Advanced Fluorescence Data Calibration for Capillary Analysis of Biochemicals

Practical informations:

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Hosts: Institut de Mathématiques de Toulouse & Adelis

Location: Campus Paul Sabatier of the University of Toulouse.

Duration: 4 to 6 months starting from February/April 2026

Candidate profile: Background in applied mathematics required, as well as taste for numerics.

Salary: The intern will be granted the usual stipend of ∼600 euros/month.

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Application: Resume, application letter and grades from previous years

Context and objectives: The company Adelis [5], based in the Toulouse metropolitan area, has developed and patented a pharmaceutical analysis technology, which consists in measuring the concentration and length distribution of cell-free DNA circulating in blood plasma, which has been shown to be a marker in several physiological and pathological conditions [2]. Its principle is to measure, along time, the fluorescence emitted by DNA fragments that are convected inside a capillary. From this fluorescence-versus-time signal, the goal is to recover a concentration-versus-DNA length distribution that can be interpreted biologically.

In order to perform this transformation, each experiment is accompanied by a calibration procedure. It consists in analyzing a reference sample, called a ladder, whose fragment lengths and concentration are known (see Figure 1).

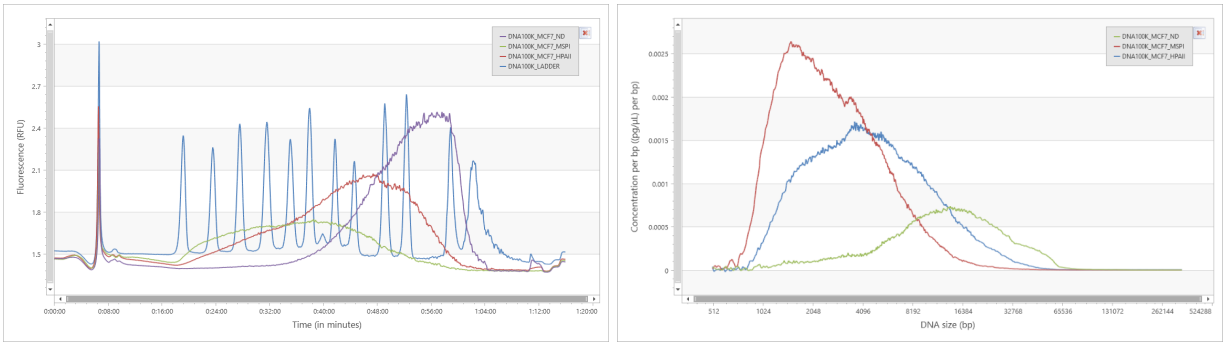

Figure 1: Fluorescence vs time measurements (left) with the reference "ladder" in blue ; Concentration vs DNA length conversion (right).

More formally, the florescence-time signal f must be transformed into the concentration-length one $g = \psi \circ f \circ \phi$ where ψ and ϕ denote the change of variables from fluorescence to concentration and length to time, respectively. The ladder provides approximate paired observations $\{(f_i, \psi(f_i))\}_i$ and $\{(t_i, \phi(t_i))\}_i$ which can be used to estimate the underlying mappings ψ and ϕ. Currently, the calibration is performed in two successive steps: first by estimating a fluorescence-to-concentration mapping and then a time-to-length mapping. This strategy however suffer from various drawbacks that will be addressed by this internship.

Topic: The objective of this internship is to design and evaluate a calibration method that performs a direct mapping from the fluorescence-versus-time domain to the concentration-versus-DNA length domain. The work can be organized into three main phases:

Modeling and literature review The first phase focuses on understanding the physical principles of the instrument and developing a mathematical model of the calibration process that accounts for the various sources of uncertainty on the data $\{(t_i, \phi(t_i), f_i, \psi(f_i))\}_i$. During this period, the intern will also receive training in smooth function estimation and kernel-based methods [4].

Method design The second phase involves designing the calibration method itself, that is, estimating the mapping from fluorescence–time domain to the concentration-length one. Depending on the insights gained from the modeling stage, this step may involve estimating smooth, monotone functions, for example by solving

$$\min_{\phi \,|\, \phi' \geq 0} \frac{1}{2} \sum_i (\phi_i - \phi(t_i))^2 + \frac{\lambda}{2} \|\phi^{(p)}\|_2^2$$

where $p \in$ is the order of the derivative used for regularization. Potential approaches include kernel methods [4], isotonic regression [1], or a joint formulation cast as a quadratic program [3].

Certification In the final phase, the proposed calibration method will be validated on samples with known distributions of DNA fragment sizes and copy numbers (per µL) to assess its accuracy and robustness.

References:

[1] Richard E Barlow and Hugh D Brunk. "The isotonic regression problem and its dual". In: *Journal of the American Statistical Association* 67.337 (1972), pp. 140–147.

[2] Audrey Boutonnet et al. "Size and concentration of cell-free DNA measured directly from blood plasma, without prior DNA extraction". In: *Analytical Chemistry* 95.24 (2023), pp. 9263–9270.

[3] Marguerite Frank, Philip Wolfe, et al. "An algorithm for quadratic programming". In: *Naval research logistics quarterly* 3.1-2 (1956), pp. 95–110.

[4] Bernhard Schölkopf and Alexander J Smola. *Learning with kernels: support vector machines, regularization, optimization, and beyond*. MIT press, 2002.

[5] Adelis Tech. *Official Website*. 2025. URL: https://www.adelis-tech.com/.