OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: Raoul Kopelman

eRA COMMONS USER NAME (credential, e.g., agency login): kopelman

POSITION TITLE: Richard Smalley Distinguished University Professor of Chemistry, Physics, Applied Physics, Biophysics, Chemical Biology and Biomedical Engineering; Member of the Rogel Cancer Center and of the Biological NanoTechnology Center, The Medical School, The University of Michigan.

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Israel Institute of Technology | BS | 06/1955 | Chem. Engineering |
| Israel Institute of Technology | Eng. Dipl. | 06/1956 | Chem. Engineering |
| Israel Institute of Technology | MS | 06/1957 | Physical Chemistry |
| Columbia University | PhD | 10/1960 | Chemistry |
| Harvard University | Postdoc | 08/1962 | Chemistry |

**A. Personal Statement
I am an expert in photonics, laser and bioanalytical chemistry, chemical biology, and molecular and nano-materials. I coined the term nanophotonics and invented the nanoscale photon source, nanoscale voltmeter, nanoscale viscometer, Bio-nanosensors (called nano-PEBBLES) for intracellular bio-chemical imaging, and the Cell Magneto-Rotation (CMR) method. I initiated the concept and practice of targeted multifunctional nanoparticles for medical applications, such as targeted theragnostic nano-carriers containing therapeutic agents (chemo, photodynamic and photo-thermal) as well as contrast agents for structural imaging, by MRI, PET, CT and PAI (Photo-Acoustic Imaging). I collaborated with radiologists, oncologists and cardiologists, resulting in (1) First targeted photodynamic nanoparticle based therapy of cancer, in 9L glioma rat models; (2) First cell-specific arrhythmia photo-ablation in live rat and sheep hearts; (3) Nanosonophores for functional (chemical) PAI, so as to quantitatively image *in-vivo*, in the tumor micro-environment (TME), the entire “triad of chemical resistance to therapy” (low O2, low pH and high K+, respectively resisting radio-, chemo- and immuno-therapy) Testing the TME in PDX models we now hope to learn more on its chemical make-up and its effects on therapy success, so as to translate specific patient information into advice for care givers about the most promising treatment, whether therapy or surgery.**

**I have mentored nearly 70 PhD students of Chemistry, Physics, Biophysics and Applied Physics, about half of them women, including the first black woman to receive a Michigan Physics PhD. Most of these PhD’s are now professors at primary universities or have senior jobs in industry and government. Also, 3 of my undergraduate students and 1 grad student received the Nobel Prize: Roald Hoffmann, Richard Smalley, Arieh Warshel and Eric Betzig.**

**B. Positions and Honors**

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| **Academic Appointments** |
| 2006-: | The University of Michigan, Richard Smalley Distinguished University Professor of Chemistry, Physics, Appl. Physics, Biophysics, Biomed. Engineering, & Chem. Biology; Member of Rogel Cancer and BioNanoTechnology Centers and the Interfaces Institute. |
| 1994-: | The University of Michigan, Fajans Collegiate Prof. of Chemistry, Physics & Appl. Phys. |
| 1971-: | The University of Michigan, Professor of Chemistry |
| 1968-71: | The University of Michigan, Assoc. Professor of Chemistry |
| 1966-68: | The University of Michigan, Asst. Professor of Chemistry |
| 1964-66: | California Inst. of Technology, Senior Research Fellow |
| 1962-64:  | Israel Institute of Technology, Lecturer in Chemistry |

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| **Other Experience and Professional Memberships** |
| 2019: | CCNE Site Visit, Review Panel, Northwestern, May 21, 2019 |
| 2017: | CCNE Site Visit, Review Panel, Northwestern, May 18, 2017 |
| 2014: | NIH/NCI IMAT Review Panel, Early-Stage Innovative Technology Development for Cancer Research (R21), March 27. |
| 2014: | NIH/NCI Review Panel, NCI Physical Sciences Oncology Centers, Nov. 12-13 |
| 2013: | NIH/NCI Jonsson Comprehensive Cancer Center (UCLA) Site Review Meeting, May 21-23 2013, Los Angeles CA. |
| 2013: | NIH/NCI IMAT Review Panel Early-Stage Innovative Technology Development for Cancer Research (R21), March 20-21. |
| 2012: | NIH Review Panel, Accelerating the Integration and Translation of Technologies to Characterize Biological Processes at the Single Cell Level (R01), May 2012. |
| 2012: | NIH/NCI IMAT "Early-Stage Innovative Technology Development” Review Meeting  |
| 2011: | NIH/NIBIB Peer Review Board, Diagnostics Without Nucleic Acid Amplification, Feb.28 |
| 2011: | NIH/NCI Special Emphasis Panel, Multifunctional Therapeutics based on Nanotechnology, July 15 |
| 2010: | NIH/NIBIB Nanotech Program Review, Jan. 26 |
| 2010: | NIH/NCI IMAT Review Panel, Oct. 13 |
| 2009: | NIH Study Section Bioengineering Sciences & Technologies IRG, Jan. 30 |
| 2009: | US Army Congressional Directed Medical Research: Peer Reviewed Cancer Program |
| 2009: | “Grand Opportunities” Cancer Nanotechnology Special Emphasis Panel, July 22-23 |
| 2009: | NIH/NCI Review Committee, Institute for Integrated Cancer Research, MIT, Oct. 20-22 |
| 2008: | NIH Study Section BST-M Topics in Computation, Imaging, and Delivery, Dec. 8 |
| 2007: | NIH Molecular Biology Special Emphasis Review Panel |
| 2007: | NIH/NIDA CEBRA (Cutting Edge Basic Research Awards Program) Review Panel |
| 2005: | NIH National Human Genome Research Institute (NHGRI) Review Panel |
| 2005: | NIH/NCI, Centers for Cancer Nanotechnology Excellence Review Panel |
| 2004: | NIH SSS-U Special Emphasis Panel, Center for Scientific Review |
| 2004: | NIH Bioanalytical, Engineering and Chemistry (BECM) Review |
| 2004: | NIH Nanoscience and Nanotechnology in Biology and Medicine Review Panel |
| 2001-02: | Visiting Prof., Institute of Biotechnology, Tel-Aviv University |
| 2001-02: | Visiting Prof., Center for Nanoscience and Nanotechnology, Tel-Aviv University |
| 2001-02: | NIH Advisory Board on Biotechnology |
| 2001: | NIH Fundamental Bioengineering and Technology Development Integrated Review  |
| 1994-95: | Visiting Prof., Tel-Aviv University, Institute of Chemistry |
| 1989: | Visiting Prof., Hebrew Univ. of Jerusalem, Dept. Applied Physics & Materials Science |
| 1988: | Visiting Prof., Swiss Federal Inst. of Technology, Zurich, Dept. of Physical Chemistry |
| 1987-88: | Visiting Prof., University of California, San Diego, Institute for Nonlinear Science |
| 1981: | Visiting Prof., University of Stuttgart, Institute of Physics |

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| **Honors and Fellowships** |
| 2013: | Etter Memorial Lecture in Materials Chemistry, University of Minnesota |
| 2011: | Pittcon Analytical Chemistry Achievement Award |
| 2006: | Distinguished University of Michigan Professor |
| 2005: | American Chemical Society Award in Spectrochemical Analysis |
| 2005: | “Nanomedicine” Editorial Board Member |
| 2003:2002:  | Nanoscience and Nanotechnology Michigan Symposium Dedicated to KopelmanHall of Fame Grand Prize for Collegiate Inventors, with student Jeff Anker |
| 1997: | American Chemical Society Edward Morley Award and Medal |
| 1995: | Lady Davis Fellowship |
| 1995: | John S. Guggenheim Fellowship |
| 1994: | Kopelman Festschrift issue of J. Phys. Chem. |
| 1994: | Collegiate Professorship (Fajans) |
| 1993: | Margaret and Herman Sokol Award |
| 1991: | Fellow, AAAS |
| 1990: | Faculty Recognition Award, University of Michigan |
| 1990: | Organizer, Gordon Research Conference |
| 1989: | J. Phys. Chem. Editorial Board |
| 1987-89: | Fulbright Research Award |
| 1987-88: | NIH National Research Service Award |
| 1986: | NSF Creativity Award |
| 1984-: | Fellow, American Physical Society |

**C. Contributions to Science**

**I. Exciton Energy Transfer and Fractal Reaction Kinetics:** A new theoretical-mathematical-computational paradigm enabled to solve basic physico-chemical problems ranging from energy transport in LASER and LED materials to intracellular biochemical reactions. Traditional theoretical frameworks were based on perfect, 3-dimensional, homogenous media of unconfined dimension. In contrast, realistic materials typically involve *Disorder*, *Random Structures and Aggregates*. Also, typical reactions occur on *catalytic surfaces, with catalytic islands, or in confined biological structures, such as cells or mitochondria.* While the Nobel Prize winning Anderson Localization theory may account for electrical insulator-to-conductor transitions, its generalization to energy transport in molecular optical materials became questionable. Kopelman’s experiments on *energy transport* transitions in the molecular solid state first established the role of *Energy Percolation in Disordered or Random Structures***,** and its associated *critical exponents***:**

*“Exciton Percolation in Molecular Alloys and Aggregates*”, **R. Kopelman**, Topics in Applied Physics Vol. 15: *Radiationless Processes in Molecules and Condensed Phases*, edited by F. K. Fong, Springer-Verlag, Berlin, pp. 297-363 (1976). [**Invited chapter**].

Related was the derivation by Kopelman of the “magic” numbers, i.e., *critical exponents* underlying critical transport phenomena, employing new mathematical simulation methods and computer algorithms, including the highly cited **Hoshen-Kopelman computer algorithm**. Surprisingly it turned out that percolation clusters have a **Fractal Dimension,** *a la Mandelbroit,* controlling exciton fusion reactions on them, which enabled Kopelman’s generalization to a new concept on chemical (and biochemical) reactions:

*“Fractal Reaction Kinetics”*, **R. Kopelman**, ***Science*** 241, 1620-1626 (1988**) [invited article].**

This discovery relied on Kopelman’s lab experiments as well as on his initiation of Monte-Carlo simulation-based reaction kinetics (first such application to chemistry). It led to the new concept of *“non-classical kinetics”* (also still called “*fractal kinetics*”); this *paradigm shift* has now trickled down to the text-book level. It improved the understanding of catalytic (including enzymatic) reactions, soil chemistry reactions, intracellular and intra-nucleus reactions:

**Kopelman Festschrift:** “*Scientific Contributions*”, K. Lindenberg, P. Prasad, J. Klafter, *J. Phys. Chem.* 1994, 98, 7225-7226;

“*Reaction Kinetics: Catalysis without a Catalyst*”, **R. Kopelman**, Nature Chemistry 2, 430-431 (2010) **[Invited].**

**II.** **Nanophotonics and Optical supermicrospectroscopy:** Kopelman defined the term “*nanophotonics*”, considered then a contradiction in terms (“violating the optical diffraction limit”), thus causing a *paradigm shift* and starting a new field of sciencecalled Nanophotonics:

*“Towards Nanophotonics: Temporal Patterns of Photons Create Spatial Patterns in Molecular Dots and Wires”*, Z-Y. Shi and **R. Kopelman**, J. *Mol. Cryst. Liq. Cryst.* **183**, 143-153 (1990).

Today there are dozens of “Institute for Nanophotonics” around the world, as well as international journals (”J. Nanophotonics”, “Nature Nanophotonics”) and a march towards “quantum computers” based on this concept. Historically, this new paradigm triggered the new fields of *Super-resolution Microscopy* and *Single Molecule Spectroscopy (SMS)*, the subject of the 2014 Chemistry Nobel Prize. Eric Betzig, one of these Nobelists, worked on *SMS* in Kopelman’s lab before publishing his prize’s cited paper. The latter was based on using an **optical fiber nano-tip** first made in Kopelman’s lab for scanning nanoscale resolution optical microscopy:

*“A Compact Near-Field Scanning Optical Microscope*”, G. Merritt, E. Monson, E. Betzig and **R. Kopelman**, *Ultramicroscopy* **71**, 183-189 (1998).

Also*,* **a Nano-sized light-source, Nano-sized optochemical sensors and** ***Nanoscale spatially resolved optical spectroscopy*** were firstachieved in Kopelman’s lab:

*“A Light Source Smaller than the Optical Wavelength”,* K. Lieberman, S. Harush, A. Lewis and **R. Kopelman**, ***Science*** 247, 59-61 (1990).

*“Submicrometer Intracellular Chemical Optical Fiber Sensors”,* W. Tan, Z-Y. Shi, S. Smith, D. Birnbaum and **R. Kopelman**, ***Science*** 258, 778-781 (1992).

**III. NanoBioDevices: Nanoparticle and nanostructure based devices:** The first such nano-device was made and used in Kopelman’s lab for measuring interface pH in a glass of water, with a laser tweezer and micro-spectroscopy:

“*Three-Dimensional pH Microprobing with an Optically-Manipulated Fluorescent Nano-Particle*”, K. Sasaki, Z-Y. Shi, **R. Kopelman** and H. Masuhara, *Chem. Lett.* **1996**, 141-142 (1996).

Called **“*nano-PEBBLEs*”** (i.e., nano-Photonic Explorers By Biologically Localized Embedding), these nano-sensors enabled intracellular biochemical studies, mapping, inside single live cells, the levels and fluxes of a long list of molecules, ions and radicals, impossible to do by just using "molecular probes”, thus resulting in **2** **Invited Book Chapters**:

*“Nanoparticle PEBBLE Sensors in Live Cells and In Vivo*” Y.E.L. Koo, R. Smith, and **R. Kopelman,** ***Annual Review of Analytical Chemistry*** *Vol. 2***,** Editors, E. Yeung and R. Zare, pp. 57-76 (2009) PMID: 20098636;

“*PEBBLE Nanosensors for In Vitro Bioanalysis*,” Y.E. Koo Lee, E. Monson, M. Brasuel, M. Philbert and **R. Kopelman**, **CRC Biomedical Photonics Handbook**: 2nd Ed., Vol. 3, Editor, T. Vo-Dinh, (2014).

With his student, Jeff Anker, Kopelman received the **Hall of Fame Grand Prize for Collegiate Inventor**s **2002** for magnetic Janus micro- and nano-particles that enabled a *4000x gain in optical signal over background and were called called* MagMOONs (*mag*netically *mo*dified *o*ptical *n*anoparticles). They also served as the basis for a new method, AMBR (*a*synchronous *m*agnetic *b*ead *r*otation) enabling measuring directly the nano-growth of bacteria, by just 50 nm, well below the resolution of optical microscopy (note: electron microscopy kills bacterial growth). AMBR finds, for any bacteria, its anti-microbial drug sensitivity, in minutes, compared to traditionally requiring hours or days:

“Asynchronous Magnetic Bead Rotation (AMBR) Micro-viscometer for Rapid, Sensitive and Label-free Studies of Bacterial Growth and Drug Sensitivity,” I. Sinn, T. Albertson, P. Kinnunen, D.N. Breslauer, B.H. McNaughton, M.A. Burns, **R. Kopelman,** *Analytical Chemistry* **(**2012) PMID: 22507307, PMC3381929.

Kopelman also invented a nanoscale voltmeter and applied it towards the first reliable measurements of electric fields produced by live cells:

“Universal, Wireless, Nano-Optical Voltmeters”, M. Philbert, K. Tyner, **R. Kopelman**, US Patent #7,923,984 B2 (April 12, 2011);

“Nano-sized voltmeter enables cellular-wide electric field mapping”, K.M. Tyner, **R. Kopelman,** and M.A. Philbert, *Biophys J* 93, 1-12, (2007).

**IV.** **NanoDrugs and** **Nanotheranostics (Nanoparticle based therapy + diagnostics, including imaging):** A most important spin-off for medicine, today called *Nanomedicine*, was conceived and achieved by Kopelman, creating *“targeted multifunctional biocompatible nanoparticles with matrix protected multiple drugs”. It* enabled *tumor-focused targeted imaging (MRI, CT, PET),* ***plus*** *targeted therapy (Chemo, PDT, PTT), as well as surgical delineation and continuous monitoring of therapy.* This concept has been pursued by at least 17 pharmaceutical companies, resulting, *inter-alia*, in the anti-Covid vaccines of Pfizer and Moderna; it also catalyzed the new paradigm of *theragnostics* (therapy + diagnostics). Originally it was aimed at **Brain Cancer**, with the treatment modality being **photodynamic therapy**:

“Brain Cancer Diagnosis and Therapy with Nano-platforms”, Y.E.L. Koo, G.R. Reddy, M. Bhojani, R. Schneider, B.D. Ross, A. Rehemtulla, M.A. Philbert, and **R. Kopelman**, *Advanced Drug Delivery Reviews*, 58 1556–1577 (2006). [**Invited review**] PMID: 17107738

Along the same line, for detection/imaging of soft tumors, Kopelman’s lab made the first targeted gold nanoparticles to serve as CT (X-ray) contrast elements:

“Targeted Gold Nanoparticles enable Molecular CT Imaging of Cancer”, R. Popovtzer**,** A. Agrawal, N. Kotov, A. Popovtzer, J. Balter, T.E. Carey and **R. Kopelman**, Nano Lett., 8 (12), pp 4593–4596 (2008) [a highly cited paper].

Subsequently, based on targeted and ultra-small nanoparticles, **ultra-quick,** **cell selective, photo-dynamic therapy of heart arrhythmia** was demonstrated by Kopelman and collaborating cardiologists; highlighted by the journal with a special editorial was the paper:

“*Left Atrium Nanoplatform-enabled Targeted Photodynamic Ablation: Preliminary Results in Vivo*”, U. Avula, H. Yoon, G. Kim, **R. Kopelman,** J. Kalifa, *HeartRhythm*, 10(11): 1747 (2013).

Furthermore, a demonstration of non-invasive, ultraquick fixing of arrhythmia in a live sheep’s heart (human heart size), was published in the highly prestigious journal:

*“Cell-selective Arrhythmia Ablation for Photomodulation of Heart Rhythm”,* U. M. R. Avula, H. K. Yoon, C. H. Lee, K. Kaur, R. J. Ramirez, Y. Takemoto, S. R. Ennis, F. Morady, T. Herron, O. Berenfeld, **R. Kopelman**, J. Kalifa,. **Science Transl. Med.** Vol. 7, Issue 311 ra172 (2015). PMID: 26511509.

**V. In-Vivo Chemical/Molecular Imaging:** Doctors could never “see” the chemistry inside a patient, just *in-vitro,* while they can “see” all physical structures *in-vivo* (CT, MRI, US, etc.)*.* The obvious reason: our body is opaque to visible light. Only limited chemical scanning can be achieved today, with superexpensive machines (e.g., PET). Notably**,** today’s chemical tests, like blood or urine tests, do not give the spatial or temporal distribution of the chemical entity. Even *biopsies* do not provide info on a tumor’s center, nor info on its O2 content. Kopelman and collaborators enabled a method of 5-dimensional chemical imaging, resolved in space, time and chemical composition. The later includes any kind of chemical entity, whether molecule, ion or radical. This chemical imaging ability will inevitably revolutionize both the biological sciences and bio-engineering, while having a foremost impact on medicine, such as guiding cancer therapy by mapping the chemical makeups of a tumor. The latter will enable personalized cancer therapy. Specifically, Kopelman pioneeredthe method of **photoacoustic chemical imaging,** *employing nanosonophores for in-vivo* O2 and pH:

*“Ratiometric Photoacoustic sensing of pH using a ‘Sonophore*,” T. Horvath, S. Ashkenazi, R. Kopelman, *The* ***Analyst*,** **133**, 747 - 749, **DOI:** 10.1039/b800116b (2008);

*Photoacoustic probing of fluorophores excited state lifetime with application to oxygen sensing*, S. Ashkenazi, S.-W. Huang, T. Horvath, YE.L. Koo and **R. Kopelman**, *J. Biomed. Opt.*, **13**, 034023 (2008).

This **PACI (PhotoAcoustic Chemical Imaging) method** *has been further developed by Kopelman and Wang to include ion-selective nanososonophores*, specifically for K+, but also for Na+, Mg+, etc., of interest to cancer as well as to other diseases, like MS, where ionic imbalances are created:

“*Chemical Imaging In-Vivo: Photoacoustict based 4-Dimensional Chemical Analysis*”, C.H. Lee, J. Folz, J.W.Y. Tan, J. Jo, X. Wang, and **R. Kopelman,** [*Anal. Chem.*  **91**, 4, 2561-2569](https://pubs.acs.org/action/showCitFormats?doi=10.1021%2Facs.analchem.8b04797) (2019). DOI: 10.1021/acs.analchem.8b04797 [**Feature Paper**].

Specifically, **PACI** was developed into a method of *in-vivo*, time and space resolved, Biochemical Analysis *of* the heterogeneous chemical makeup of subsurface tumors, done *noninvasively*, based on the same photonic methods used for cells under the microscope, specifically for its pH, O2 and K+:

Jo J, Lee C, **Kopelman R**, Wang X, “*In Vivo* Quantitative Imaging of Tumor pH by Nanosonophore Assisted Multispectral Photoacoustic Imaging”, ***Nature Communications* 8:** 471 (2017);

Jo, Janggun; Lee, Chang; Folz, Jeff; Tan, Joel; Wang, Xueding; **Kopelman, Raoul**, *“In vivo Photoacoustic Lifetime based Oxygen Imaging with Tumor targeted G2 Polyacrylamide NanoSonophores”, ACS Nano,* ***13****, 12, 14024-14032 (2019);*

Joel W. Y. Tan, Jeff Folz, **Raoul Kopelman**, and Xueding Wang, “*In Vivo* Photoacoustic Potassium Imaging of the Tumor Microenvironment”, ***Biomedical Optics Express, 11 (7),*** 3507-3522, (2020).

The importanceof such **5-dimensional biochemical imaging of tumors *in-vivo*** relates to its potential for **precision cancer medicine,** i.e.,helping the clinician to make the **right early treatment choice,** among **(1) Chemotherapy, with its many drugs that are stifled by low pH, i.e., acidity, (2) Radiation Therapy, which is suppressed by low O2,** and **(3) Immunotherapy, which is undermined by the tumor microenvironment (TME) having an excess of K+ ions.** In short, this wouldenable **chemical imaging guided therapy, vs. a timely decision re surgery,** thus resulting in **precision oncology.**

**Publications** (**700+ total Peer-reviewed publications, 40+ Patents, 30,000+ citations, H-index 86):**

**Complete List of Published Work in Google Scholar:** <https://scholar.google.com/citations?user=7m9fvhcAAAAJ&hl=en&authuser=2&oi=ao>