



IAEA

International Atomic Energy Agency

**Technical Meeting on Emerging Applications of
Plasma Science and Technology**

Sep 19 – 22, 2023 at IAEA Headquarters, Vienna



Low temperature plasma life innovations: Functional reaction networks of radical chemistry

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Center for low-temperature plasma sciences



Nagoya University plasma science platform – 165 of originally-developed apparatus
– for low-temperature plasma sciences and innovations



- Fundamental, basic (source, diagnostics)
- Green & nano, DX
- Bio, medicine & agri
- Semiconductor



FREE RADICAL RESEARCH
<https://doi.org/10.1080/10715762.2023.2230351>



REVIEW ARTICLE

OPEN ACCESS Check for updates

Generation and measurement of low-temperature plasma for cancer therapy: a historical review

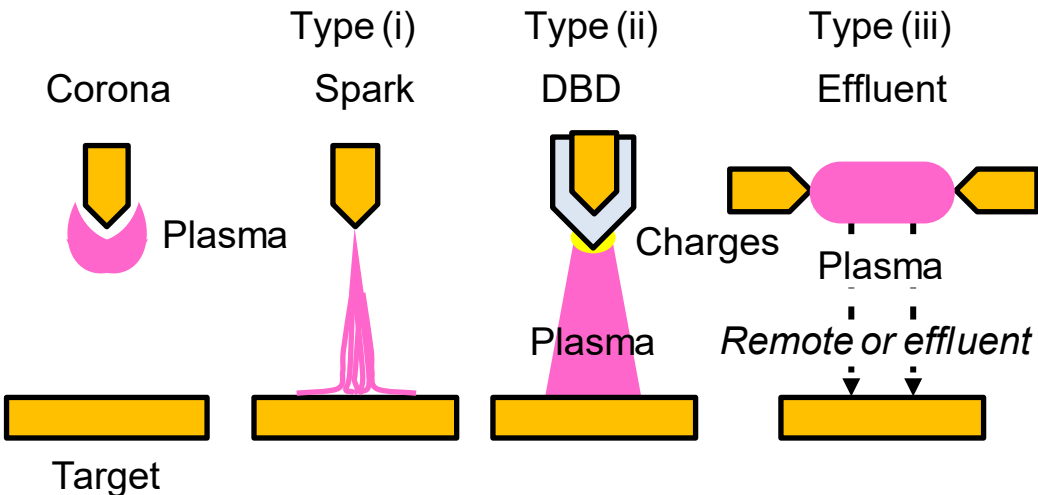
Kenji Ishikawa^a, Keigo Takeda^b, Shinji Yoshimura^{a,c,d}, Takashi Kondo^a, Hiromasa Tanaka^a, Shinya Toyokuni^{a,e}, Kae Nakamura^{a,f}, Hiroaki Kajiyama^{a,f}, Masaaki Mizuno^g and Masaru Hori^a

^aCenter for Low-temperature Plasma Sciences, Nagoya University, Nagoya, Japan; ^bDepartment of Electrical and Electronic

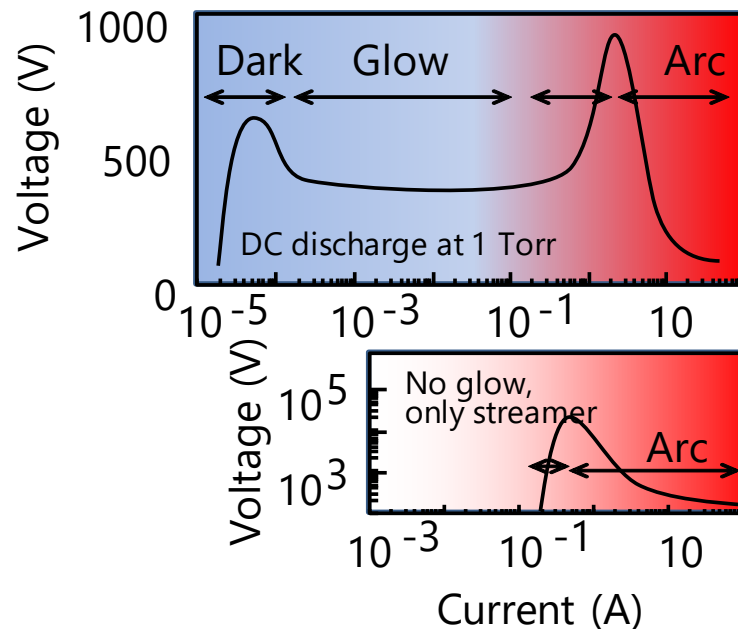
Free Radical Research (2023), 57 (3) Pages 239-270

DOI: 10.1080/10715762.2023.2230351

Plasma sources & mode transition



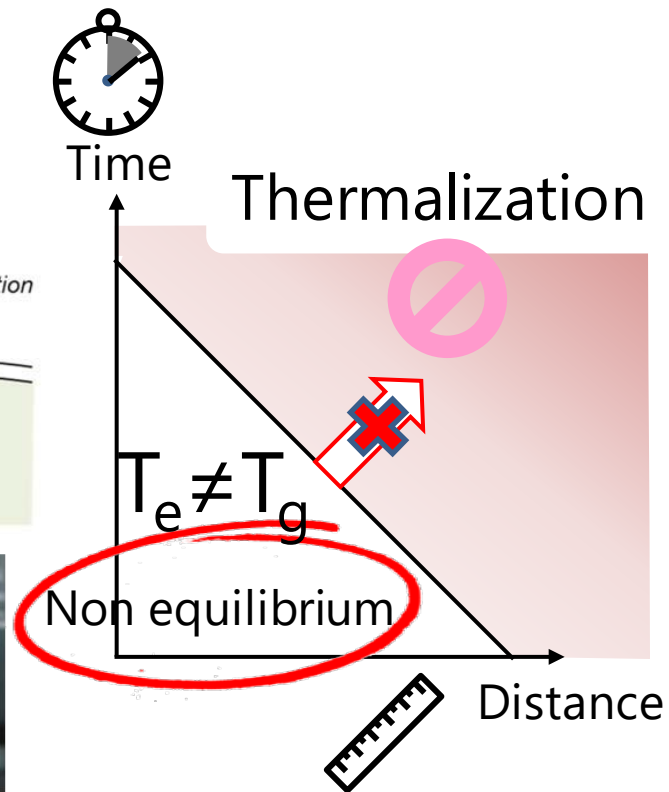
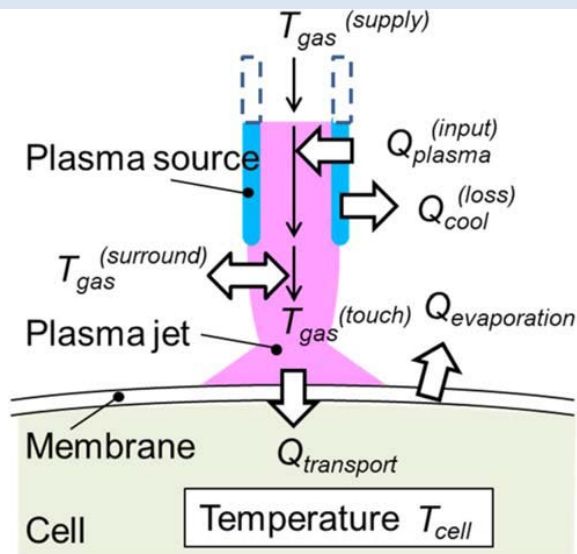
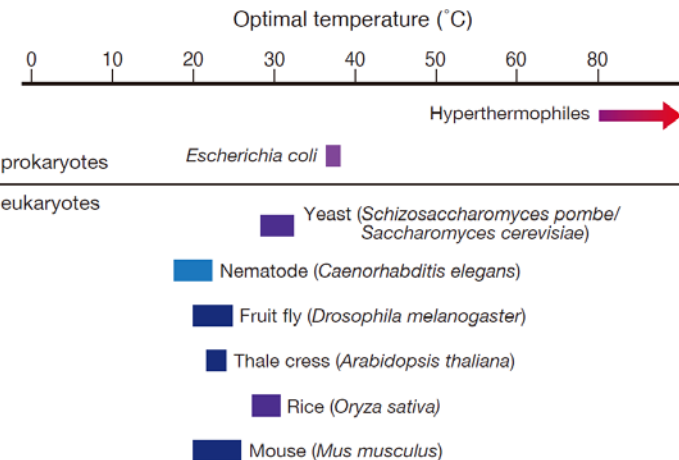
Joule heating in the discharge path of high electrical currents.



Optimal temperature range is narrow



A balance between source input and consumption-loss of energy determines the resulting temperature of the living organism, which is surrounded by the environment.



Temperature should be controlled for biology

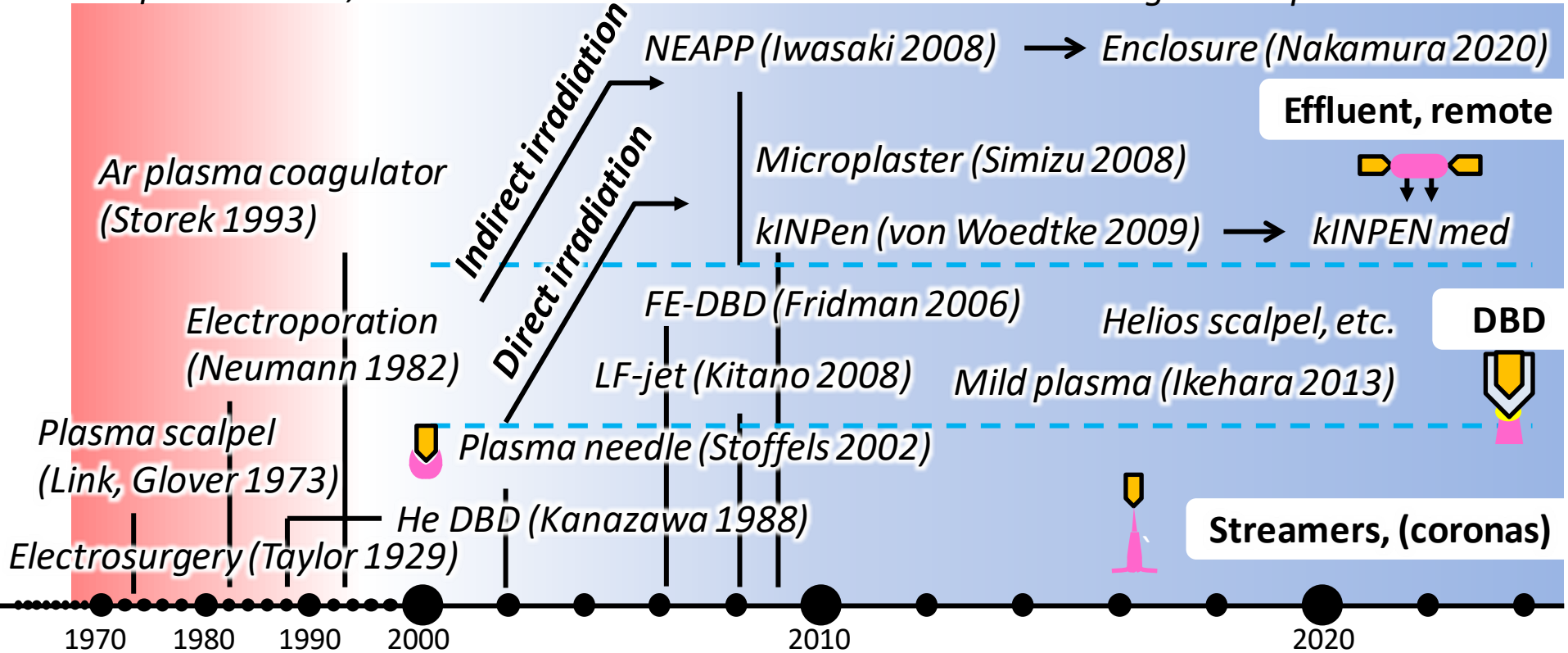
History of direct & indirect irradiations



Gas temperature >10,000K

~300K

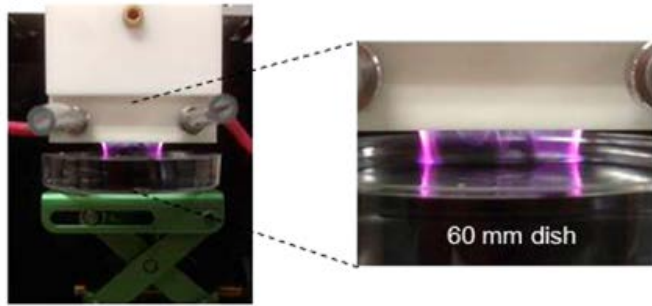
≡ Biological temperature $\pm 1^\circ\text{C}$



Indirect - PAL: Plasma-activated solutions



Plasma-activated Lactec : PAL



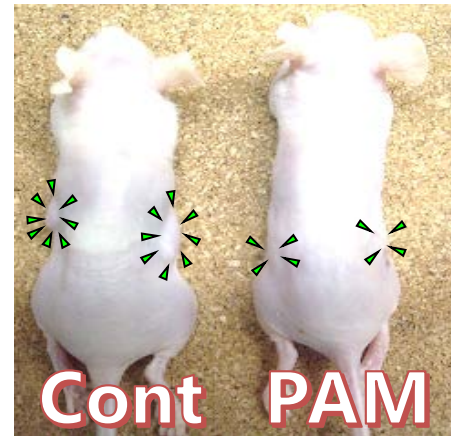
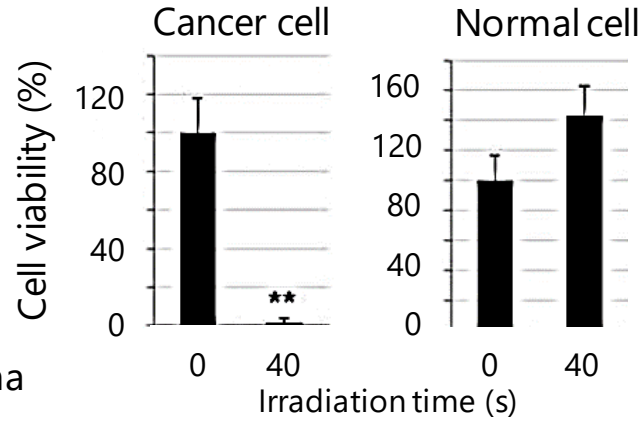
Ringer's lactated solution (Lactec) + plasma

- NaCl
- KCl
- $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$
- Lactate Na



intravenous infusion

➤ Antitumor effect on PAL



In vitro and In vivo



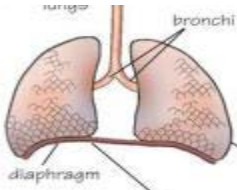
Plasma medical innovation – cancer therapy



Plasma cancer treatments

DDY

Lung



Brain
Glioma
Skin

Melanoma

Breast

Liver

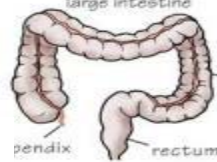


Pancreatic



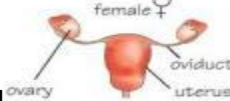
Stomach

Colon



Prostatic

Uterine
Cervical



- Preferential killing of tumor cells



- Issues
- Clarification of **plasma diagnostics** and the antitumor mechanism of Plasma-activated liquids

H. Tanaka

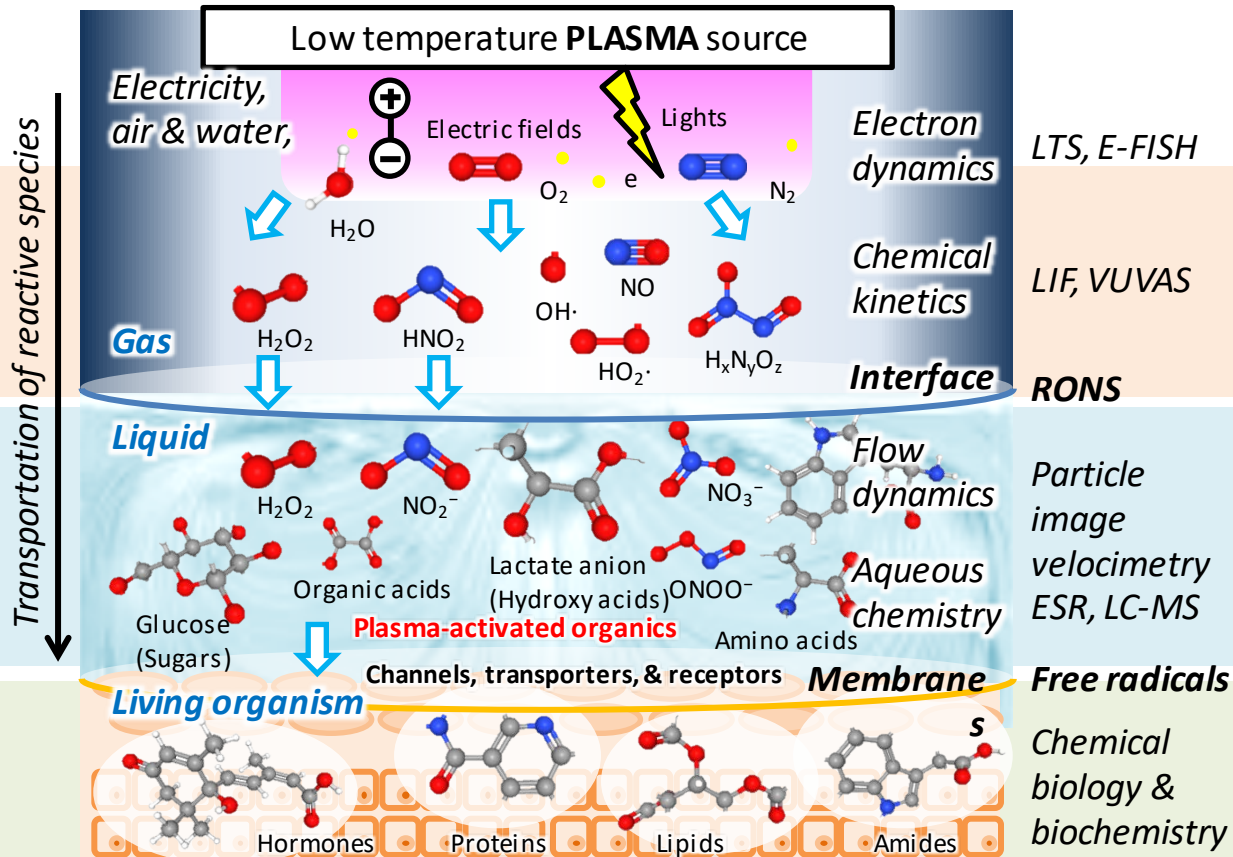
Hierarchical complex systems -diagnostics



Laser diagnostics



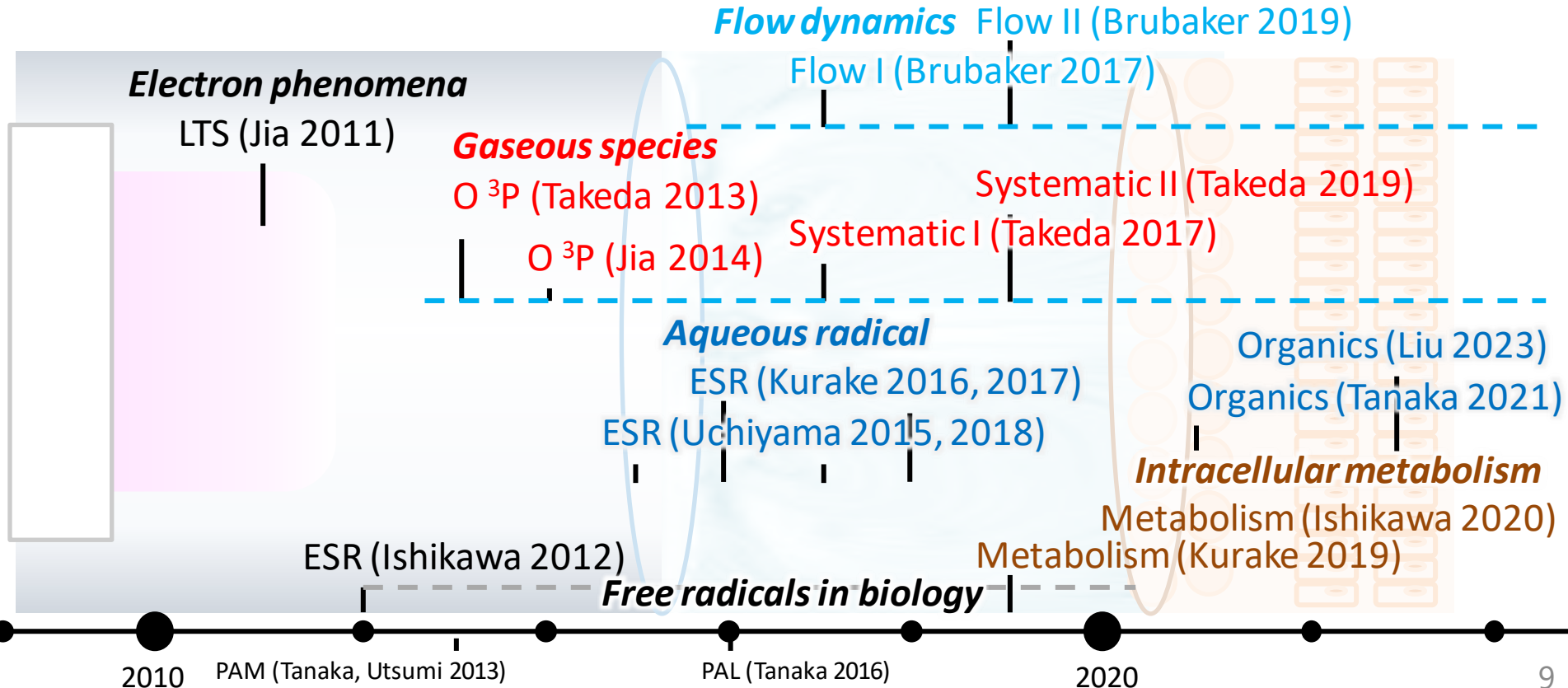
Electron spin resonance (ESR)



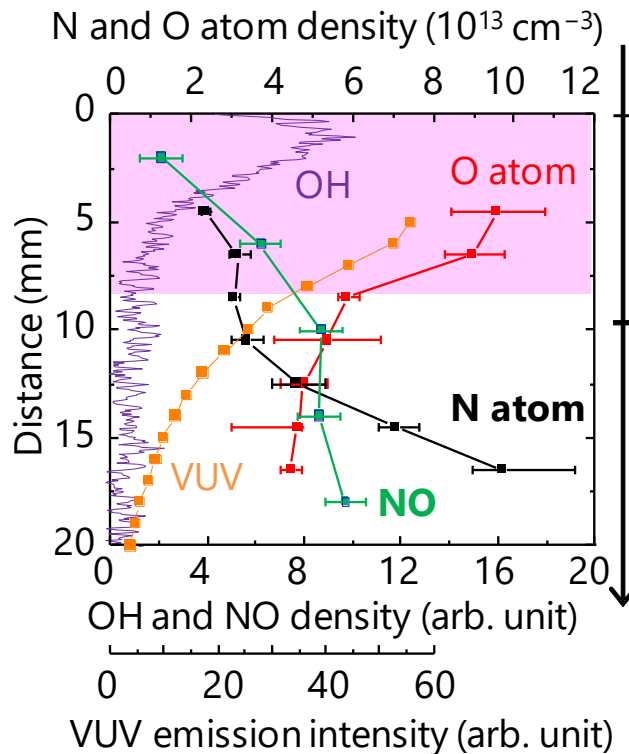
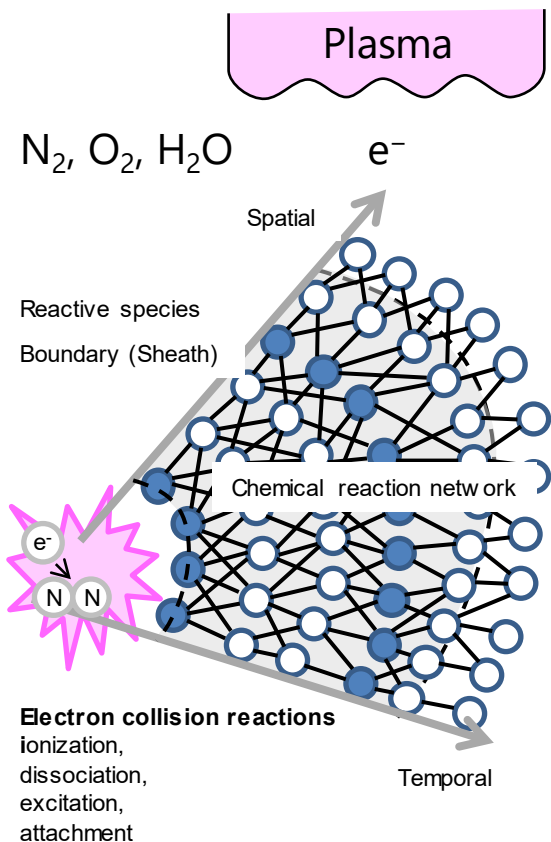
History of diagnostics



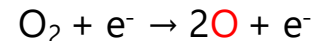
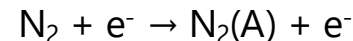
Plasma source ↔ *Gaseous chemistry* ↔ *Aqueous chemistry* ↔ *Plasma-biological interaction*



Gaseous - nonequilibrium physicochemical reaction field



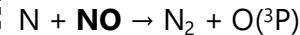
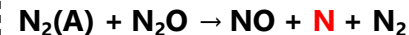
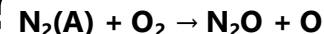
Plasma head



Plasma region

--- Approximately 8 mm

Remote region



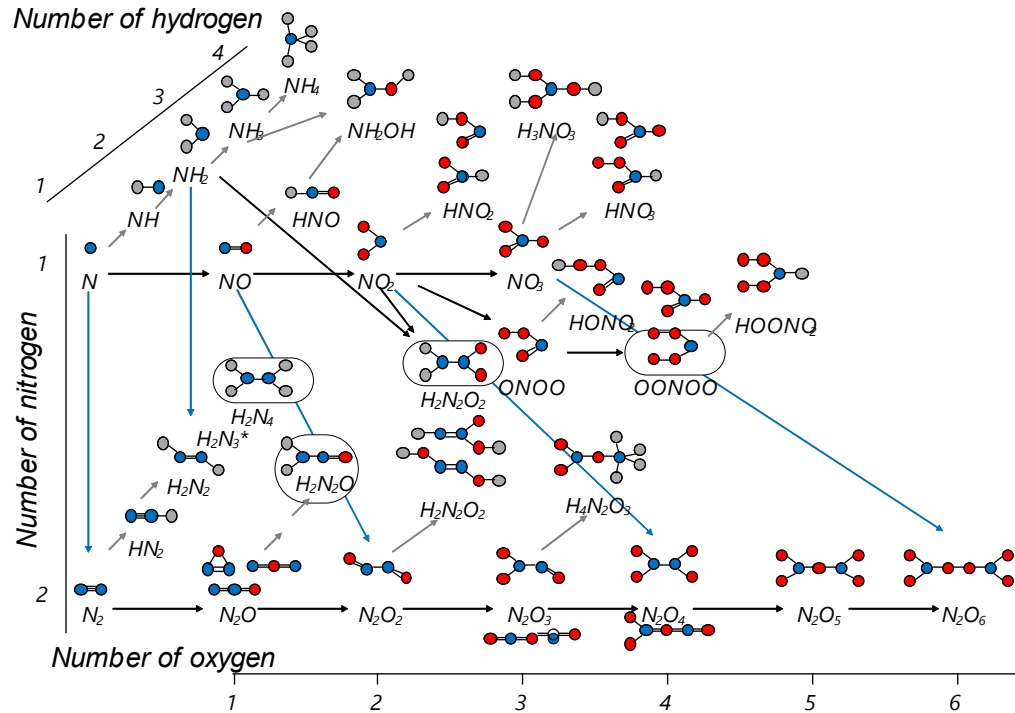
Laser diagnostics

K. Takeda, *J. Phys. D* **50**, 195202 (2017).

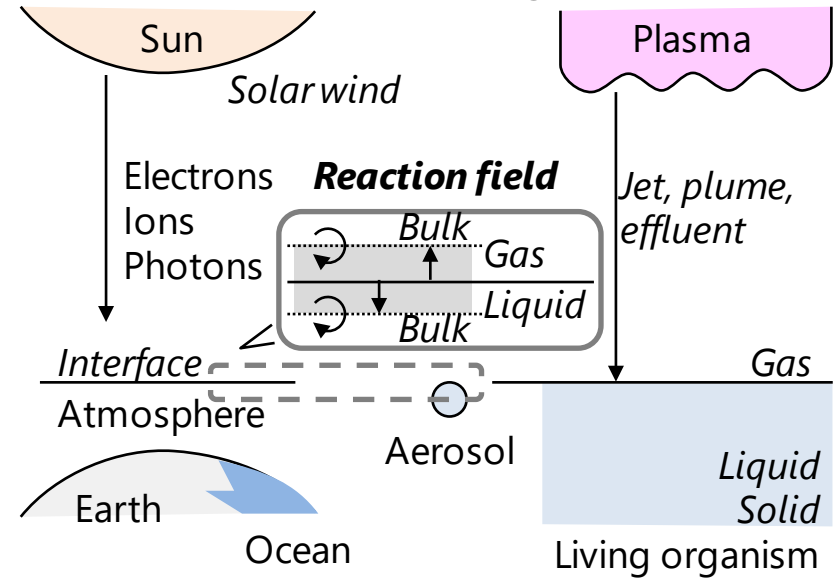
Chemical network - Artificial and natural systems



Chemical network of nitrogen derivatives

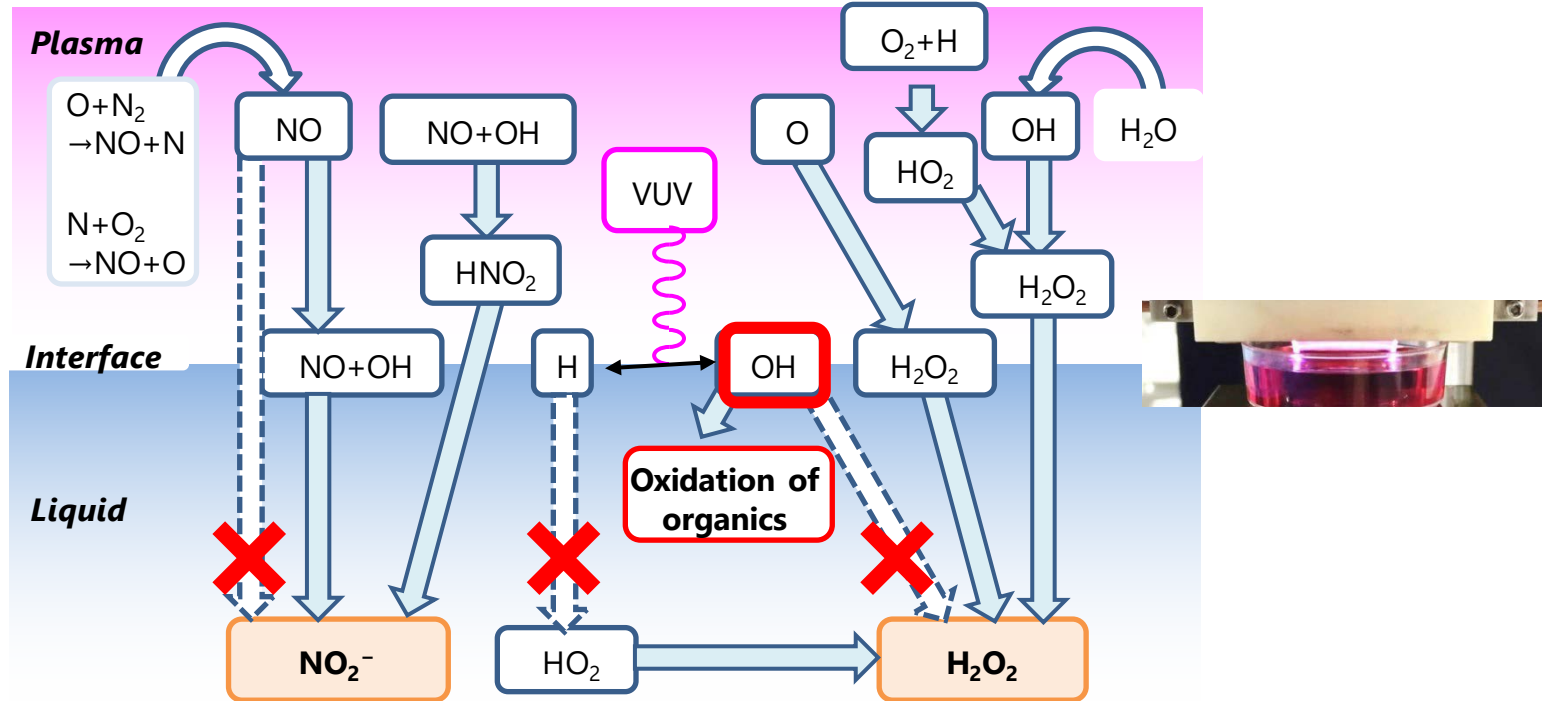


The **plasma-liquid interactions** associated with a plasma discharge are similar to those occurring in the Sun





- Nitrous oxides dissolve and OH radical oxidizes organics

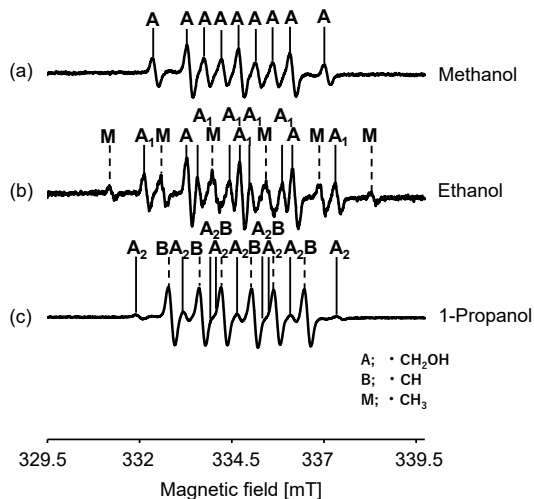


N. Kurake et al., *J. Phys. D: Appl. Phys.* **50**, 155202 (2017); H. Uchiyama *ibid* **51**, 095202 (2018); *PLoS One* **10**, e0136956 (2015). Toyokuni et al., *Plasma Medical Science* (Elsevier, 2018).

OH radical mediated reactions



Aqueous radical detection by electron spin resonance (ESR)



Pyrolysis (in sonochemistry)

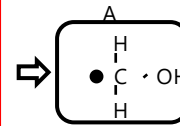
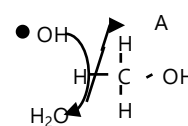
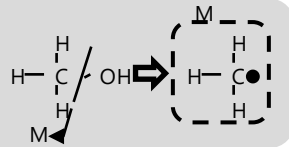
Photolysis

Reactions under **Plasma**

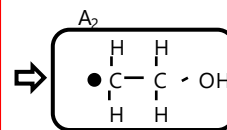
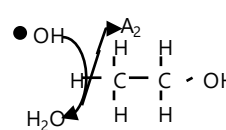
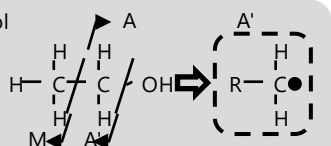
Thermodynamic control

Kinetic control

Methanol



Ethanol



Plasma

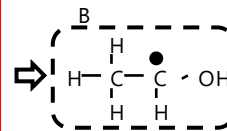
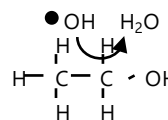
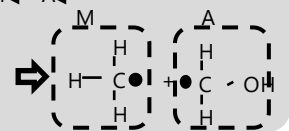
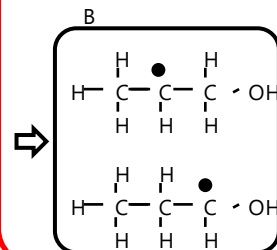
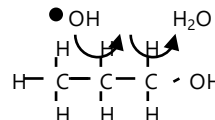
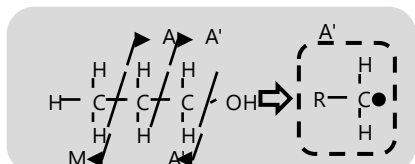


Photo-

1-propanol (or 1-butanol or 1-octanol)

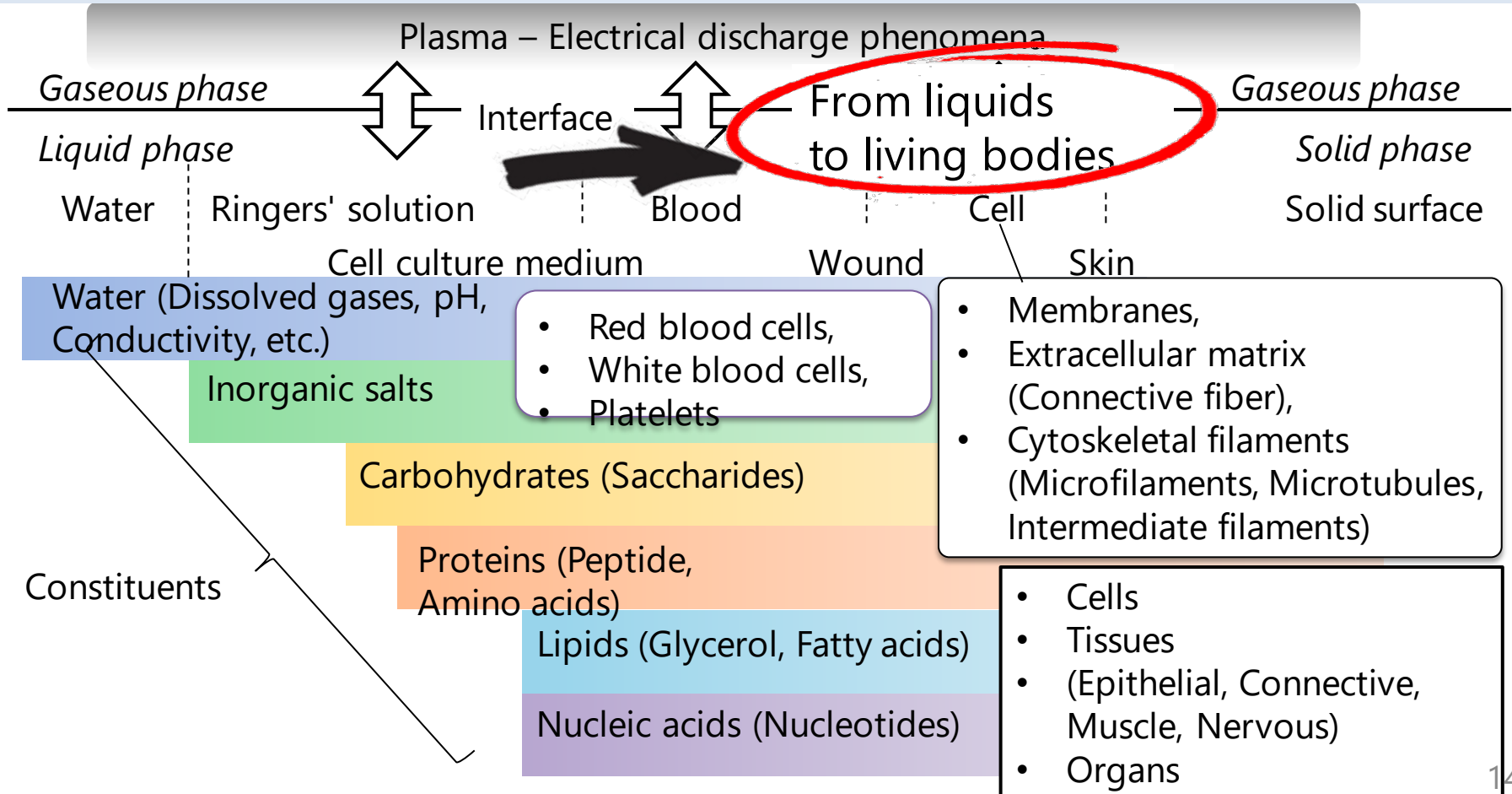


: detected in CAP : non-detected in CAP

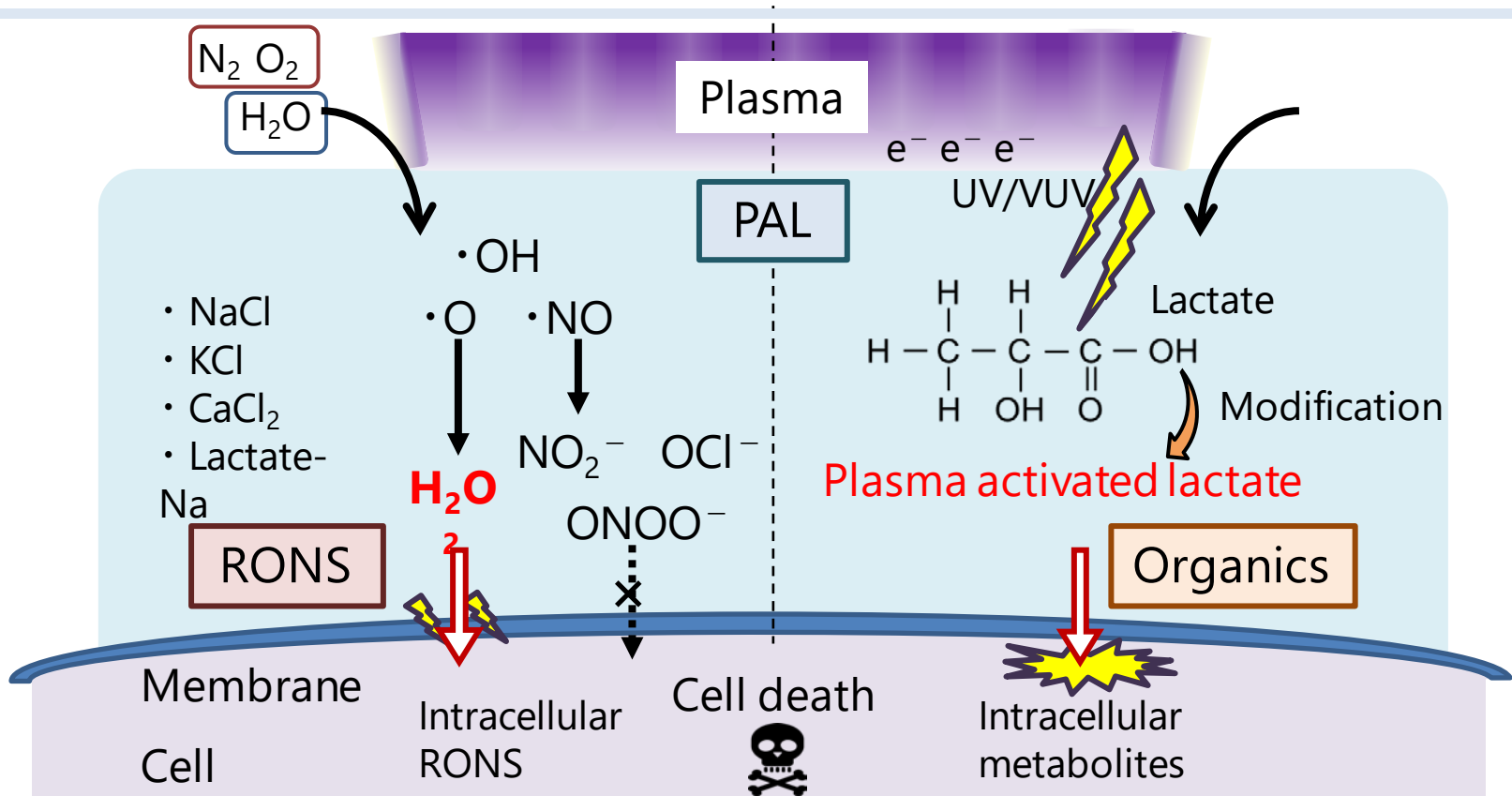
Uchiyama *et al.*, *J. Phys. D* **51**, 095202 (2018).



Effects of plasma-liquid interactions



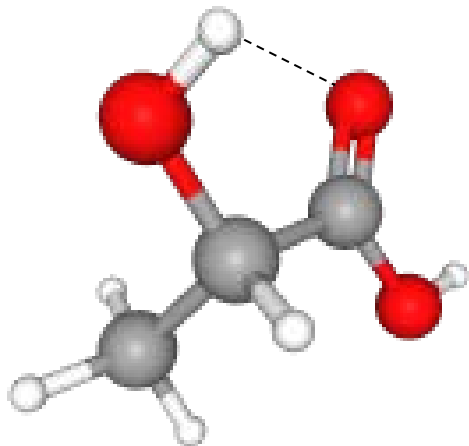
Inorganic and organic antitumor agents



Antitumor agents and intracellular response in PAL.

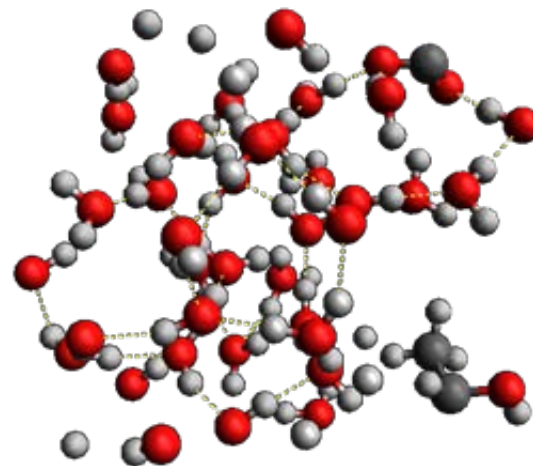
Aqueous reaction lactic acid and OH

- Conformation



Solvated water molecules

Acidification in water
(Alberty-Legendre transform
in Thermodynamics)



Alcohol (OH)/Aldehyde(C=O)/Carboxylic acid (COOH)

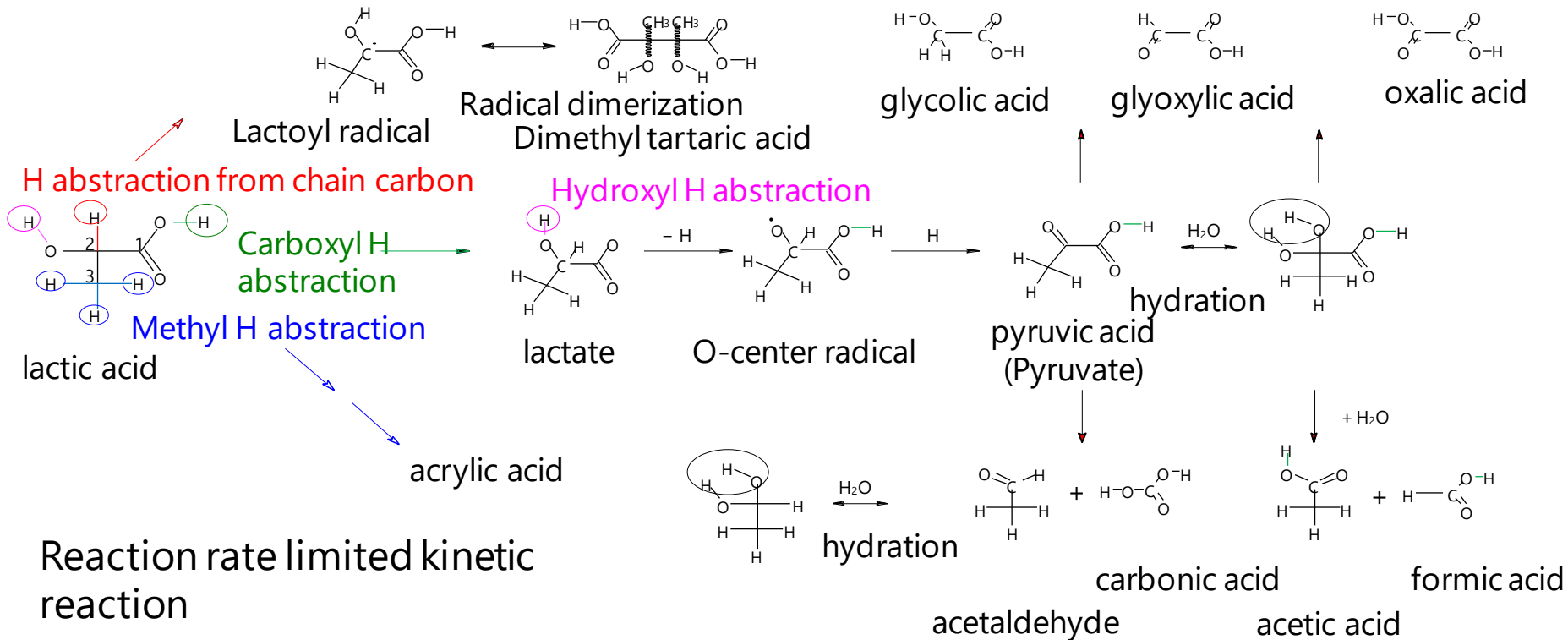
$C_3H_6O_3 \rightarrow C_{>3}$ synthesis, C_3 modification, $C_{<3}$ decomposition

Organic chemistry, Physical chemistry, Photochemistry, Electrochemistry,
Organic electrochemistry

Plasma-induced aqueous chemistry



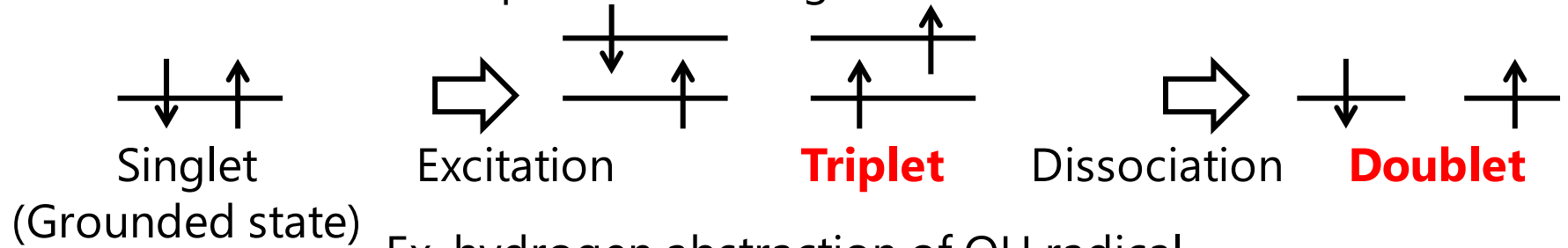
- Hydrogen abstraction



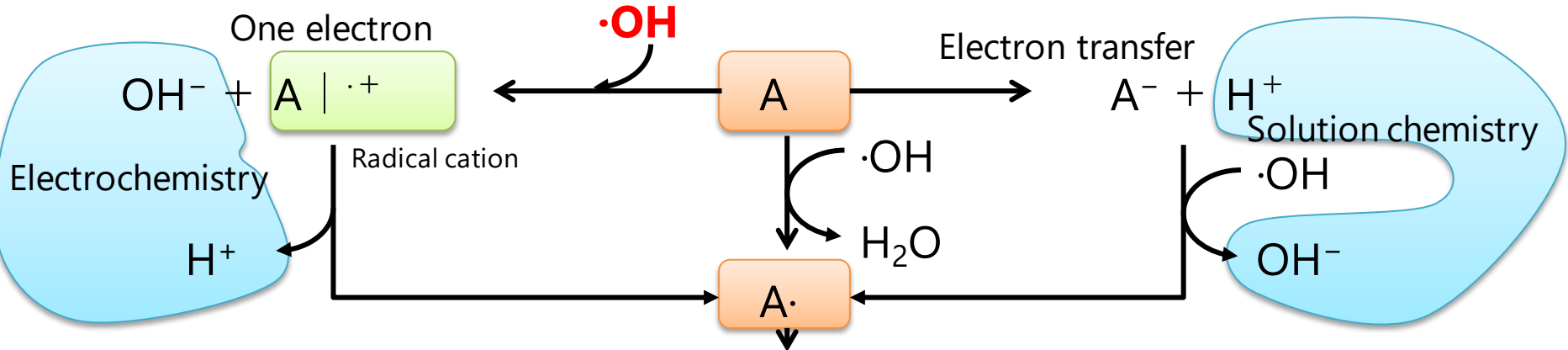
Chemical aspect - Radical reactions



Generation of reactive species involving radicals

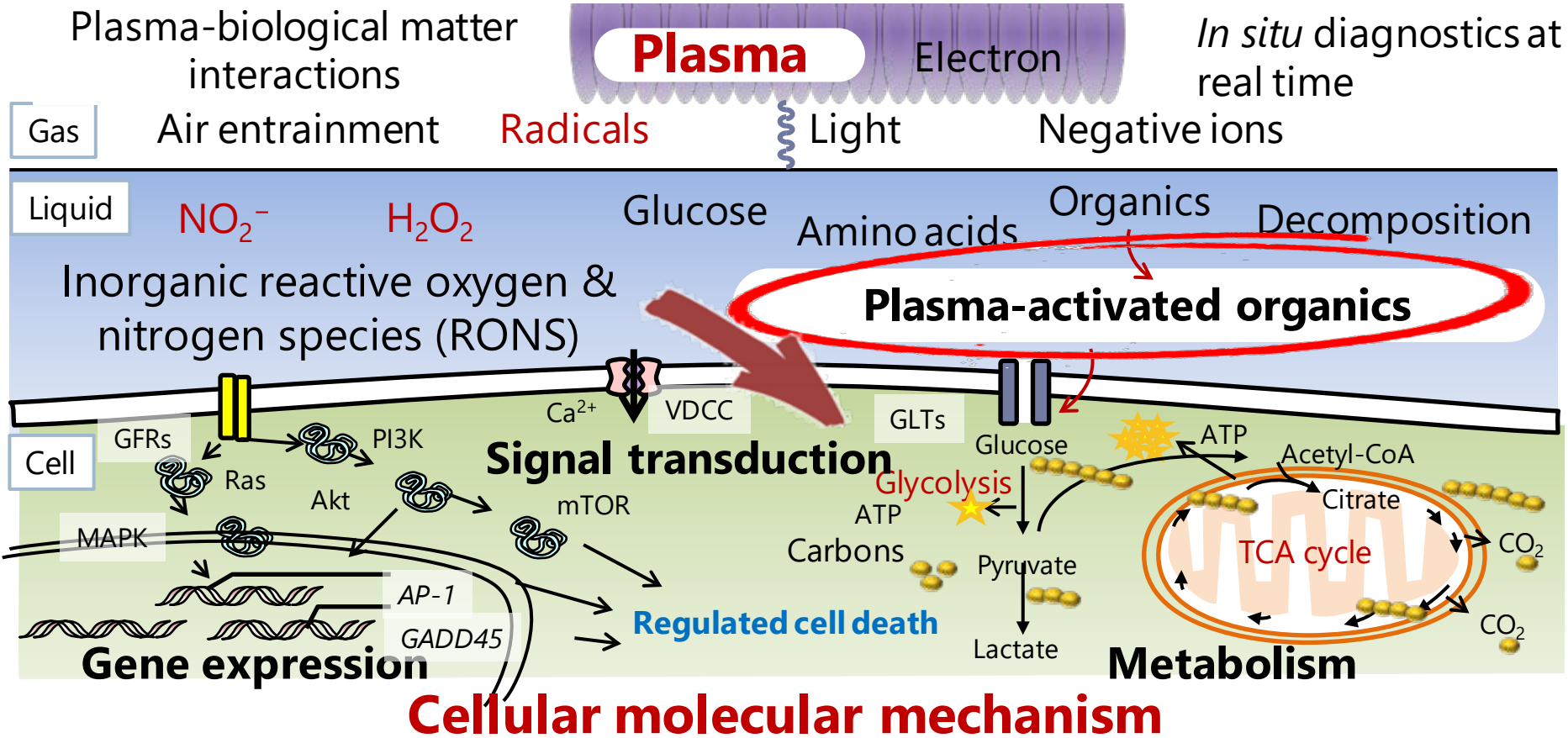


Ex. hydrogen abstraction of OH radical



Rich aqueous chemistry in plasma induced reactions.
Physical actions Chemical reactions. (PACR)

Induction of cellular responses



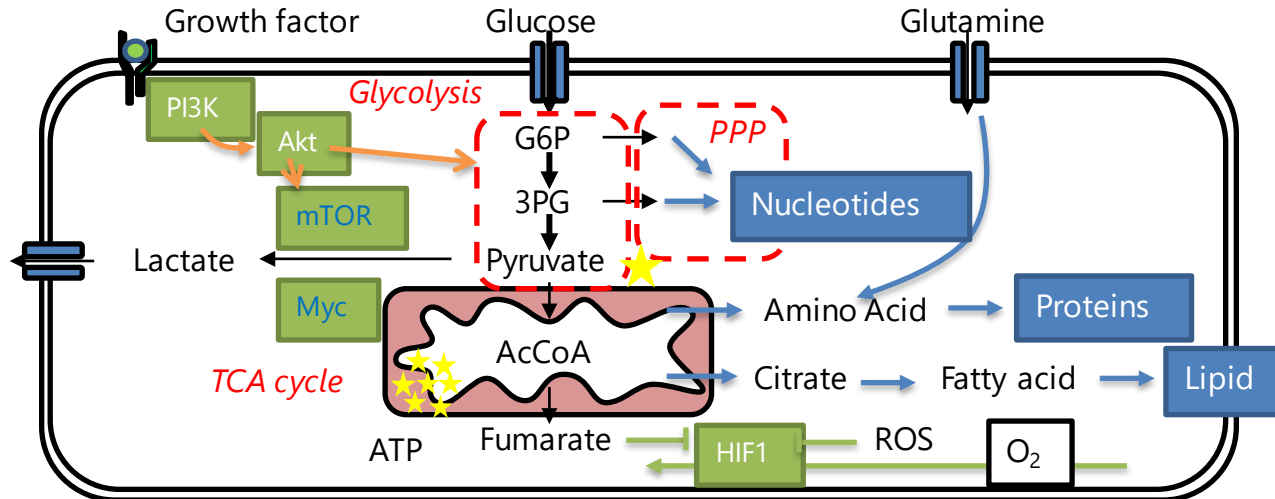
Cellular molecular mechanism

How plasma induced intracellular reactions ?

Intercellular metabolism

- Metabolic reprogramming: Nutrient acquisition and **metabolism** of malignant cells (**Aerobic glycolysis**, "Warburg effect")

- **Bio-energetic** (Glucose oxidation, ATP, etc.)
- **Bio-synthetic** (Amino acids, Lipids, Proteins as biomass)
- **Redox balance** (NADPH, GSH/GSSG, etc.)



Differences in metabolites

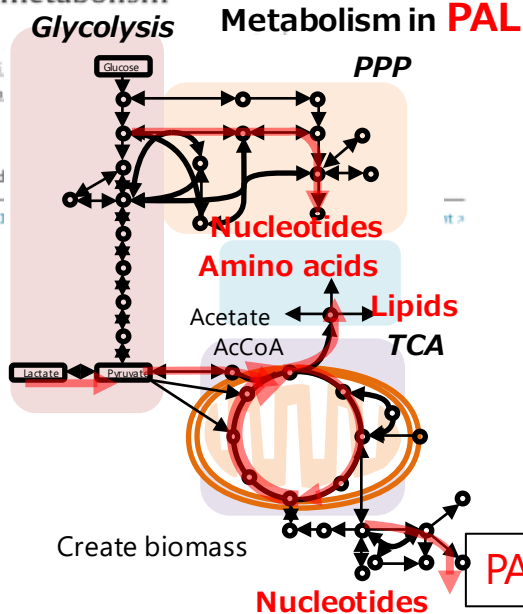
Non-thermal plasma-activated lactate solution kills U251SP glioblastoma cells in an innate reductive manner with altered metabolism

Kenji Ishikawa,*
Shinya Toyokuni,
Masaaki Mizuno

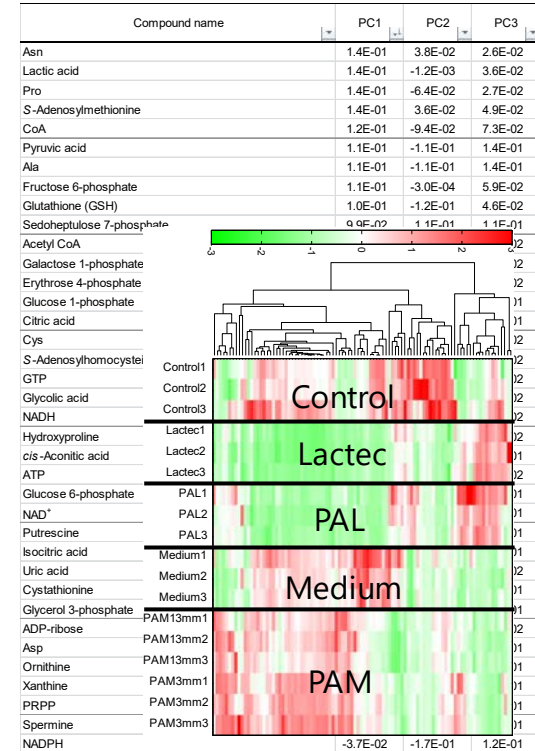
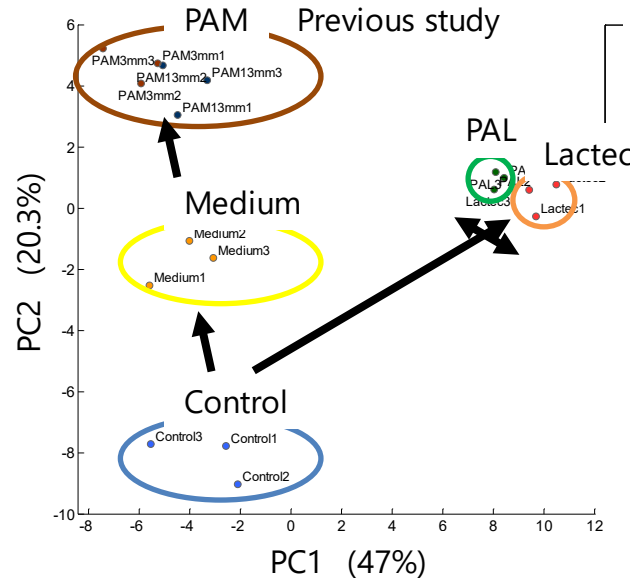
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<https://doi.org/10.1016/j.ab.2020.108414>



Principle component analysis

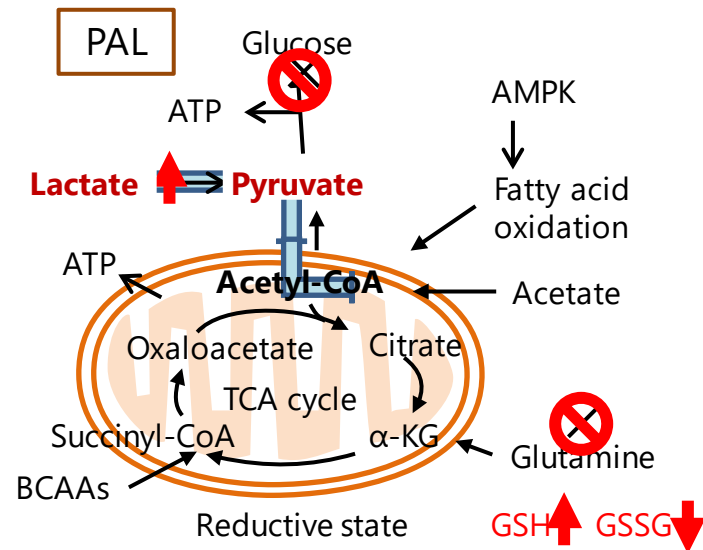
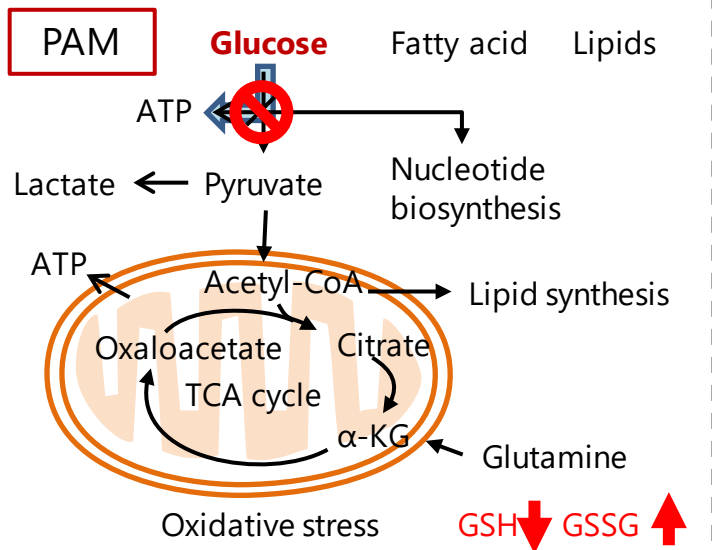


PAL modified the metabolic profiles



Key results in metabolism

	Growth	Apoptosis Caspase	Energy	Biomass Sugar	Amino acid	Fat	Electrons ROS
DMEM	↑	—	—	Catabolism	—	—	—
PAM	↓	↑	Glycolysis↓	↓	—	—	Ox
Lactec	?	—	—	Anabolism	—	—	Red
PAL	↓	↑	TCA→	↓	↓	↓	Red



NO in plasma-induced ferroptosis



Redox Biology
Volume 43, July 2021, 101989



Research Paper

Lysosomal nitric oxide determines transition from autophagy to ferroptosis after exposure to plasma-activated Ringer's lactate

Li Jiang^{a,1}, Hao Zheng^{a,1}, Qinying Lyu^a, Shotaro Hayashi^{a,b}, Kotaro Sato^a, Yoshitaka Sekido^c, Kae Nakamura^{b,d}, Hiromasa Tanaka^{d,e}, Kenji Ishikawa^d, Hiroaki Kajiyama^{b,d}, Masaaki Mizuno^e, Masaru Hori^d, Shinya Toyokuni^{a,d,f}

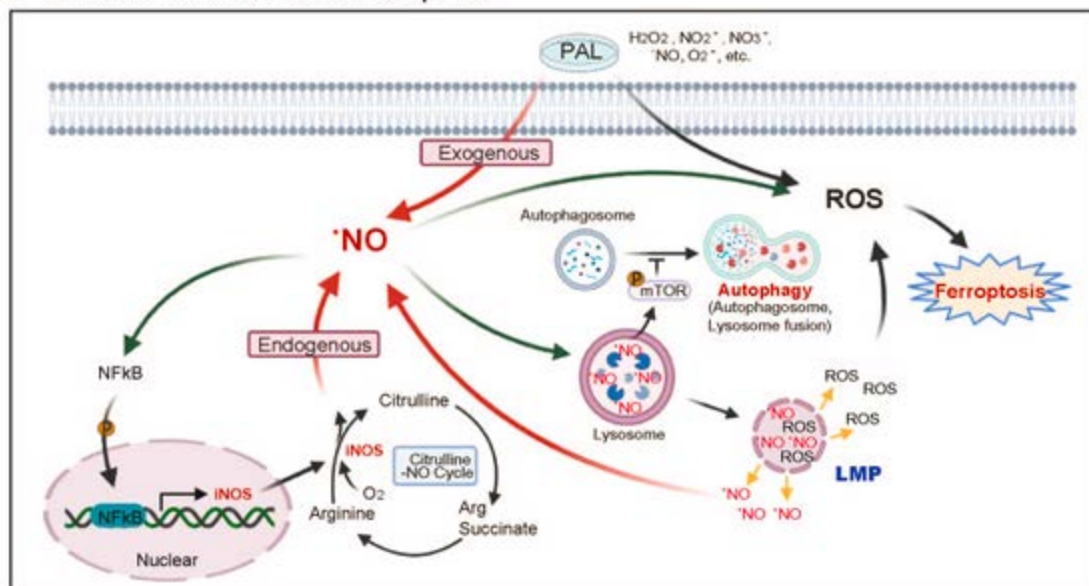
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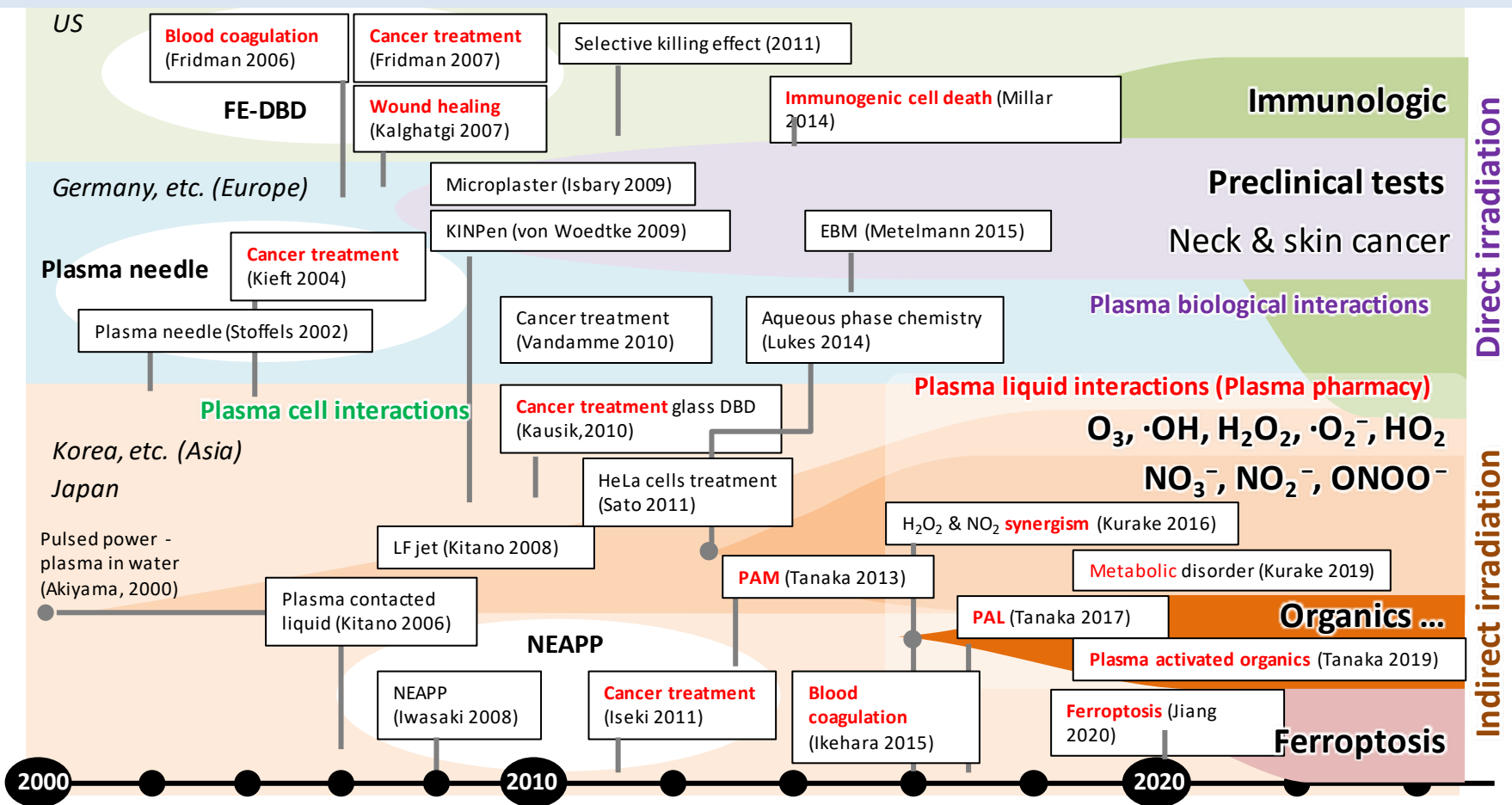
<https://doi.org/10.1016/j.redox.2021.101989>

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A The role of NO in PAL-induced ferroptosis



Plasma-liquid & living organism interactions

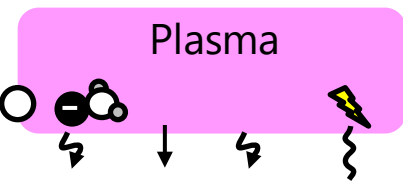


Pathology – plasma pharmacy

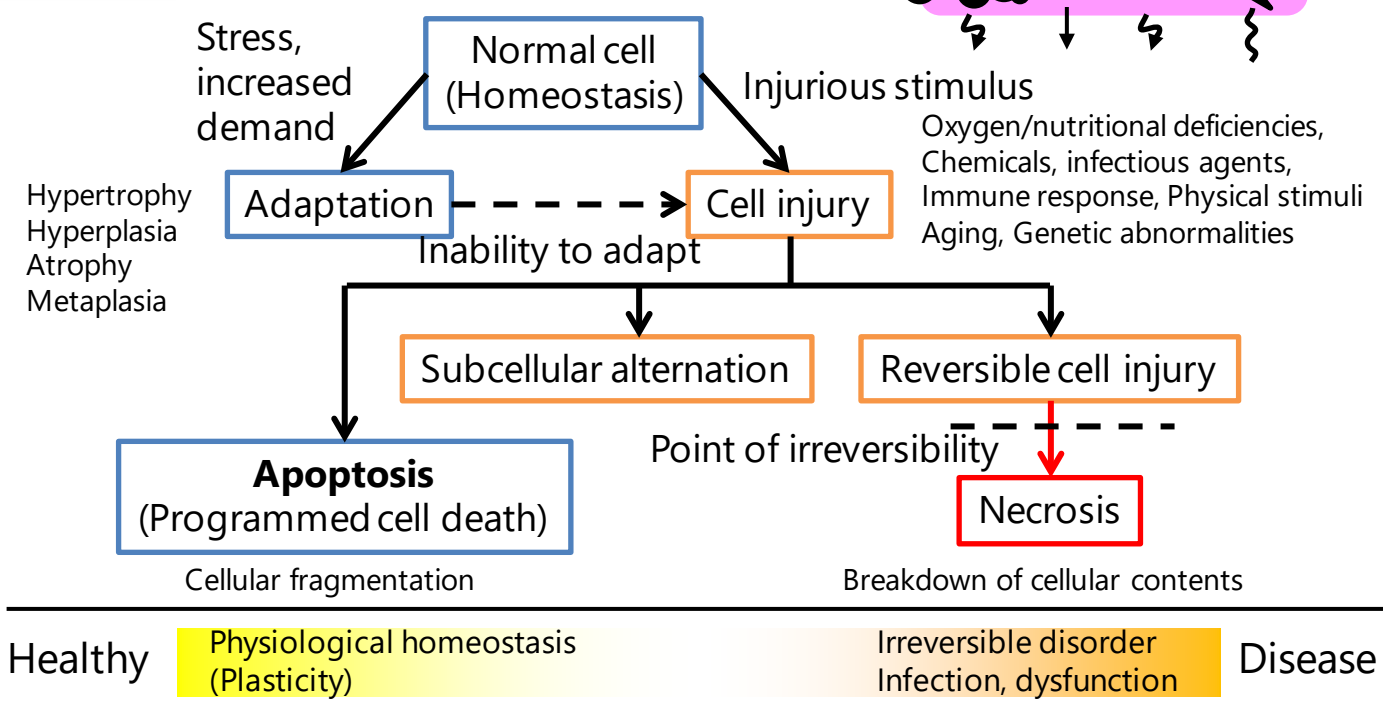


Plasma stress

Physics
(Collision)



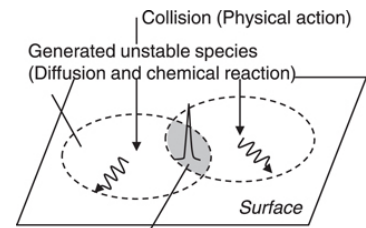
Chemistry
(Reactions)



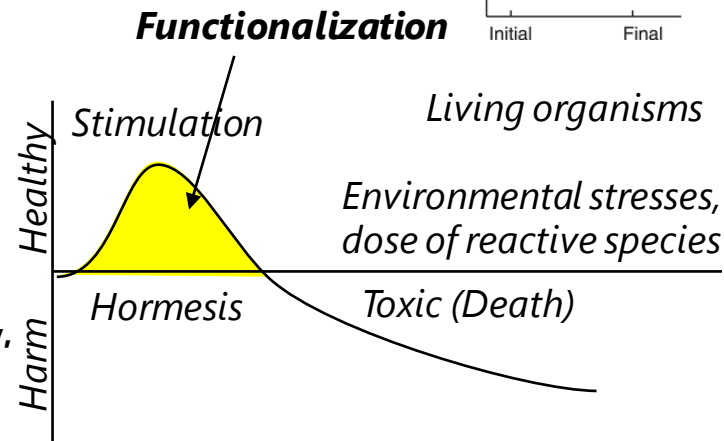
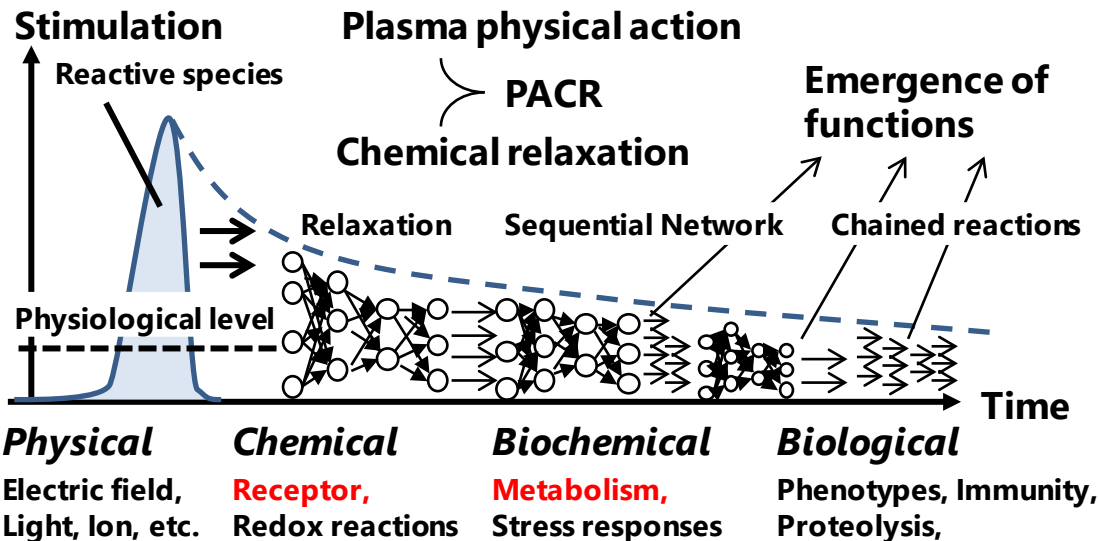
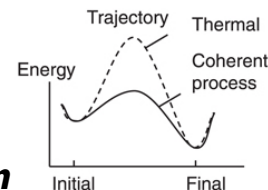
Plasma triggers nonequilibrium reactions



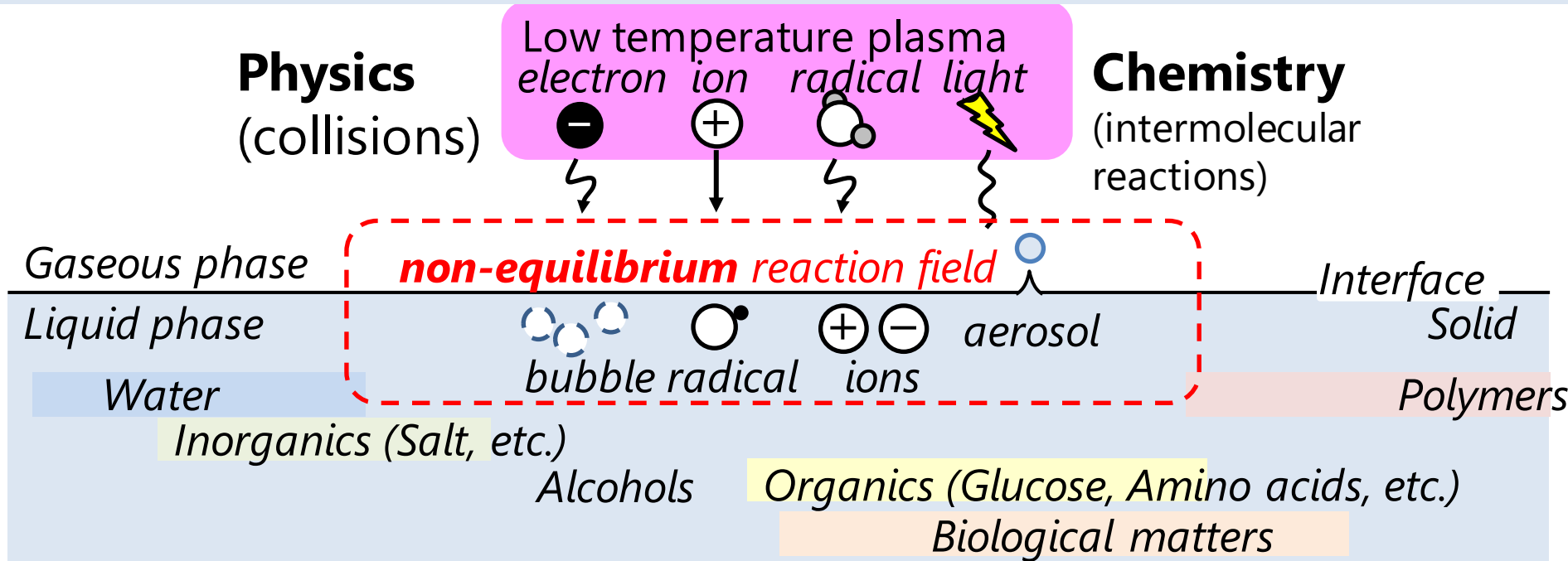
- The relaxation of the initiating physical impulses that exceed a physiological stress level propagates this network so act as stimulations. Thus, the plasma-induced reactions are both dynamic and reversible. These subsequently react with other species and generate various products as a consequence of **physical actions and chemical relaxation (PACR)**.



Coherent process: Wave field dynamics



Conclusion - plasma as a tool to open life innovation



- Low temperature plasma surface interactions – physics and chemistry - *kinetic* control of reactions
- To elucidate physical actions, chemical reactions (PACR) using multiple in situ analyses at real time during processing.

Acknowledgements



- The authors would like to thank Profs **M. Hori, H. Tanaka, C. Miron, S. Toyokuni, M. Mizuno, H. Kajiyama, K. Nakamura**, (Nagoya U), **H. Toyoda, N. Ohno**, (Nagoya U), **M. Ito** (Meijo U), **Y. Ikehara** (Chiba U); **M. Shiratani**, and **K. Koga** (Kyushu U); **H. Sakakita** (AIST); the **center for low-temperature plasma sciences** and the **Ishikawa-Tanaka (Hori-Sekine) laboratory** members for technical assistances.
- This study was partly supported by JSPS-KAKENHI nos. 20H00142, 21H01073, and 21H04451.

科研費
KAKENHI



Understanding of complex plasma reactions



- Similarities and differences between animate and inanimate systems. All the multiple pathways quantitatively are analyzed by multiple *in situ* and real-time measurements during this process.

