due to the lack of the time, we are not presenting here the deeper content-related analysis. First of all, content-related analysis would be needed to divide papers to the detector and source oriented studies. At that would be important to bring out the new ideas in the field of detectors and sources, e.g. beginning of introduction of nanowires and graphene ribbons etc. Also it could be useful to try to visualise the map of most powerful research groups in Europe and in the world. This could give the useful background for better coordination of activities within the COST Actions BM1205 and MP1204.

2.2. Monitoring of the THz research activities relevant to different device solutions

Here we discuss the publication activity results obtained from the Reuters Web of Science. All searches were made by using inquiries in the form:
(“terahertz” AND “device” in title) OR (“THz” AND ”device” in title)

In the place of “**device”** were studied the following choices:
a) transistor (mainly to assess the increasing activities related to the FET detector arrays)
b) diode (to see the basic activity level of using different diodes in THz applications)
c) bow-tie (to assess the usage of new simple bow-tie diode detector structures)
d) bolometer (to assess usage of this old classical heating-based detector type)
e) microbolometer (to assess introduction of new microscale bolometer structures)
f) nanowire (to see attempts to use those small 1D FET structures for detecting)
g) nanotube (to see beginning of using those popular nanostructures in the THz field)
h) graphene (to see beginning of using of this future material in the THz field)
i) nanoribbon (to see if graphene nanoribbon transistor idea has been extended to THz applications)

The relevant publication statistics is summarized below in Fig. 2.1.

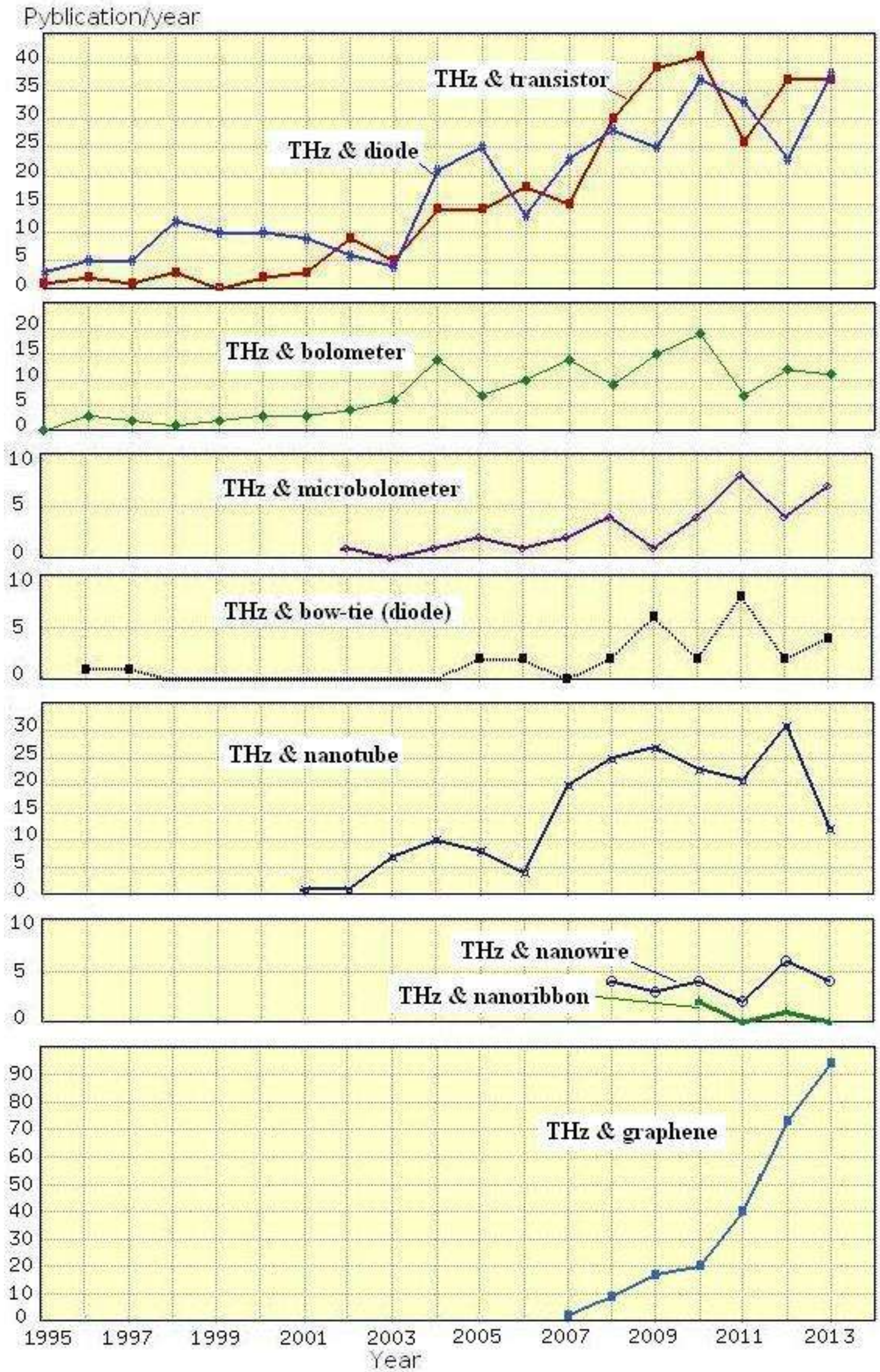

Fig. 2.1 Summary of terahertz research activity from viewpoint of used device solutions. Results are obtained from the Web of Science database.

Note: Here publications may be accounted multiple times, e.g. “graphene nanoribbon transistor” in title could yield the triple accounting.

2.3. Conclusion

Results collected in Fig. 2.1 allow to formulate several interesting conclusions:

1. Noticeable increase of usage of transistors started after the year 2003. Still remarkable number of studies uses the different types of diodes. It seems that there were a peak in transistor publications in 2009-2010 when remarkable success was achieved in development of FET-based focal plane arrays for imaging.

2. During last 10 years have been taken into the use the microbolometers and the bow-tie diodes. Still number of relevant publications has remained rather low in the range of 5-8 publications per year.

3. Surprisingly great number of publications around 10-25 per year have been dedicated to nanotubes during last 10 years. At the same time the interest towards nanowires and nanoribbons is in the very beginning stage.

4. The real exponential boost may be observed relevant to the use of graphene in terahertz technology, The number of publications per year (93 in 2013) is reaching the same order than all other considered device categories together.

3. The overall short summary of STSM

Description of the work carried out during the STSM:

1. Visit to the Biophotonics Laboratory at the University of Latvia, Skunu str. 4, Riga (LV) (Head of Lab. Prof. J. Spigulis, BM1205 MC member).
2. Work in the Terahertz Lab. of Optoelectronics Dept. of the State research institute Center for Physical Sciences and Technology, Goštauto str. 11, Vilnius (LT) (Dir. Prof. G. Valušis , BM1205 MC member, Head of Lab. Dr. I. Kašalynas, BM1205 MC subst. member).
3. Giving scientific presentation in Terahertz Laboratory 07.03.2014.
4. Visit to the Vilnius Univ. Division of the Materials Engineering, Sauletekio str.10, also to the Dept. of Quantum Electronics (Sauletekio 9).
5. Visits to the other laboratories of the Optoelectronics Dept. of the State research institute: Ultrafast Optoelectronics Lab, Optoelectronics Technologies Lab, Semiconductor Optics Lab (MP1204 MC member Prof. A. Krotkus and MP1204 subst. member Dr. R. Butkute).
6. Work with literature and completing overviews on using THz in biomedical applications and on using different device solutions for THz sources and detectors.
7. Discussing further cooperation plans on theoretical and computer-aided analysis of new THz sources and detectors based on quantum well structures.

The main conclusions from this STSM were the following:

1. Vilnius seems to be one of the strongest semiconductor technology and laser technology centers in Europe. Due to strong support from government and European funds and building of new research facilities this strength is even growing during the next years. This would be reasonable to take into account in planning of cooperation within the BM1205 and MP1204 actions to achieve the general goals.

2. Overall world research intensity in the field of application THz radiation for skin cancer and other cancer types detection is surprisingly low. Thus the action BM1205 can improve remarkably the situation in this area.

3. Riga Biophotonics Laboratory has developed the excellent practical handheld devices on the basis of visible LEDs and near IR LEDs for skin analysis. The BM1205 action partners could consider possibilities to extend this experience to longer IR wavelength regions and to usage of additional possibilities offered by coherent laser radiation.