Inquiry on Medical Physics

And potential machine learning application

Fujimiya Amane

Department of Physics

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Outline

Introduction

This report is about examining *machine learning*, and its virtuous application in *medical science* and **research**. From there, we also move to small applications and practical cases.

Interests:

1. **The nature of machine learning (for application, important!).**
2. An overview of medical research and developments.
3. An inquiry on applicable approaches for optical physics. [1]

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The nature of machine learning

Machine learning can be thought of as a fundamentally powerful method for **automatic modelling**. Or, more simply said, to make "programs without being explicitly programmed".

What does that mean?

$\rightarrow$ Machine learning history is born out of mathematical optimization, statistical analysis, mathematical modelling, and computational processes. The word *learning* is the charm, however, its meaning varies.
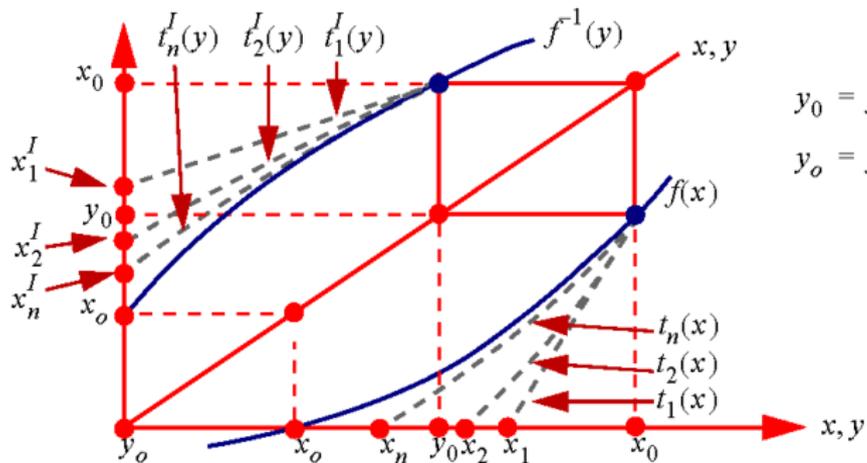
Figure: At its core, machine learning is somewhat mathematical optimization, and approximation of functions.

In actuality, machine learning is interpreted of another step toward *automation*. In such sense, it is the bridge between laziness - of connecting and transferring **abstract models** and knowledges to **realizable, specific subjects** of interest.

Abstract Knowledge $\rightarrow$ Quantified Models (With numbers)

Example

From the perspective of mathematical modelling (which machine learning *relies on*), modelling is to describe our beliefs, and understanding of the world.
How about **population of a given world?**

Supposed the world of population $p(t)$. Then, dp/dt is the time-derivative of the population over time.

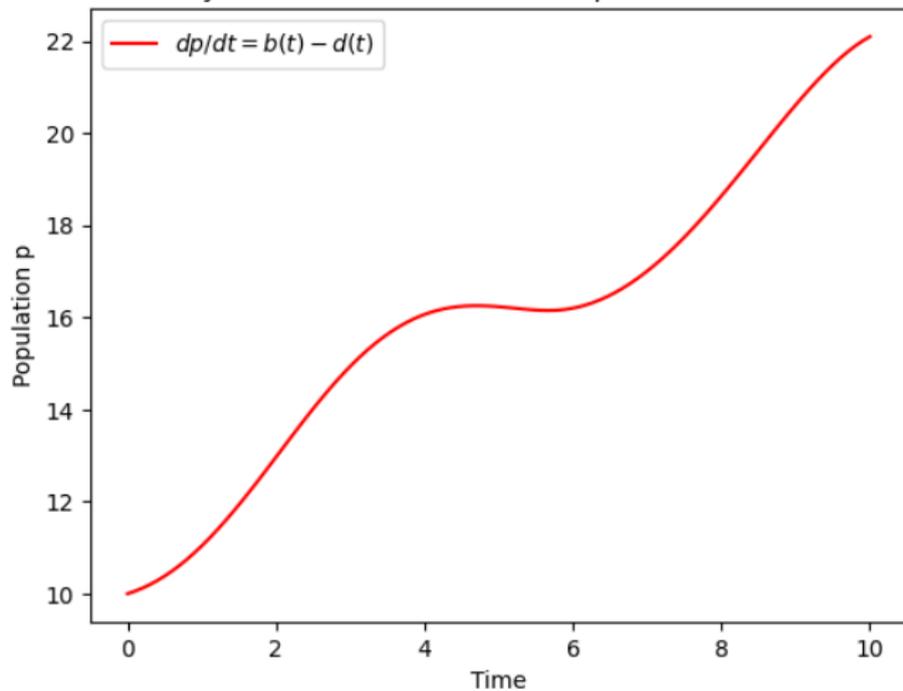If, we take $dp/dt = ap$ for arbitrary $a \in \mathbb{R}$:
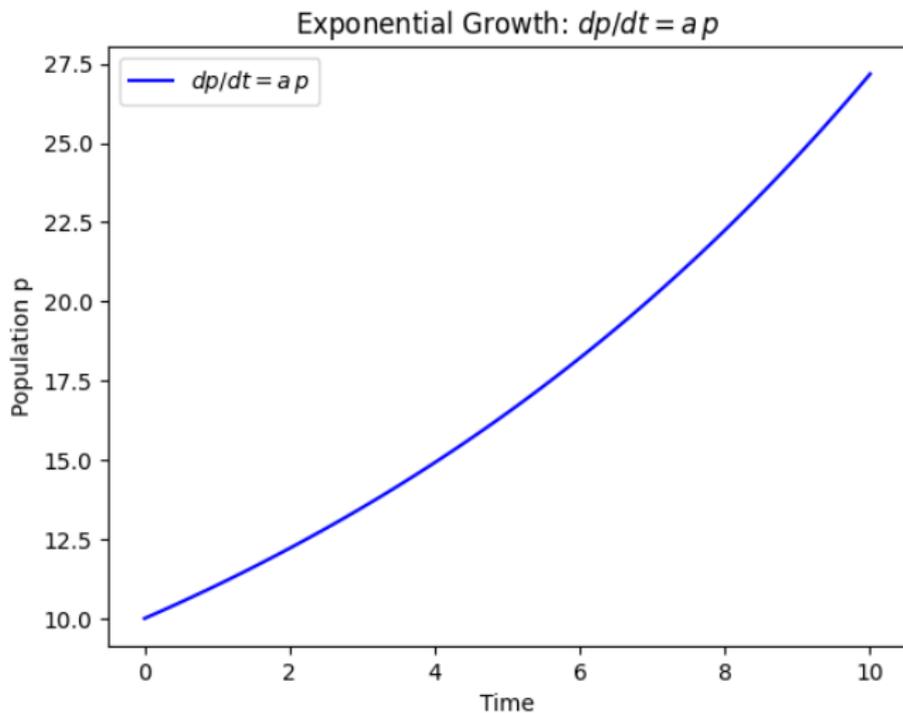
If, we introduce the concept of **birth** and **death**, for $b(t)$ and $d(t)$ as two parameters. Then
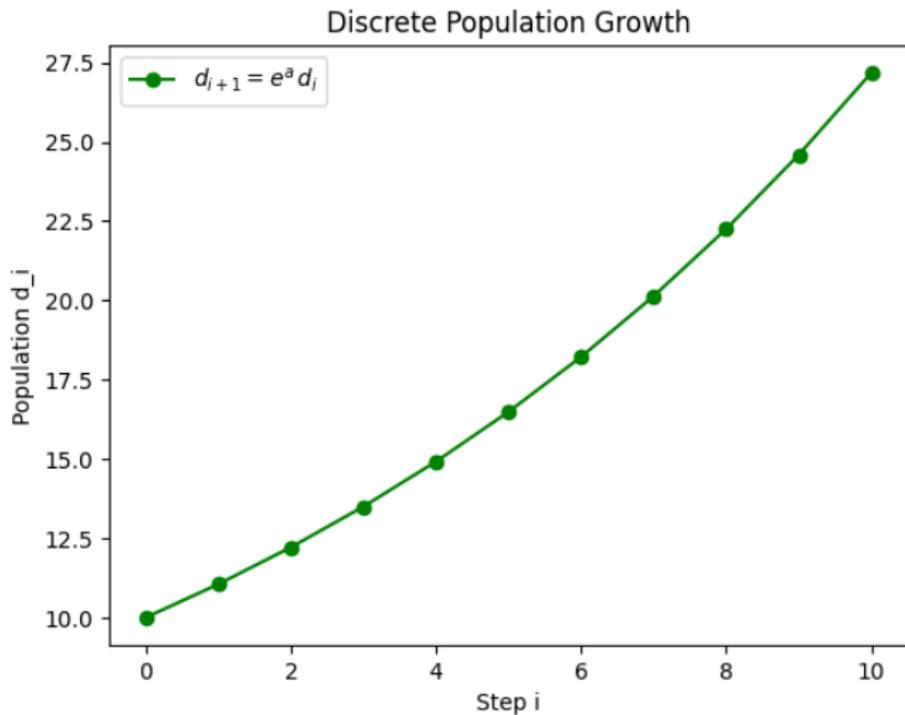
$$dp/dt = b(t) - d(t) \longleftarrow \begin{cases} b(t) = 2 + \sin{(t)} \\ d(t) = 1 + 0.5\cos{(t)} \end{cases} \qquad (1)$$

For an arbitrary choice of both.

Or, by some virtues, you want it to be **discrete time-step**.

In one way or another, **machine learning** goal is to automate this process.

> We know the differential equation, we know the functions, we just need implementation. Machine learning automate that.

Expressing the world, we need the world's observations to make models $\rightarrow$ data.
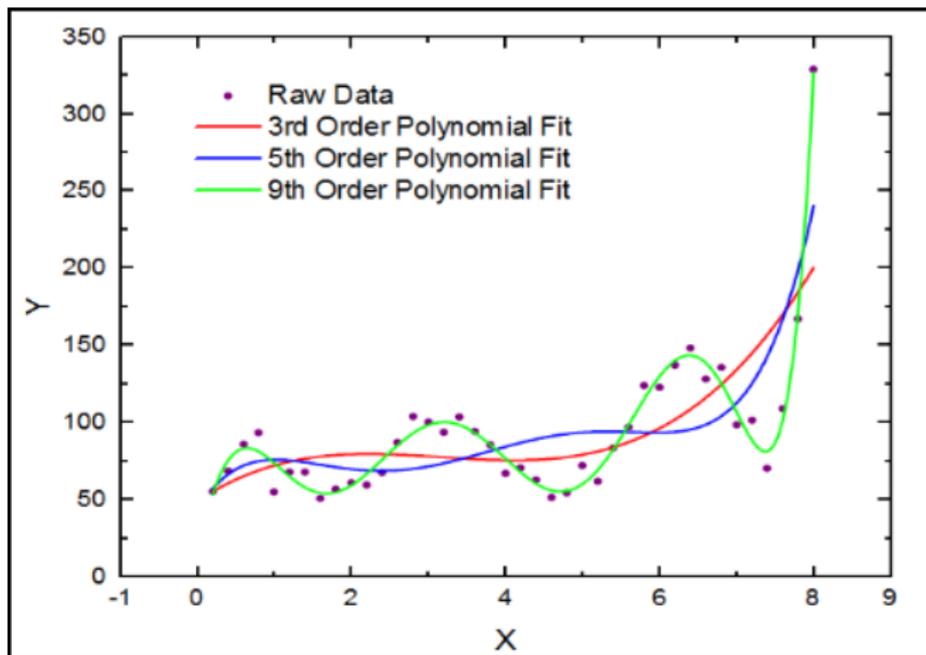
Figure: A machine learning model approximating data with the assumption of it being polynomial. Can you do better than it?

Usefulness

Machine learning hence is inherently useful for *prediction*, *pattern recognitions*, *estimation*, and regressions/approximation.

Furthermore, any tasks that require large data processing will benefit from the use of **machine learning theoretics** in their operations.

Usefulness

And most of all, as a model itself, it can mimic certainly, a *dynamical system* or at least a model of understanding for any given phenomena.

Medical science

Medical (biomedical) research and science, by its naive mean and understanding, is the use of *scientific methods* with the aim to produce knowledges about human bodies, human diseases, the prevention and treatment of illness.

By the nature of medical research, the typical interests of medical research relevant to our interest is:

1. **Diagnosis of diseases, illness, and monitor of health.**
2. Understanding functions of human body and its ecosystem, interactions and effects. Monitoring of human bodies.
3. Effects diagnosis and prediction.
4. Treatment formulation of specific diseases and illness.
5. Monitoring, stability analysis and examination on treatment procedures and method.

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The role of ML

The role of ML is dubious. As for medical science taking on increasing difficulties and complexity in their method and executions, and with more data available, data processing is thoroughly required Roy et al. (2023).

Conversely, ML thrives where there is a lot of data.

ML methods can be used to answer questions for studies that may fall within the following categories: prediction, estimation, understanding causal associations, and decision support.

ML can also help support main analyses as an auxiliary tool through missing data imputation, inverse propensity score weighting, dimensionality reduction, and variable selection.
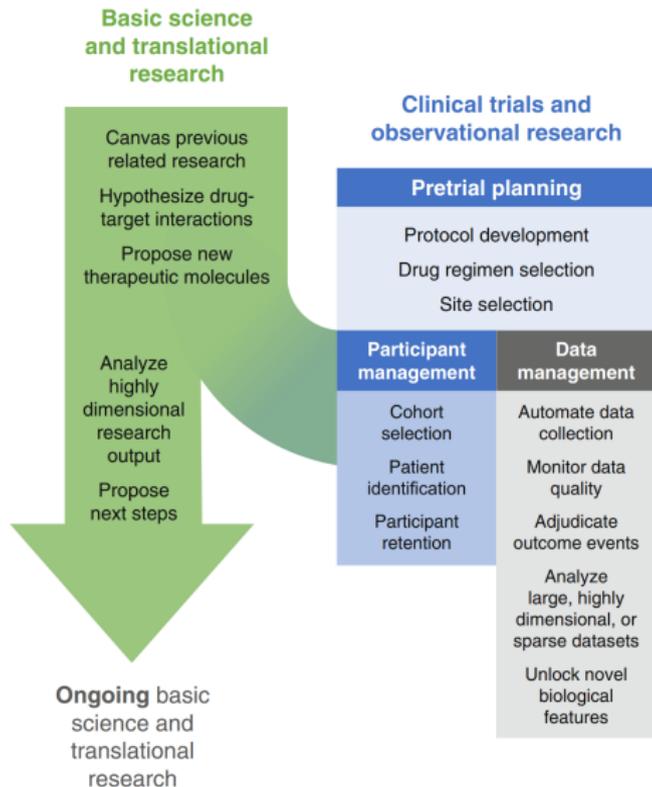
Figure: Areas of machine learning contribution to clinical research, with focus on clinical trials applications.

Optical physics and interests

For a long time, it has been customary that optics/photonics is mostly involved per medical science as a mean of medical physics - either by the supposition of medical imaging and others diagnosis-based method.

Optical physics and interests

Incorporating both optical physics, machine learning for medical science, especially **Raman spectroscopy**, we identify the following (Ozaki (1988)). The more general one.

1. Medical imaging: diagnosis, analysis, monitoring.
2. Drugs manufacturing: evaluation, analysis-based decision.
3. Personalized nanomedicine, AI-driven therapeutics (treatments).
4. Biomaterial studies, material selection.
5. Clinical testing, pathological examination.

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Raman-based application (of course without AI)

We analyse Ozaki (1988); Qi et al. (2024) for applications of Raman spectroscopy in medical science, *without AI* - fair enough.

Remember the notion of **automating is ML's job**? Let's find out what we can automate in such cases.

Medical application of Raman spectroscopy started as a natural extension of its biological application (1970s).

Since then to 1986, applications ranges to:

1. **Viruses and eye lenses (Thomas et al., Yu et al., 1974)**
2. Blodd testing by Raman (Larsson and Hellgren)
3. Laser Raman microprobe.
4. Pshysiology.
5. Vriology.
6. Laboratory medicine.
7. Pathology.
8. Internal medicines.
9. Ophthalmology.
10. Anesthesiology.

and else (urology and surgery - Suzuki et al., Daubon et al., 1973)

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Studies of biomedical materials

Raman application to biomedical materials is important for elucidating:

- ▶ Structure.
- ▶ Functions.

Thus form the basis of clinical application of Raman spectroscopy.

Studies of biomedical materials

The most famous *old-school* (1970-1986) examples are *ocular lenses, muscle fibers, viruses, mitochondria*, and teeth (not so important). [2]

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[2]Of all, ocular lenses seems in line with optical application the most - they are also the optical components of the eye.

Ocular lens

For ocular lens, Raman measurement can also be used for either *intact lens*, or straight from living animal.

Ocular lens

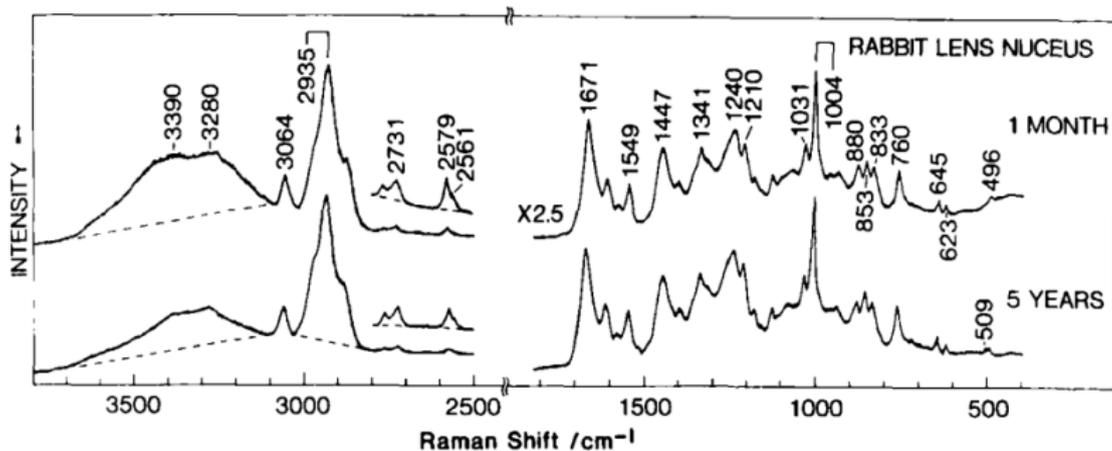There, we can use Raman spectroscopy for elucidation of aging and opacification, at molecular level.

FIG. 1. Whole region of Raman spectra of rabbit lenses (nucleus center, 1 month and 5 years old). Instrumental conditions: excitation wavelength, 488.0 nm; laser power, 120 mW; spectral slit width, 7 cm^{-1}; time constant, 4 s; scan speed, 25 cm^{-1}/min.
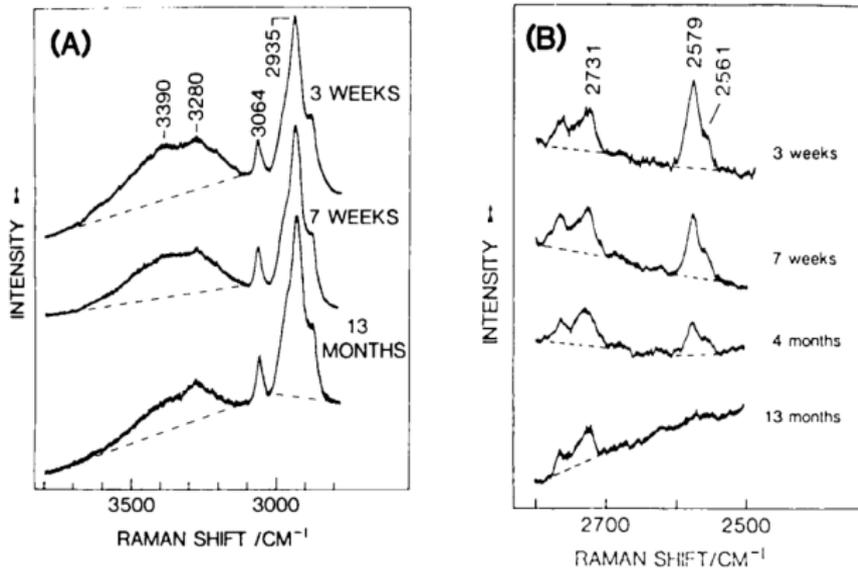
Ocular lens -aging

Lens aging brings about a decline in **transparency**, **lens hardening**, and lens pigmentation.

This can be measured by using Raman spectra of lenses at various time (in vivo). [3]

Figure: (A) Age-dependent Raman spectral changes in the 3800-2800 cm^{-1} region of SD-strain rat lens nuclei (3 and 7 weeks and 13 months old). (B) Those in the 2800-2500 cm^{-1} region (3 and 7 weeks and 4 and 13 months old).

Ocular lens - aging

Connection varies. Raman spectroscopy in such case (Ozaki et al.) for SD-strain rat lens indicates various correlation, for example, between lens dehydration, and S-S intermolecular bonds.
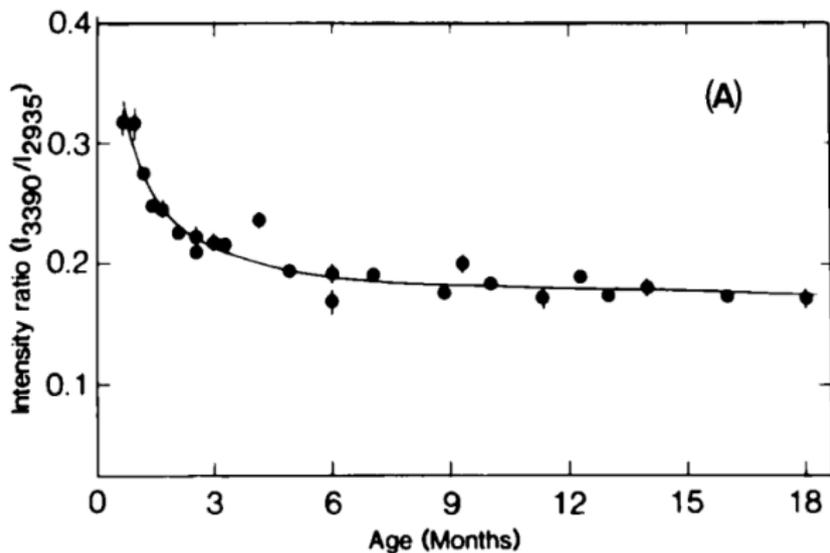
Figure: Intensity ratio of the Raman bands at 3390 cm^{-1} (OH stretching mode of lens water) and 2935 cm^{-1} (CH stretching modes of lens protein) versus age for SD-strain rat lens nuclei.

Generally, it is interesting to investigate the correlation between physical analysis and compositions in lens, and the observed microenvironmental changes and its effects.

Muscle fibers

Similarly, we can use Raman spectroscopy for analysing muscle fiber, which by its structure is a highly ordered system of *protein lattice*.

From that, we can investigate properties - for example, muscle constraction and strucrual changes of proteins.
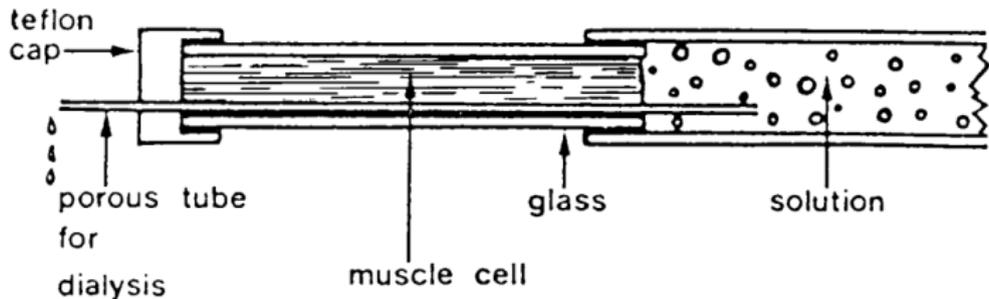
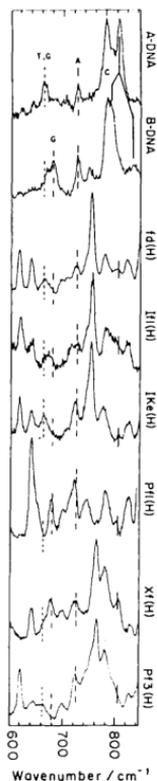Figure: A specially devised Raman cell for an internally perfused muscle fiber.

Virues

Virus has been traditionally investigated through X-ray crystallography. However, few viruses give crystal suitable for analysis. Their dynamic structure in aeuqous solution cannot be probed by X-ray crystallography. Hence,
Raman spectroscopy finds a place here, not just complementary, but major roles.

Virues

Usually, Raman spectrum of an intact virus is an overlap of the nucleic acid and proteins involved.

Figure: Raman spectra in the 1800-300 cm^{-1} region of six filamentous viruses: fd, Ifl, IKe, Pfl, Xf, and Pf3. Diferences between class I (fd, IF1, IKe) and Class II (Pf1, Xf, PF3) lies in filament symmetry.

Figure: Raman spectra in the 840-600 cm^{-1} region of six filamentous viruses at high salt concentration and of A- and B-DNA. The broken vertical lines indicate the positions of nwleoside markers while the unbroken ones (at 830 and 810 cm^{-1}) denote those of expected bands of A- and B-DNA backbones.

Those experiments conducted helps to analyze **structure transitions** of various viruses, as well as their DNA nucleoside conformations (850-600cm^{-1} range). Raman data (Ozeki et al.) suggests insight on interaction of DNA and protein structures for living viruses.

Approaches similar to those employed in virus research have been successfully applied to related Raman studies, like ribosomes, chromatin, gene regulatory complexes. (Thomas et al.)

Clinical analysis and testing

Clinical analysis are often grounds for diagnosis of a disease. Raman spectroscopy, at the time of 1986, might be a unique tool for clinical analysis and testing.

Blood testing

For blood testing, Raman spectroscopy helps instrumentally (Larsson and Hellgren, 1974) - requiring 0.1mL of blood, while giving reliable results. Those tests use **Raman-Fluorescence** methods for obtaining Raman spectra.
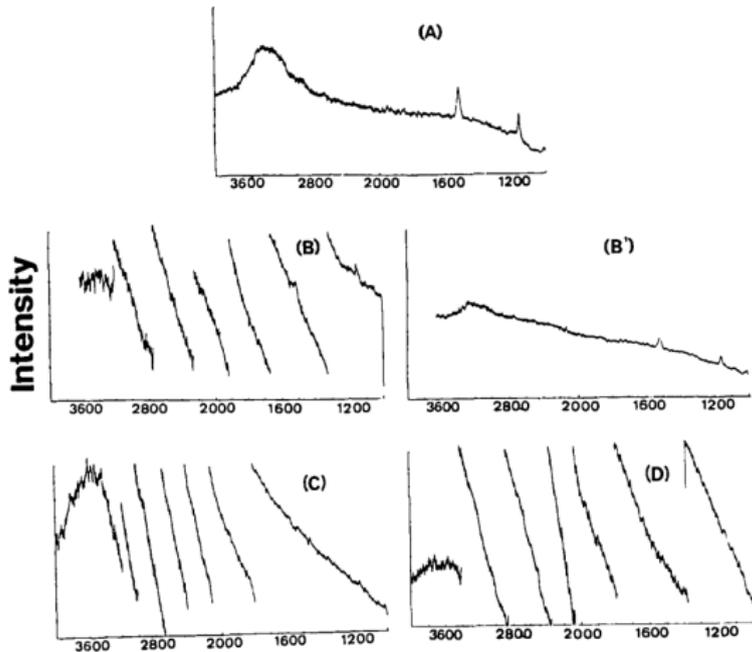
Figure: (A) Raman spectrum of blood plasma from a 23-year-old healthy woman, (B) and (B') Raman spectra of blood plasma from a 20-year-old woman with homologous serum hepatitis, where (B) was recorded during the icteric period and (B') was taken 20 days later when the patient was clinically recovered, (C) Raman spectrum from a 62-year-old woman with infiltrating mammary carcinoma, and (G) Raman spectrum from a 64-year-old woman.

Drug Analysis - Surface-Enhanced Raman

Under the condition of surface-enhanced Raman scattering (SERS), detection limits for various Raman bands for suitable analysis are increased by factor of 10^3. Generally, RR spectroscopy also is a very potent method, raising the limits of detection substantially [4]

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[4]RR spectroscopy is *Resonance Raman Spectroscopy*. So, it's all in the family.
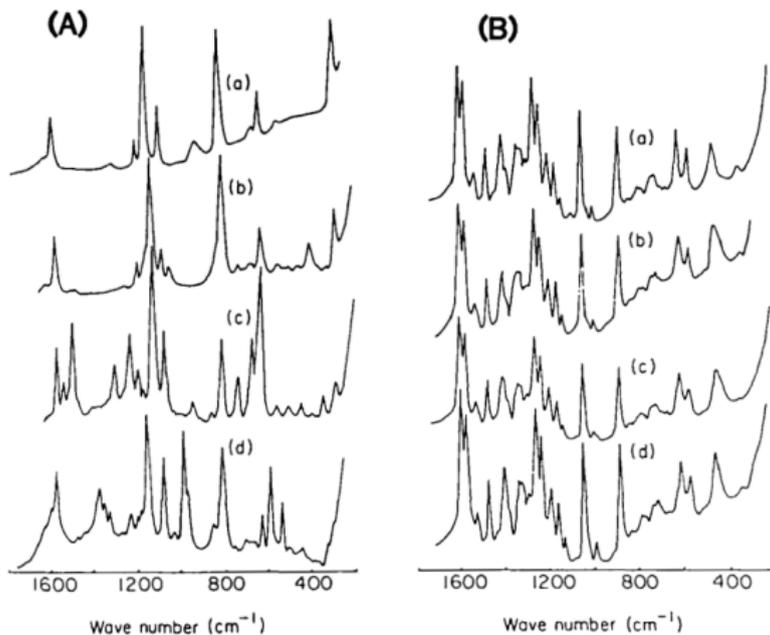
Figure: (A) Raman spectra in about 0.1M aqueous solutions: (a) sufanilamide (b) sulfaguanidine (c) sufathiazole (d) sulfisomezole and (B) the alternative Resonance raman spectra.
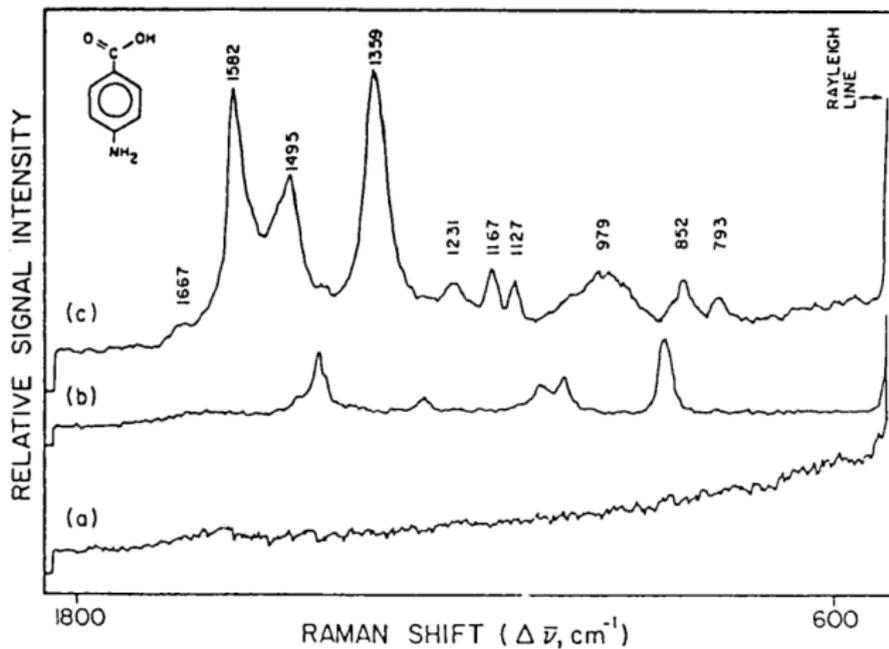
Figure: (a) Raman spectrum of the silver hydrosols. (b) Raman spectrum of $80\ \mu g/mL$ PABA in water. (c) SERS spectrum of $50\ \mu g/mL$ PABA in silver hydrozols.

Pathological Examination

▶ For pathological examination, the purpose is to *diagnose* a disease and elucidate its cause by investigating the morbidity of tissues and materials.

▶ In such, the first microanalyses of pathological specimens with Raman microprobe is in 1979. It is then used extensively for identification.

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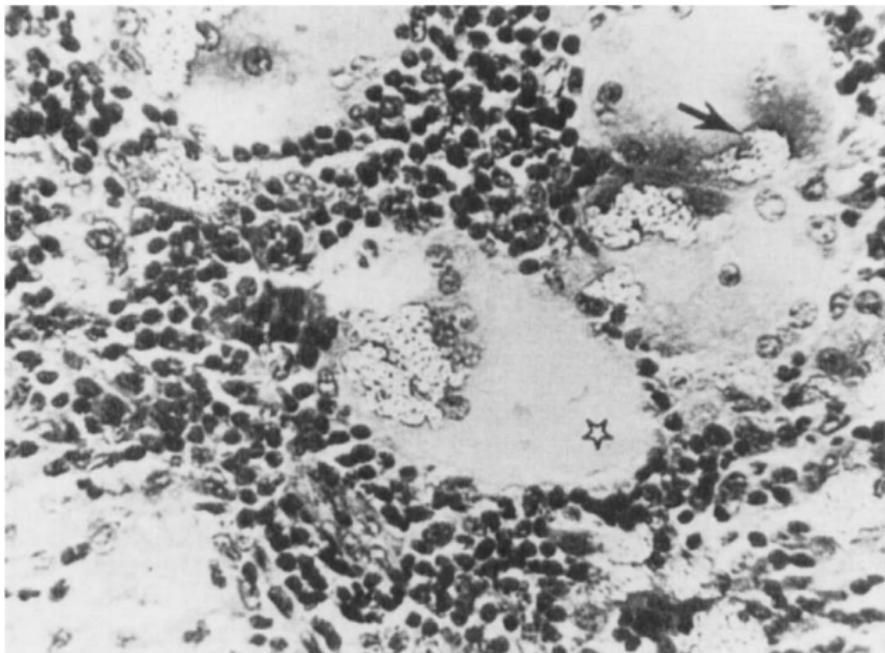
Identification of Inclusions in Lymph Nodes

Lymph node is a very important component of the body's immune system. Under an invasion period of foreign bodies, this can be changed to multinucleated giant cells, or any other form of wrecked lymph node.

Identifying them can be done with Raman spectroscopy. [5]

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[5]This can be coupled with various methods, for example, even using image-based analysis.

Figure: Light micrograph of a stained section ($5\mu m$) of lymph node with foreign bodies within multinucleated giant cells. Arrowhead indicates one of the foregin bodies, asterisks shows cyptoplasmic area for Raman analysis.

# Identification of Inclusions in Lung Tissues

Raman microprobing techniques can be used for investigating inclusions in lung tissue (Buiteveld et al.). Identification of components of the particles is very important to clarify the source of the pollution which causes the disease.
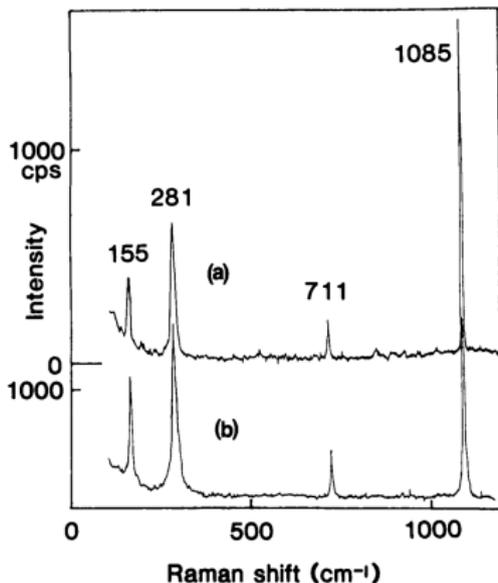
Figure: (a) Raman spectrum of an inclusion in lung tissue from a patient with silicosis. (b) Raman spectrum of a reference calcite particle.
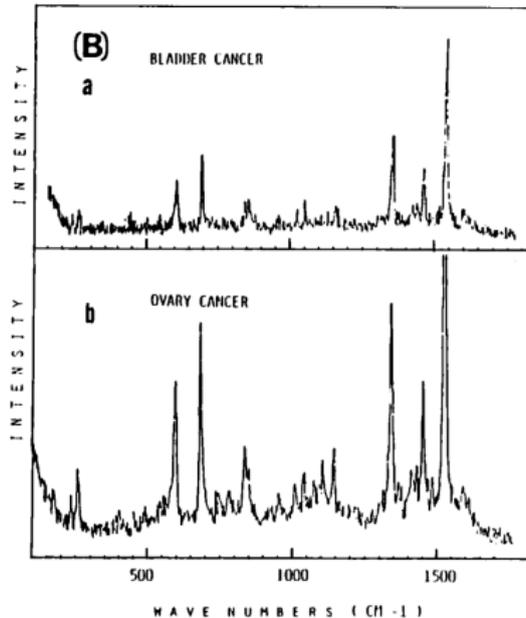
Blue particles in Cancerous Organs

One of the more important example of pathological examinations by the Raman microprobe method is an investigation of blue particles - found in cancerous tumors of human and animal origins.
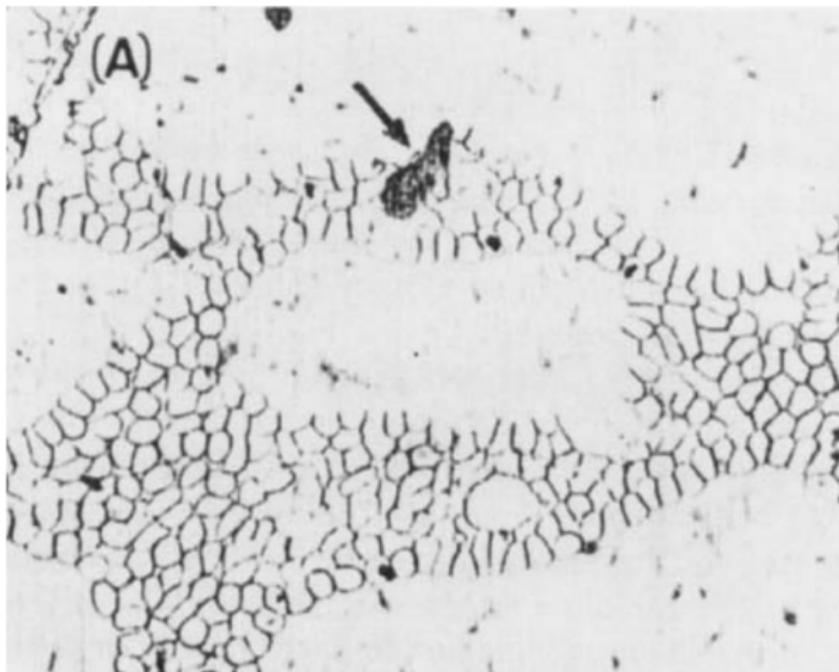
Figure: (A) Blue particle (arrow) in unstained blood smear from a canerous patient.

Of such, RR spectroscopy can help identify specific blue particles for certain type of diseases.


Figure: RR spectra of blue particles in cancerous organs: (a) bladder cancer, (b) ovary cancer.

At least of the 1988 report, there has been no substantial succcesses in identifying blue and green particles, Huong and Plouvier suggested some assignment bands of 300-240cm^{-1} region to Cu-ligand stretching modes, or the oxidation states of certain copper compound easier to identify.

Modern investigation

In a more modern view, The role of Raman spectroscopy has increased substantially, mostly still in biomedical sciences. Some of Raman spectroscopy methods has been used in diagnosis of Covid-19.
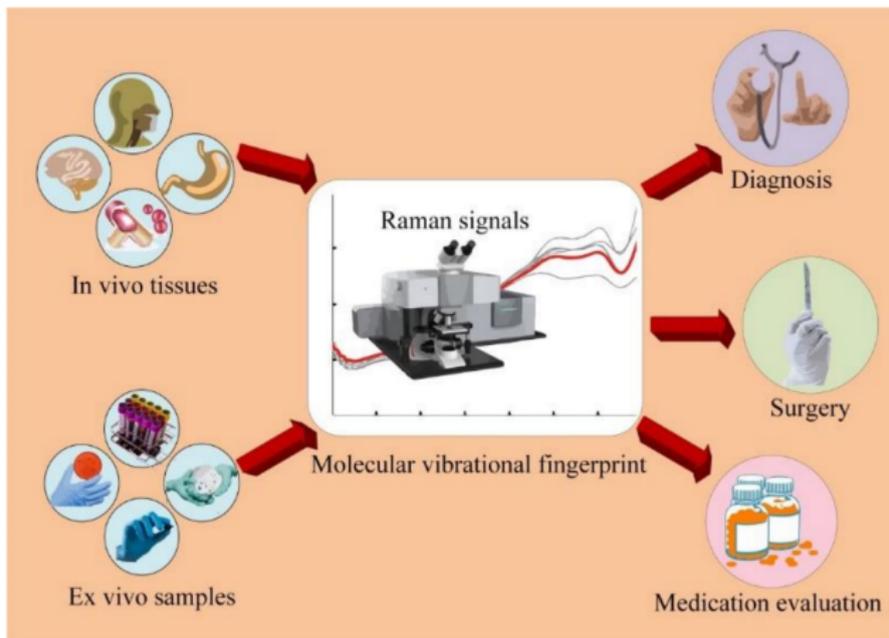
Figure: Application of Raman spectroscopy in biomedical sciences.

Ex vivo tissues detection

Raman spectroscopy in this aspect is considered alternative technique and complementary tool for tissue biopsy. This then has been performed on:

- Liver.
- Cervical.
- Brain.
- Lung.
- Breasts.
- Skins.

As tissue smears are becoming popular, Raman spectroscopy helps in that tissue smears is also a form of **biomarkers**, with high accuracy.

In vivo tissue detection

Reman spectroscopy in vivo biological studies provides robust data and technically foundation for analysis.

The application of Raman spectroscopy here can be applied directly to live tissues without processing, and can be used for substitute of various methods. Qi et al. (2024)

Acquisition method evaluation

Now, the new review also provided us with analysis on drawbacks and popular, well-used methods of acquirring Raman data.

| Classifications	Types	Theoretical foundations	Advantages	Disadvantages
Coherent Raman Spectroscopy	CARS	Four-wave mixing	Almost no fluorescence interference; high imaging sensitivity and speed; strong signal intensity	Signal is affected by a co-generated coherent background signal

SRS	Four-wave mixing	Superior in maintaining undistorted Raman spectra; high imaging sensitivity and speed; strong signal intensity; low detection limit	Signal is affected by co-generated coherent background signals
RRS	Resonance effect	Suitable for biological chromophores; high signal-to-noise ratio; selective signal enhancement	Chemical groups that do not participate in the electronic transition cannot be observed; Fluorescence interference

Enhanced Raman Spectroscopy	TERS	Local optical, electromagnetic field enhancement	Allow detection in tiny feature sizes; high sensitivity	Diffraction-limited spatial resolution; low stability
	SERS	Chemical enhancement via charge Transfer; Electromagnetic enhancement	High probability of obtaining Raman enhancement; high sensitivity; low detection limit	Stringent requirements for analytes and substrates

6

Autofluorescence imaging

Autofluorescence imaging (AFI) is also promising, wide-field imaging modality, which suffers from specificity, and lack of ability.

Integration of Raman-based technologies with optical modalities provides excellent solutoin to overcome this limitation.
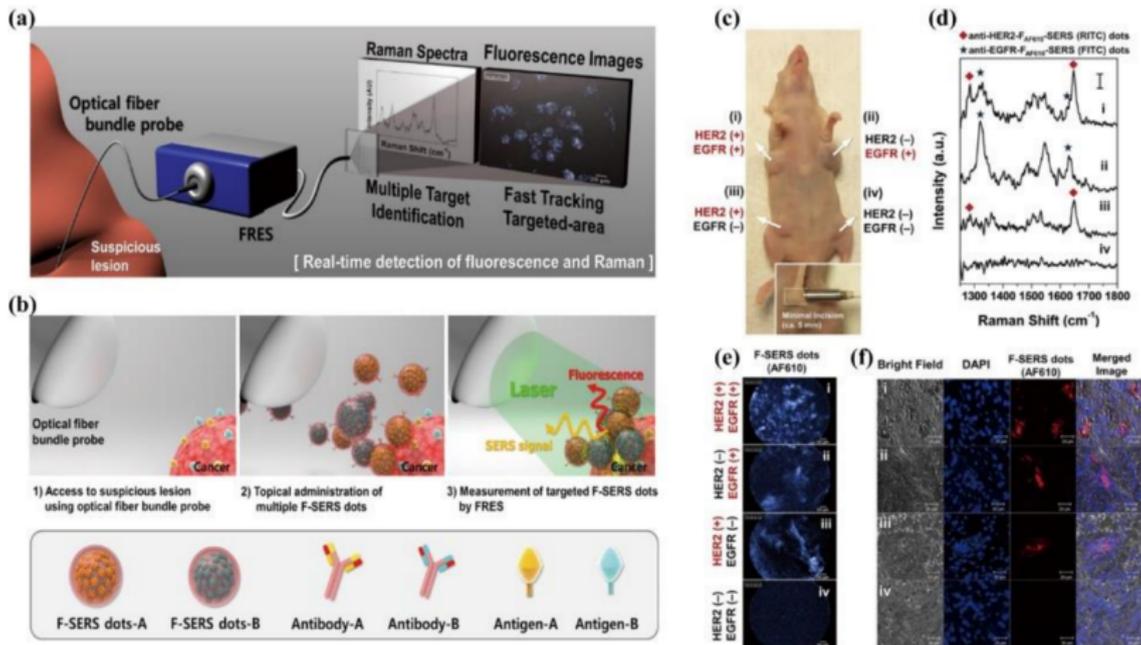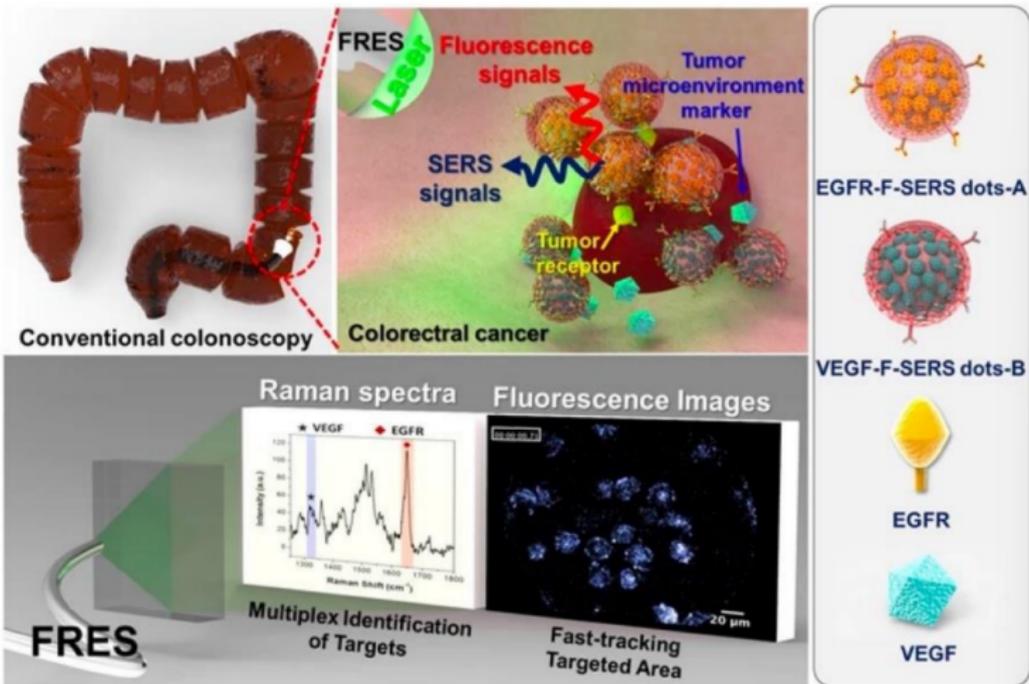
Figure: Schematic illustration of real-time multiplexed imaging using Fluorescence-Raman endoscopic system (FRES) and surface-enhanced Raman scattering nanoprobes (F-SERS dots)

Cancer diagnosis

Again, on the outset of cancer treatment, it is also observed that Raman spectroscopy, especially as mentioned, NBI-guided fluorescence-Raman spectroscopy can diagnose unfounded cases using endoscopes. [7]

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[7]Endoscpes based on white light reflectance were the standard for detection of cancers and surveilance of precancers.

Figure: Schematic illustration of the in vivo multiplex molecular diagnosis on colorectal cancer using simultaneous fluorescence-Raman endoscopic system (FRES).

Data analysis and machine learning

When it comes to machine learning, certain data analysis techniques, data interpretations and overall integration ranges widely in a lot of aspects.
Machine learning-assisted Raman spectroscopy analysis for biomedical application has a lot of implication in diagnosis, surgery and disease treatments.

Table 2. Recent Advances in combining machine learning methods with Raman spectroscopy for biomedical applications: diagnosis, surgery, and disease treatment.

Applications	ML Algorithms	References
Screening of cerebral ischemia and cerebral infarction	PCA, PLS, MRMR, SVM, KNN, PNN, DT	Fan et al. [101] (2022)
Classify the types of Isocitrate dehydrogenase mutations in gliomas	XGBoost, RBF-SVM	Sciortino et al. [102] (2021)
Classification of glioma biopsies	RF, GB	Riva et al. [103] (2021)
Alzheimer's disease (AD) diagnosis based on saliva analysis	ANN	Ralbovsky et al. [104] (2019)
Rapid screening of AD	SVM, RF, XGBoost, CatBoost	Wang et al. [105] (2022)
Effective primary screening of COVID-19 by serum Raman spectroscopy	SVM	Yin et al. [106] (2021)
Detection of COVID-19 infection by Raman spectroscopy of saliva	MILES	Ember et al. [107] (2022)
Classify breast cancer subtypes	PCA-DFA, PCA-SVM	Zhang et al. [108] (2022)

Diagnosis of lung cancer	CNN	Qi et al. [111] (2021)
Lung cancer diagnosis based on the Raman spectra of exosome	ResNet based deep learning model	Shin et al. [112] (2020)
Screening of ovarian cancer	BPNN, PCA	Chen et al. [113] (2022)
Predict gastric cancer	CNN, RF, SVM, KNN	Li et al. [114]

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