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An in silico approach to monitor and predict haemodynamics during safety pharmacology studies

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ABSTRACT

The present work is related to develop *in silico* models in order to **predict the impact of drugs (vasoconstrictors and vasodilators) on the haemodynamics**. More precisely, we propose a mathematical model to reproduce the **ROTSAC** experiment (i.e., the Rodent Oscillatory Tension Set-Up to study Arterial Compliance, [1]).

The objective of this work is twofold: first, numerically reproduce the experimental data; second, to get some insight on two hypotheses on the impact on the mechanics of **vasoconstrictors** and **vasodilators**:

- **H1**: the compound only acts on the **smooth muscle cells (SMCs)**.
- **H2**: the SMCs can impact the fibronectin and indirectly affect slightly the **endothelium stiffness**.

METHODS

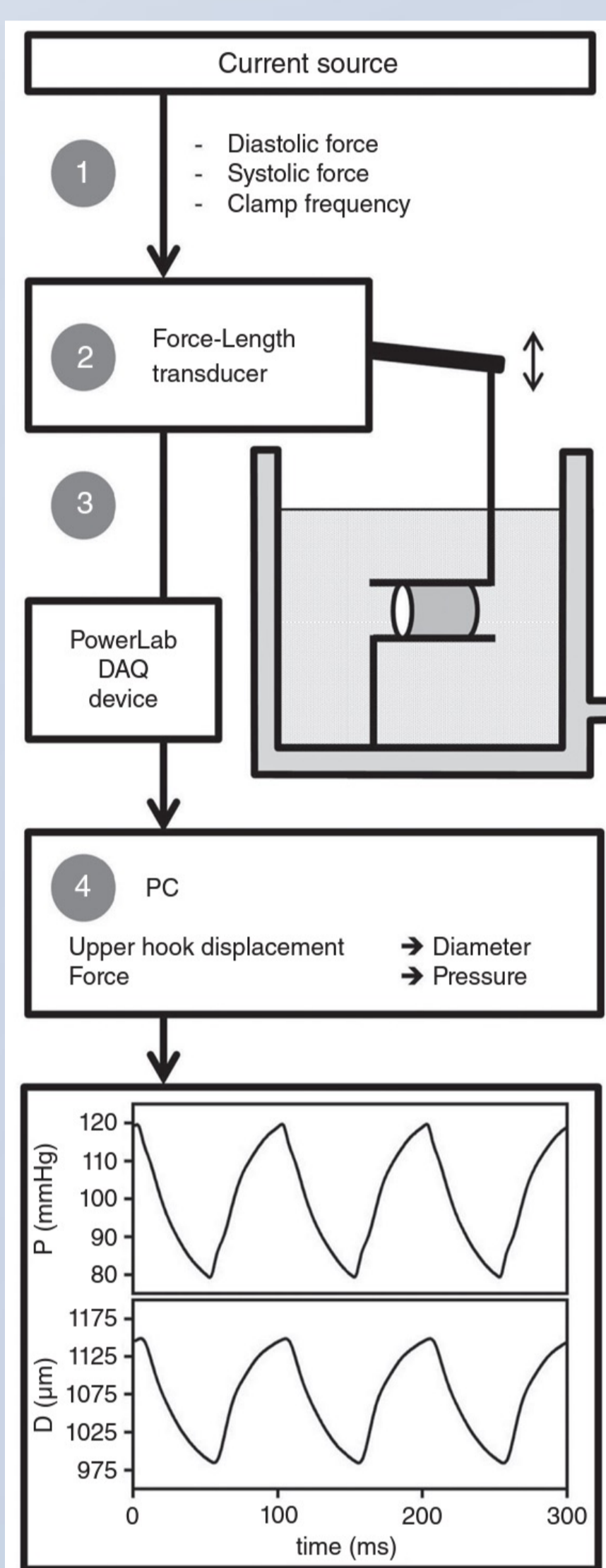


Figure 1. Schematic diagram of the ROTSAC.

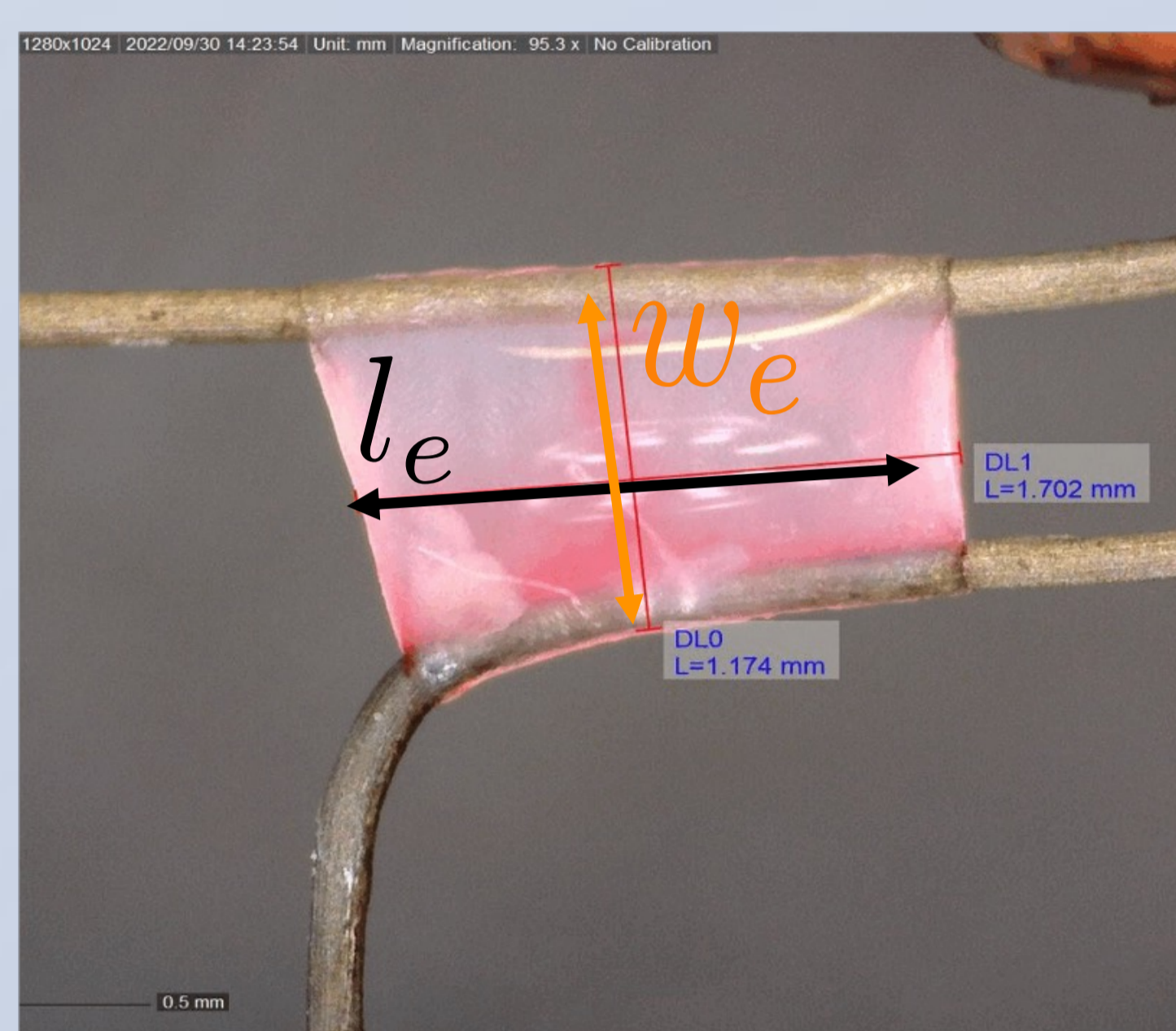


Figure 2. Image of the aortic segment.

We build a **mathematical model** [2] that contains a set of **parameters (Young modulus, E, active pre-stress, k_0 , and elastic modulus, k_1 , of the fibers, initial length, l_0 , width, w_0 , and thickness, h_0 , of the aortic segment)** and that aims at describing the ROTSAC experiment. It is important to note that these **parameters are unknown** and must be determined through a process named **calibration**.

We solve a **fundamental mechanics equation** of the form

$$G(F, E, k_0, k_1, l_0, w_0, h_0; l_s, w_s) = 0,$$

where we need to give as **input** the force measured, F , in the experiment and the parameters describing the behaviour of the material (mentioned above). The numerical solution of this model provides as **output** the **displacement** (in length, l_s , and width, w_s) of the aortic segment. In this model, we have considered an **hyperelastic material** with a constitutive law **Ciarlet-Geymonat** [3].

The purpose of the calibration is **estimating** some unknown inputs of the model such that the outputs match the experimental measurements. For that, we solve our model until we get the parameters that minimize the value of the following **cost function**

$$J = \sqrt{\sum_{i=1}^m |l_s^{(i)} - l_e^{(i)}|^2 + |w_s^{(i)} - w_e^{(i)}|^2} + \sqrt{\sum_{i=1}^n |\bar{w}_s^{(i)} - \bar{w}_e^{(i)}|^2},$$

where $l_e^{(i)}$ is the experimental value of the length, $l_s^{(i)}$ is the predicted value of the length, $w_e^{(i)}$ is the experimental value of the width and $w_s^{(i)}$ is the predicted value of the width at each force $i = 1, \dots, m$ during the calibration; $\bar{w}_e^{(i)}$ is the experimental value of the width and $\bar{w}_s^{(i)}$ is the predicted value of the width at each force $i = 1, \dots, n$ during the oscillation.

RESULTS

The **calibration** procedure makes it possible to estimate the unknown model parameters from the ROTSAC static and dynamic data.

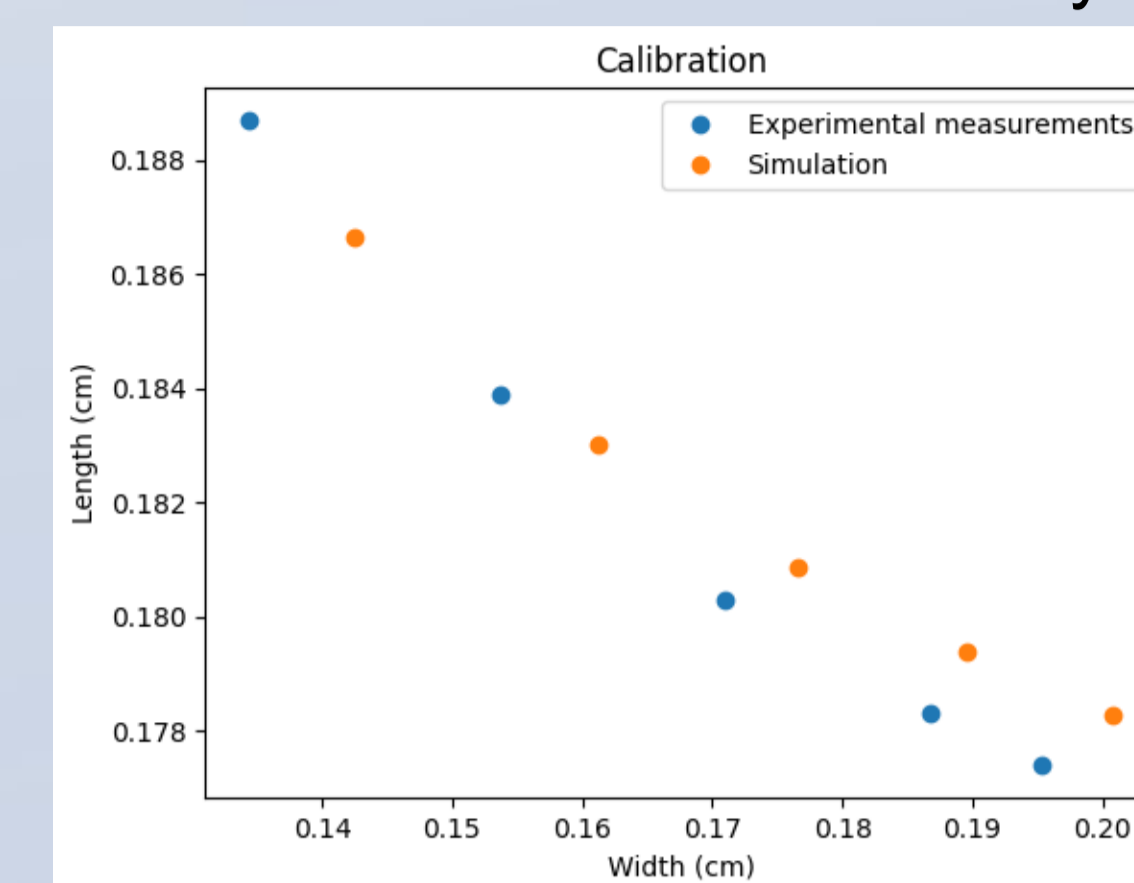


Figure 3. Comparison between experimental and simulation data during the calibration.

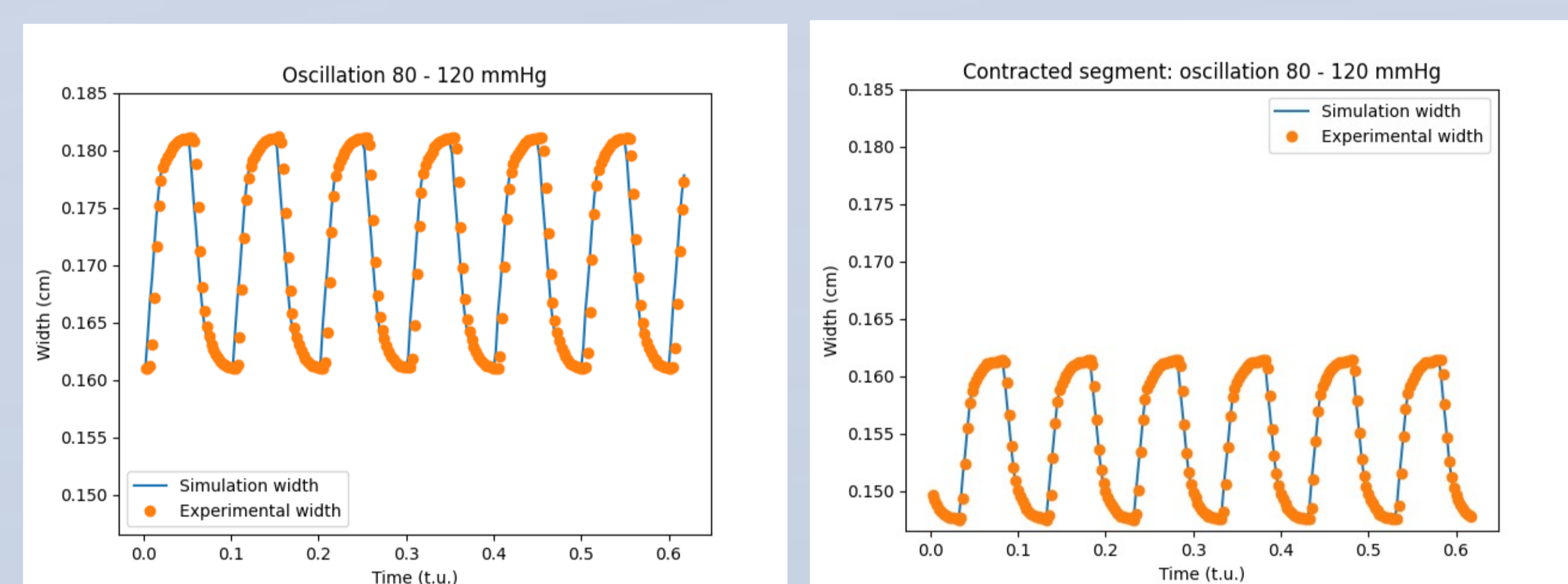


Figure 4. Comparison between experimental and simulation data during the **oscillation** without a compound (left) and after adding a vasoconstrictor (right).

	E (dynes/cm ²)	h_0 (cm)	k_0 (dynes/cm ²)	k_1 (dynes/cm ²)
Without drug	850 000	0.00967	100	2 042 750
Vasoconstrictor	876 569	0.00918	117 565	3 420 650

Table 1. Comparison of the change in **parameters** (pre-stress and elastic modulus of the fibers) before and after adding a vasoconstrictor to the aortic segment.

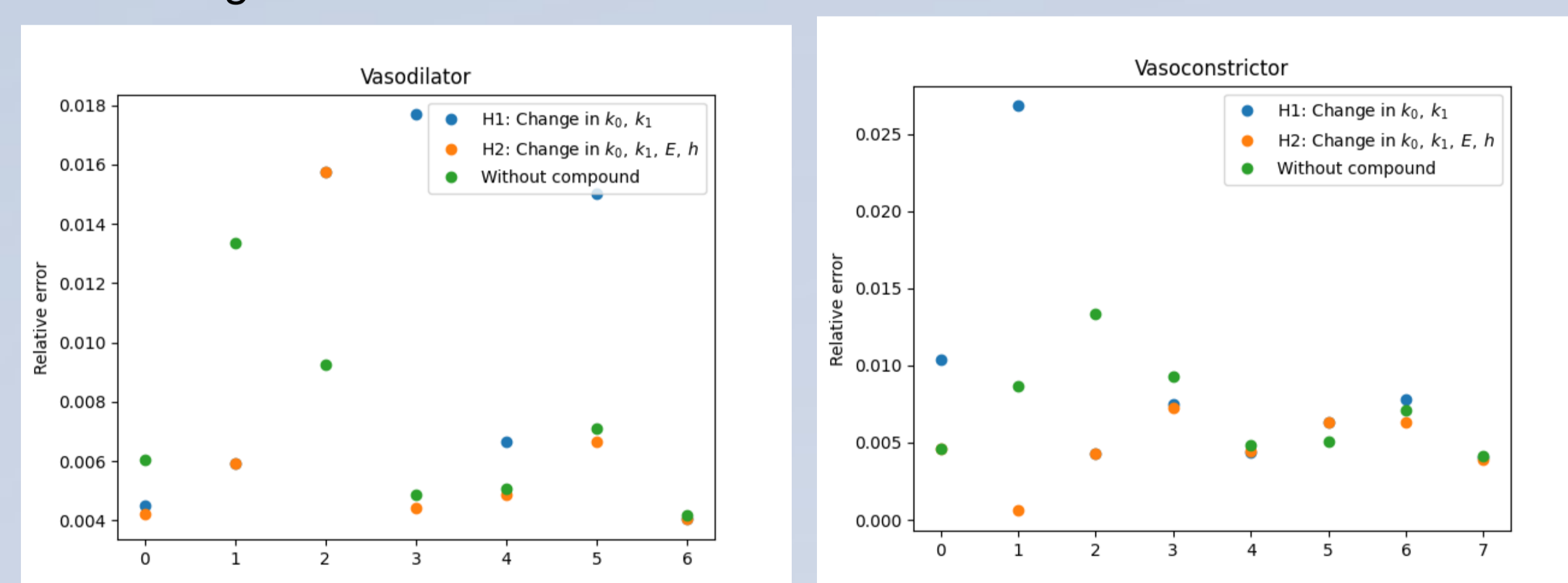


Figure 5. Comparison of the **relative mean squared error** between the experimental data and the simulation data during the oscillation. Left: without compound and with a vasodilator. Right: without compound and with a vasoconstrictor.

CONCLUSIONS

Thanks to the **calibration** we have access to physical parameters that cannot be directly measured from the ROTSAC experiment. This **estimation** can be used to understand the **underlying mechanisms** of a **drug** on the vessel mechanics.

According to the results in a cohort of aortic segments, not only the pre-stress (k_0) and the elastic modulus (k_1) of the fibers of the tissue are changing after the addition of the drug, but also the Young modulus (E). From the results shown in Figure 5, we can observe that the relative error between the experimental and the simulation data is smaller when we also **change the Young modulus**, so H2 is the most plausible hypothesis.

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