Translating Exosome Biology into an Optical Signature for Classification

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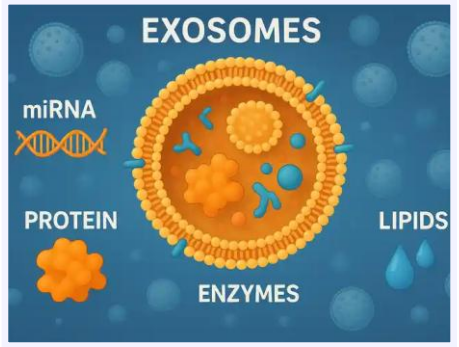
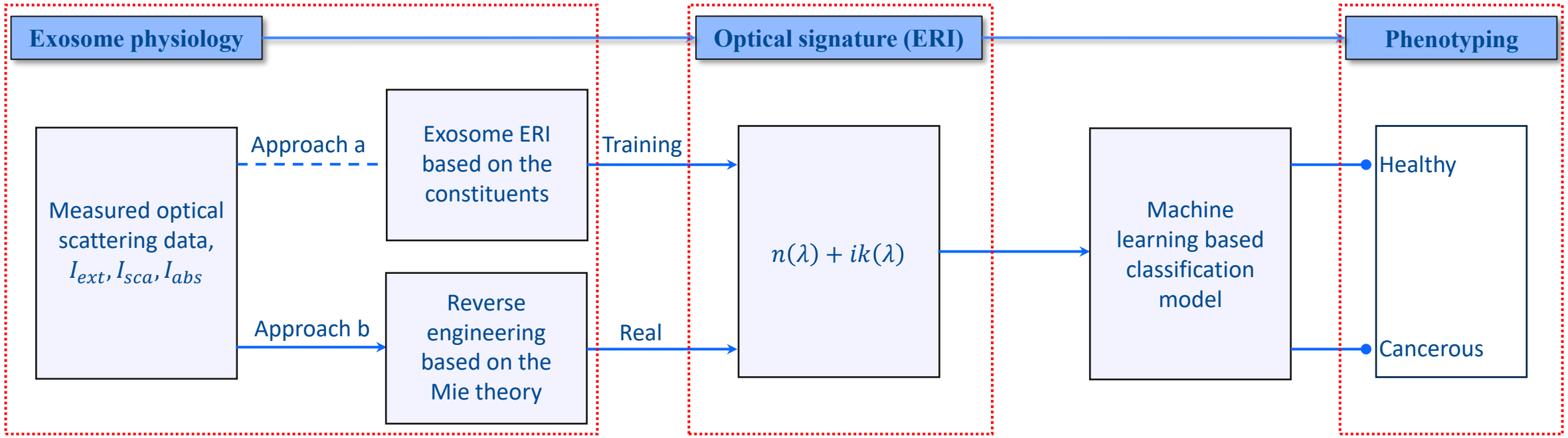
Motivation

- Translating the biological characteristics of exosomes into their optical signature; aka effective refractive index (ERI).
- Enabling label-free, minimally invasive diagnostics based on the optical signature
- Phenotyping using machine learning based classification

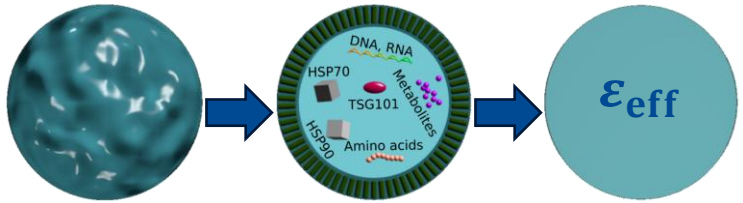


Outline


Exosome physiology
Optical signature (ERI)
Phenotyping
Measured optical scattering data, $I_{ext}, I_{sca}, I_{abs}$
Approach a
Exosome ERI based on the constituents
Approach b
Reverse engineering based on the Mie theory
Training
Real
$n(\lambda) + ik(\lambda)$
Machine learning based classification model
Healthy
Cancerous

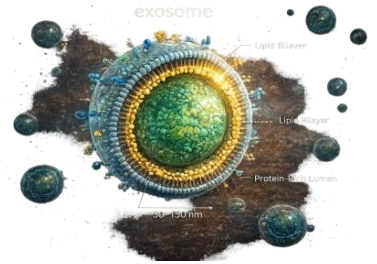
Outline

- Approach a)



  - ➢ Lumen refractive index
  - ➢ Exosome health state
  - ➢ Exosome ERI
  - ➢ Machine learning based phenotyping

- Approach b)



  - ➢ Optical scattering data
  - ➢ Inverse Mie theory
  - ➢ Label-free phenotyping

Approach a)

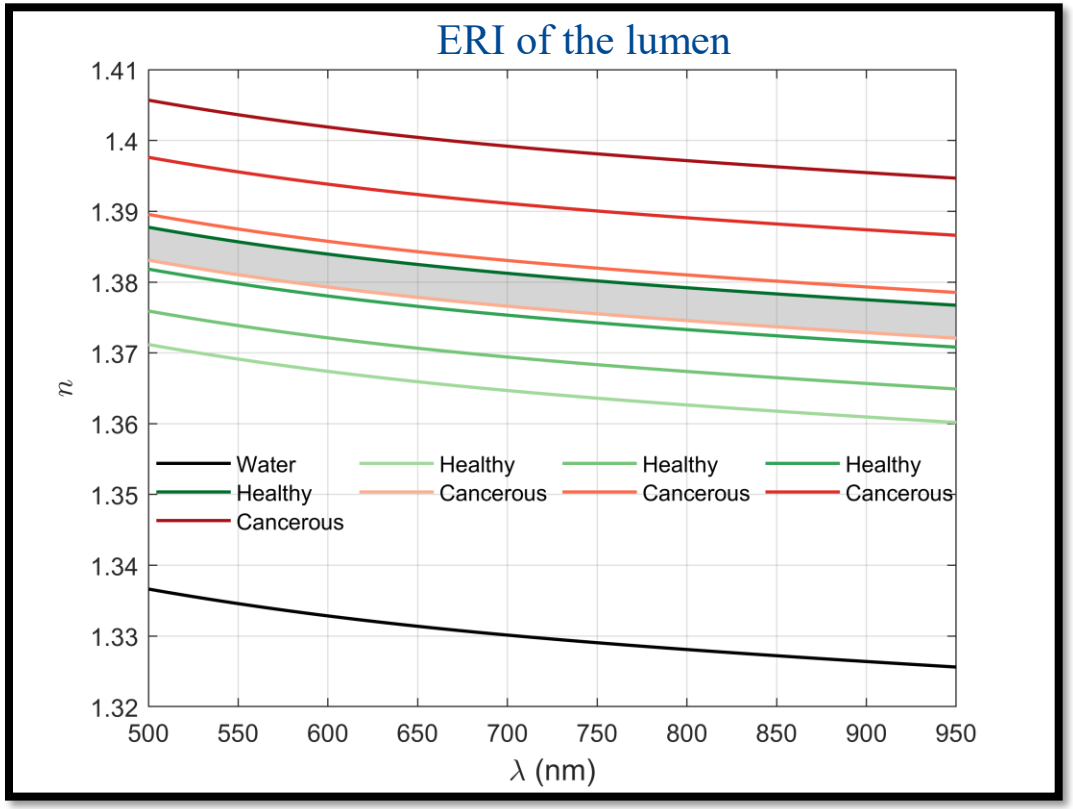
Lumen refractive index

Two-substance (Barer) mixture

$$n_{\text{core}}(\lambda, T) = n_{\text{water}}(\lambda, T) + \sum_i \left[\frac{dn}{dc}\right]_i (\lambda, T)\, c_i.$$

- Protein $dn/dc \approx 0.190\ \mathrm{mL\,g^{-1}}$ (narrow distribution).
- Nucleic acids (DNA/RNA) $dn/dc \approx 0.170\ \mathrm{mL\,g^{-1}}$.
- Water dispersion from Daimon–Masumura over 0.18 µm–1.13 µm.

Type	c_{protein} [g/mL]	c_{NA} [g/mL]
Healthy-like	0.18–0.26	0.002–0.010
Cancer-like	0.24–0.35	0.005–0.015



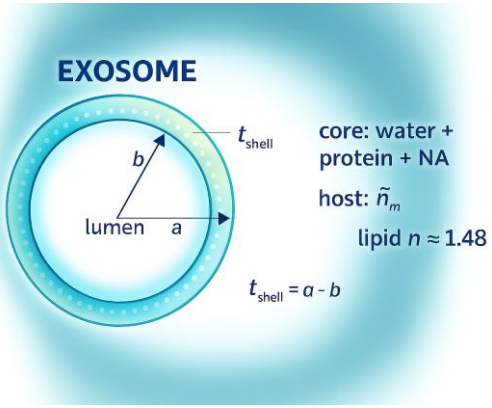
Barer (1957); Zhao et al. Biophys. J. 2011; Daimon & Masumura Appl. Opt. 2007; Jia et al. 2021.

Approach a)

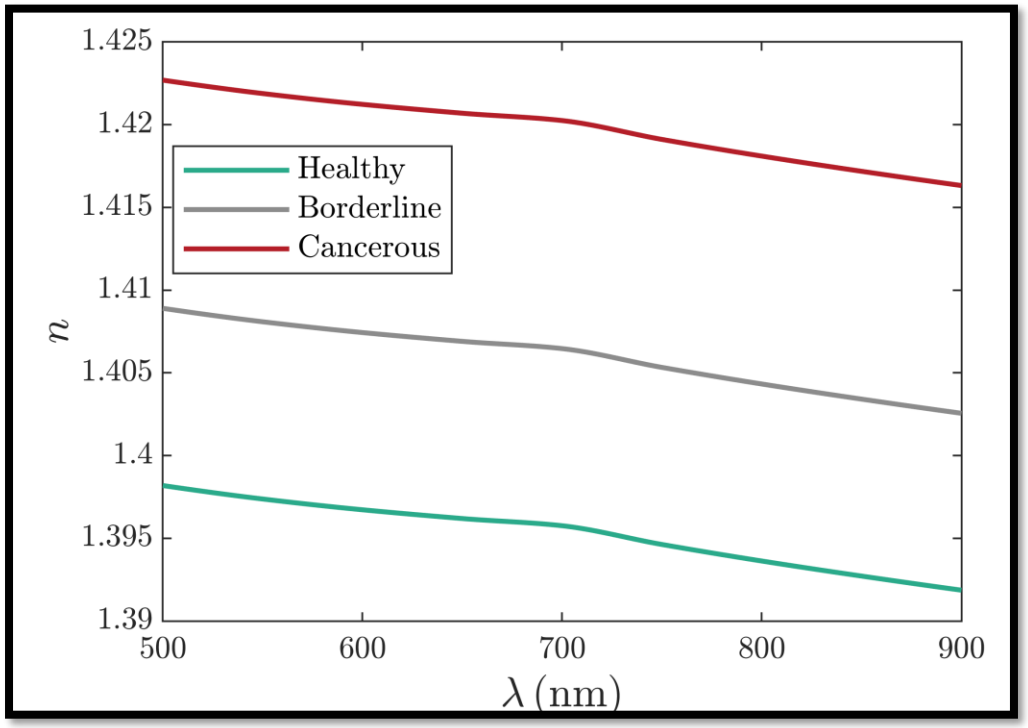
Exosome ERI

- To obtain an ERI for the entire exosome (core plus lipid shell), a full-wave driven-mode simulation of the core shell sphere in *Comsol Multiphysics* is carried out.
- The reason for considering exosomes as core-shell structures is to increase the sensitivity to the slightest changes in the core, i.e. variations in the protein/NA content.

$$\varepsilon_{\mathrm{eff},r}^{D/E} = \frac{\langle D_{\parallel} \rangle}{\varepsilon_0 \langle E_{\parallel} \rangle},$$



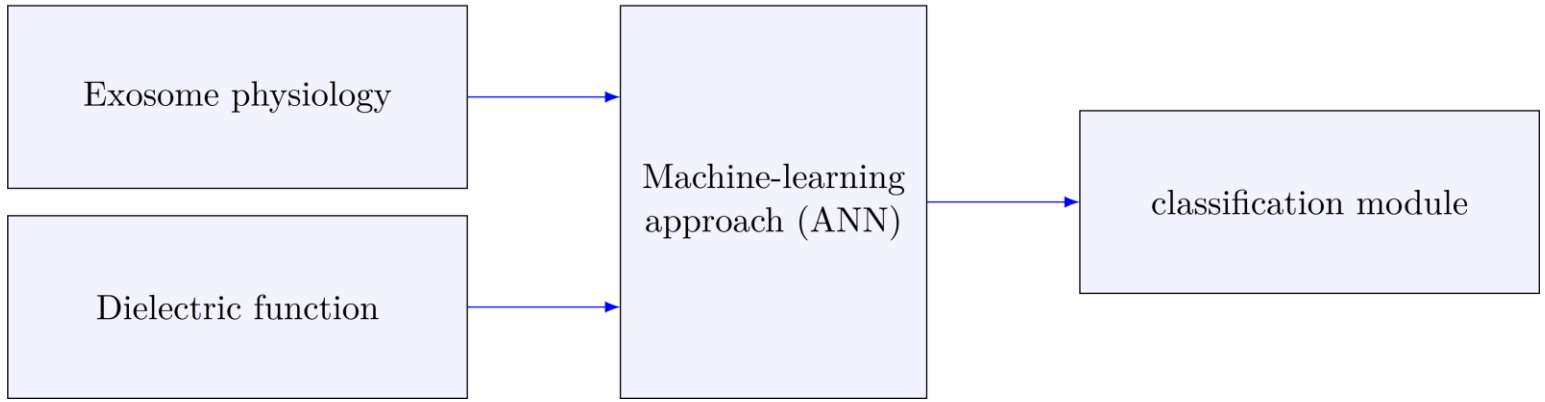
ERI of the Exosome



Approach a)

Machine learning based phenotyping

- The spectral response of the exosome (core-shell structure) is used as the data set, based on which the machine learning algorithm is trained.
- A machine learning model will be developed that based on the determined ERIs can classify the exosome's health state.



Approach b)

Retrieval of ERI of a single exosome

- We intend to retrieve the ERI of a single exosome based on optical scattering data: scattering, absorption and extinction coefficient.
- The retrieval will be based on measured optical scattering data but the algorithm is developed using synthetic simulated results.

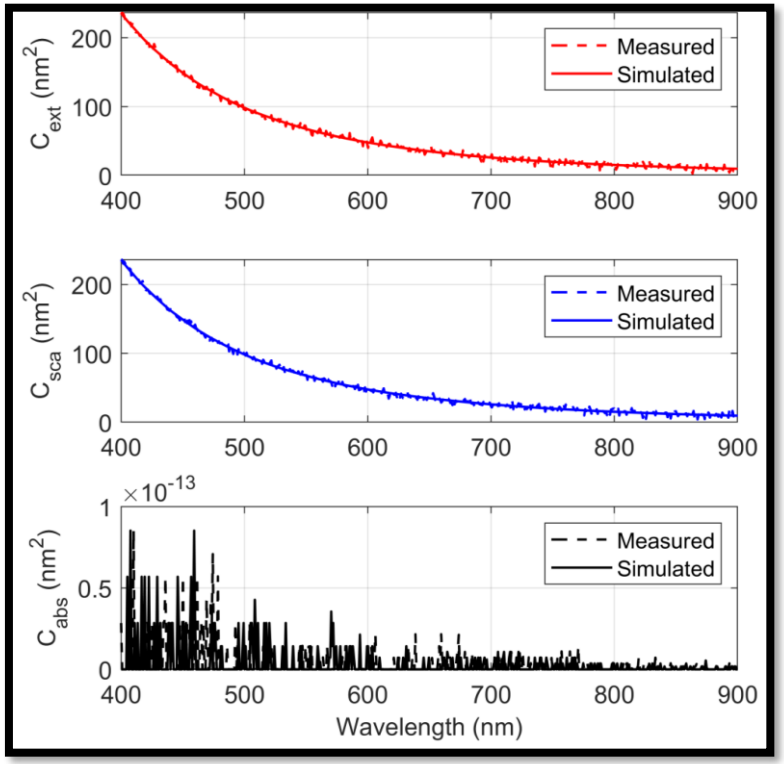
Approach b)

Inverse Mie-Theory

- **Modelling**: Each vesicle is modeled as a **spherical core–shell particle** (protein-rich core (40.5 nm) plus 5 nm lipid bilayer, dispersed in air, water, or PBS). The forward map is the **core-shell Mie theory.**

- **Inversion:** Retrieve a complex core refractive index from measured the spectra, through minimize a noise-normalized log-residual:

$$J(n.k) = \sqrt{\frac{1}{2}\left(\left|\frac{\log_{10} C_{\text{ext}}^{\text{mod}} - \log_{10} C_{\text{ext}}^{\text{meas}}}{\sigma_{\log}}\right|^2 + \frac{\log_{10} C_{\text{abs}}^{\text{mod}} - \log_{10} C_{\text{abs}}^{\text{meas}}}{\sigma_{\log}}\right)}, \quad \sigma_{\log} = \frac{noise}{\ln 10}$$



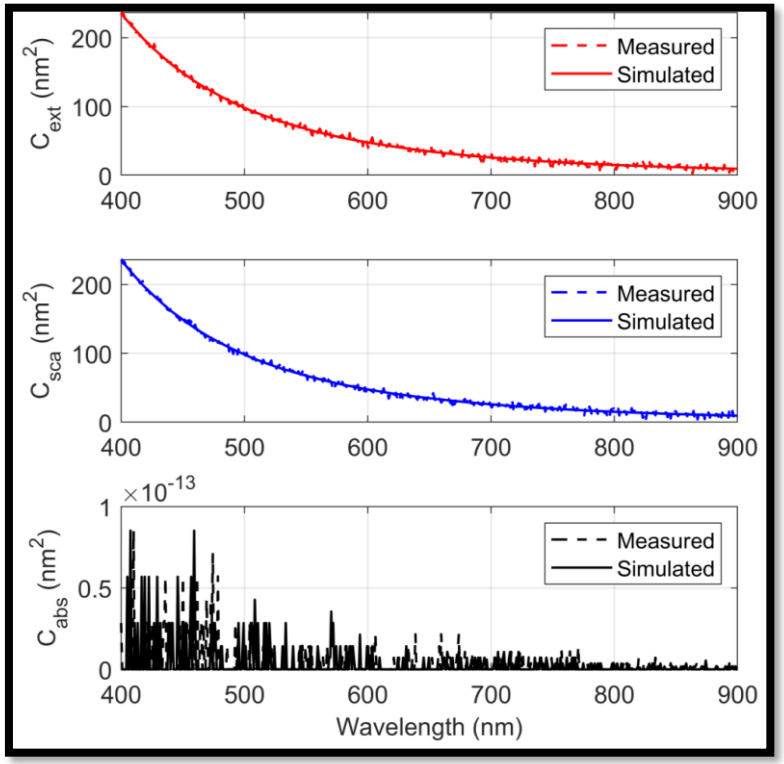
Approach b)

Inverse Mie-Theory

Solver & initialization: Solve a bounded, constrained least-squares with Sequential Quadratic Programming (SQP) via fmincon, wrapped in MultiStart.

Noise injection (synthetic tests): To emulate measurement conditions, Additive Gaussian noise (at 1–10 % of the mean signal per spectrum).

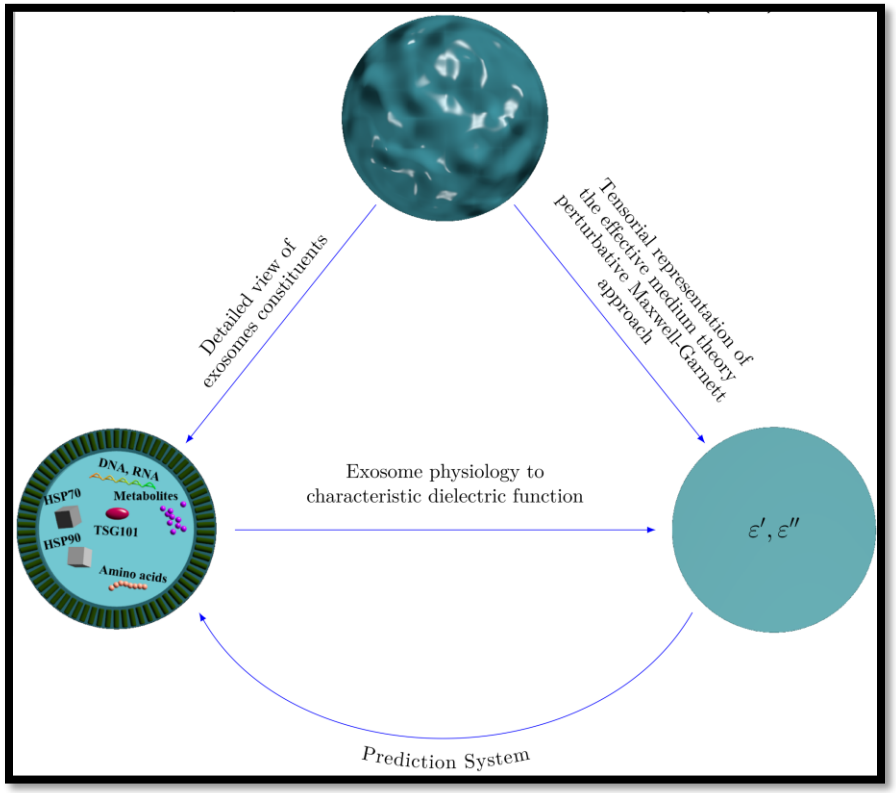
Output: ERI $n(\lambda) + ik(\lambda)$



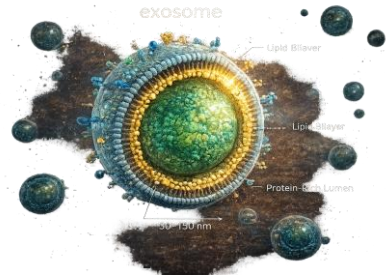
Approach b)

Label free phenotyping

- The machine learning model will then use the inversion algorithm data to determine the corresponding exosomes health state based on their ERI.
- This enable us to develop an early-stage cancer diagnosis biosensor in a minimally-invasive, label-free method.



Thanks for your attention



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