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A new approach for a physicochemical characterization of nanoparticles in complex media: a pilot study.

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Background. Current techniques used to measure the physicochemical characteristics of nanoparticles in simple media are poorly predictive of their behavior observed during in vivo experiments¹. As a consequence, some pharmacokinetic or toxicokinetic issues are detected too late.

Objectives

In this contribution, we are proposing an innovative approach for the physicochemical characterization of nanoparticles in complex media. The main objective is to quickly identify which medium compounds interact with the NP surface. In this pilot study, the goal is to demonstrate the proof of concept.

Methods

The proposed solution is composed of three main steps:

1. Sample preparation
2. Measurement phase
3. Statistical analysis

1) **Sample preparation** relies on a set of (n) serum-free media initially designed for cell culture but used herein to mimic heterogeneity of biological context. Each culture medium is composed of a large number (p), around a hundred, of biological compounds (proteins, vitamins, mineral salts, etc.), which may individually and synergistically interact with the nanoparticle surface. The nanoparticle to be characterized is added to each medium of the kit with the same concentration.

2) **Physical characterization.** The resulting mixtures are then analyzed by an appropriate technology compatible with complex media to measure the size distribution of constitutive nano-objects. In this pilot study, the nanoparticle size distributions were measured by a Dynamic light scattering system (Nanosight, Malvern), as illustrated in Fig.1.

3) **Statistical analysis.** In a third step, all the experimental data coming from the (n) series of measurement are used to solve a "large p small n " regression problem. This statistical analysis informs about the most likely medium compounds to affect the size distribution of nanoparticles compared to their initial dimensions. This communication presents the first results of a pilot study in which the proposed approach was tested on gold nanoparticles mixed in $n=9$ cell free culture media provided by Thermo Fisher Scientific. A partial least squares method was used to solve the "large p small n " regression problem. The tested media was composed of $p=82$ compounds split up into four families: amino acids (AA), vitamins (V), mineral salts (S), and other compounds (OC) Preliminary results confirms significant changes of the size distribution between the culture media and the feasibility of the statistical method to identify a set of medium compounds that may explain those variations.

Results

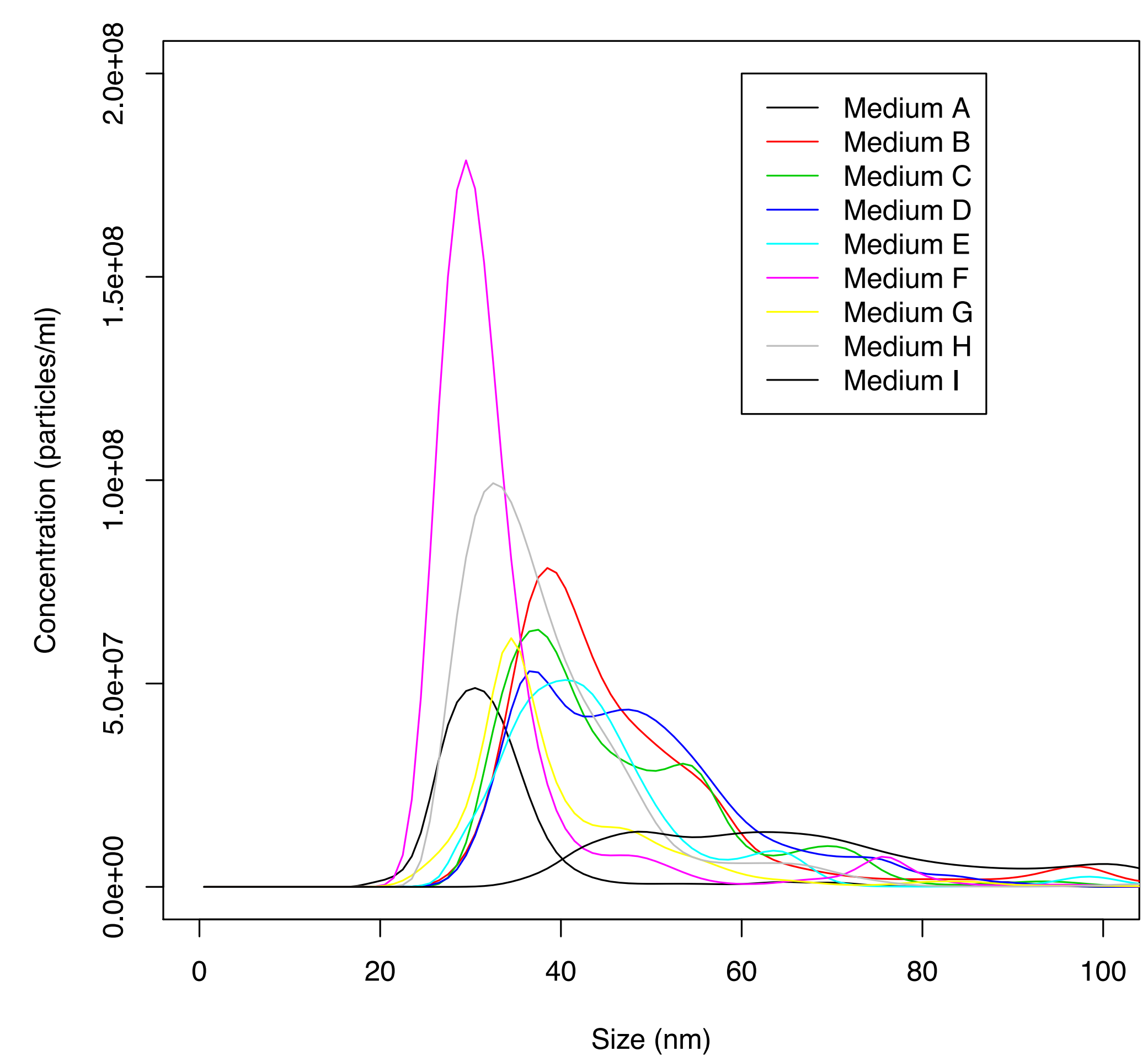
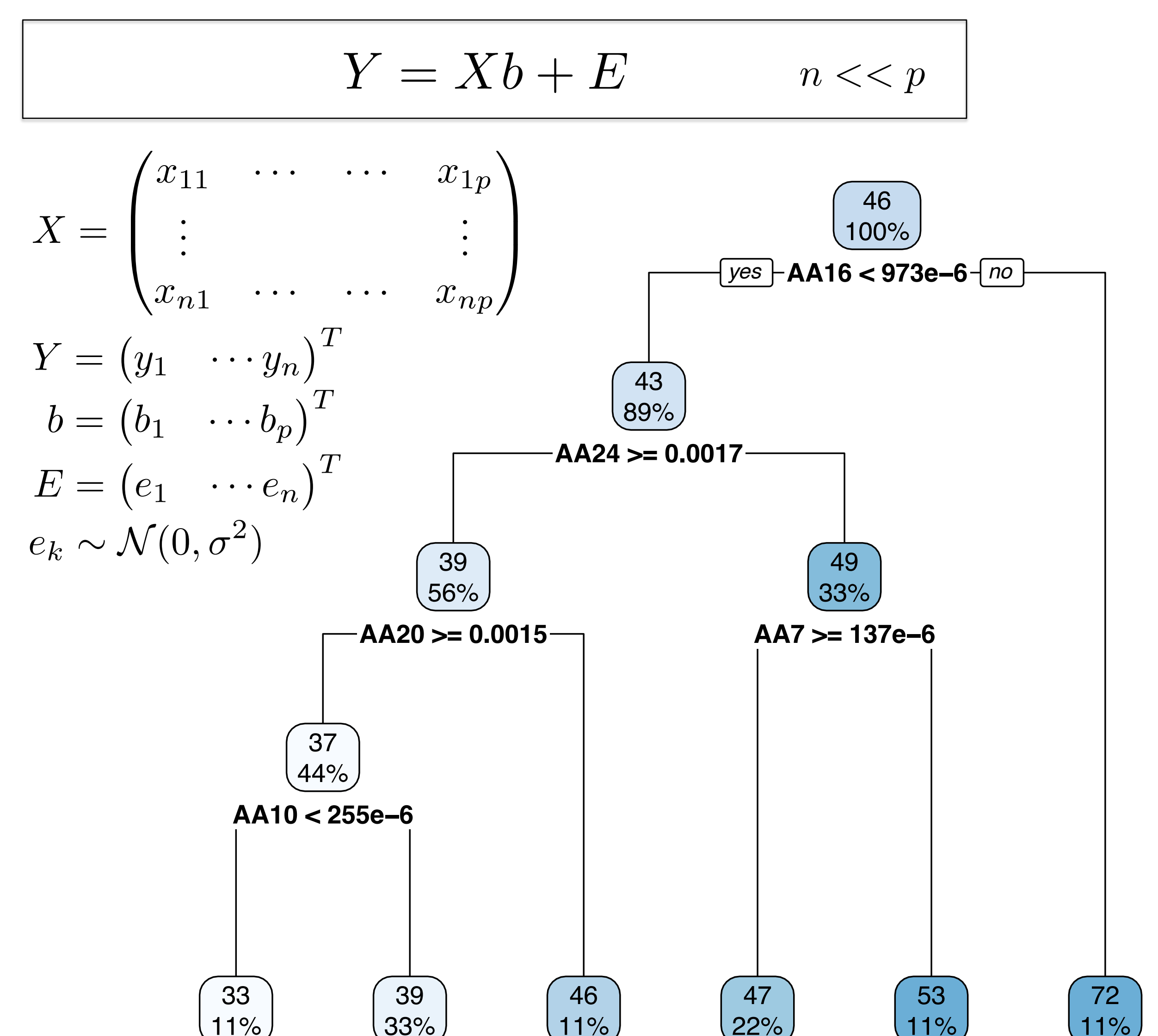


Fig.1: Measured average size distributions of particles for nine samples in which the same concentration of gold nanoparticles are mixed in nine different serum free culture media. Those data are then used in a "large p small n " regression problem to identify biological compounds of the medium that modify the size distribution of the nanoparticle.



Conclusion

This study demonstrates the proof of concept of the proposed approach by identifying at least 5 amino acids that strongly interact with the surface of the tested NP.

1. C. Gollwitzer, et al., "A comparison of techniques for size measurement of nanoparticles in cell culture medium," Analytical Methods, vol. 8, no. 26, pp. 5272–5282, 2016.
2. T. Bastogne, "Improvement process of media cultures for the physico-chemical characterization of nano-materials in complex and serum free and controlled biological media." INPI Patent Deposit, No. 1661671, 2017.