MASTER INTERNSHIP PROPOSAL

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PhD after internship: YES **PhD funding:** YES (ANR)

TITLE: Electrical and biochemical control of hair-cell mechanosensitivity in the inner ear

GENERAL AIM: Sound mechanoreception by the inner ear's hair cells begins with the deflection of their hair bundle—a cohesive tuft of protruding stereocilia that serves as the hair cell's mechanosensory antenna. Hair-bundle deflections modulate mechanical tension in elastic elements that pull on mechanosensitive ion channels and, in turn, modulate the influx of cations into the hair cell—the transduction current. Reciprocally, the opening and closing of the mechano-electrical transduction channels—channel gating—exerts a force on the hair bundle, called the gating force, which reduces the hair-bundle stiffness, even leading to negative stiffness (Fig. 1). Remarkably, a dynamic interplay between channel gating and an active feedback mechanism gives rise to active hair-bundle movements—reverse transduction, including spontaneous hair-bundle oscillations. **This proposal aims at studying how external and internal control parameters modulate the mechanical and electrical correlates of transduction-channel gating to specify active and passive mechanosensitivity of the hair cell.**

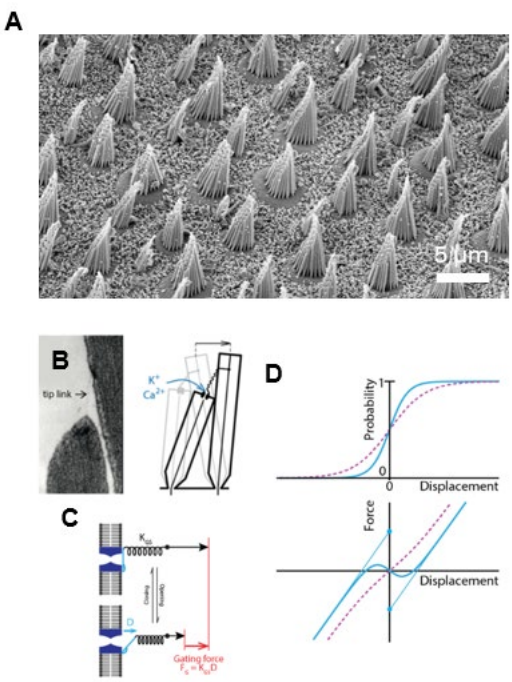

Fig. 1 : Hair cells and gating-spring model of mechanoelectrical transduction. (A) Electron micrograph showing hair bundles protruding from the apical surface of hair cells in a sensory tissue from a frog's ear. (B) A deflection that increases tip-link tension opens ion channels at the lower end of the tip link, increasing the influx of K^+ and Ca^{2+} ions into the hair cell. (C) The concept of gating force. When the transduction channels open, tension in the gating springs is reduced (black arrows); this mechanical correlate of channel gating is called the gating force, $F_G = K_{GS} D$, where K_{GS} is the combined stiffness of all the gating springs operating in parallel in the hair bundle and D is the gating swing of each channel. (D) Electrical and mechanical responses to hair-bundle displacement. Top: sigmoidal relationship of channel open probability to displacement in the case of weak (dashed magenta line) and strong (solid blue line) gating force. The larger the gating force, the steeper the sigmoid and the more sensitive is the hair cell to displacement of its hair bundle. Bottom: Correspondingly, the force–displacement relationship displays a shallow nonlinearity when sensitivity is low (dashed magenta curve) and a strong nonlinearity when sensitivity is high (smooth blue curve) The gating force is given by the vertical shift between the two linear limbs of the force-displacement relation; it is here shown in the case of high sensitivity as the distance between the two disks

RESEARCH HYPOTHESES: Based on preliminary observations, our working hypotheses are (i) that the mechanical correlates of transduction-channel gating—the gating swing and the gating force—can be modulated by the electrical potential across the hair-cell epithelium and the extracellular Ca^{2+} concentration, (ii) that the hair bundle can switch between two functional states of strong and weak gating force or, correspondingly, high and low mechanosensitivity, and (iii) that the lipid membrane that houses the transduction channel constitutes a target for channel regulation. **We thus view the transduction channels as active modulatory devices whose mechanosensitivity can be tuned by the hair cell depending on physiological control parameters.** Active hair-bundle motility has been studied most extensively in ex-vivo preparations of the frog's ear while its relevance for auditory detection in mammals remains heavily debated. Based on our observations of similar active hair-bundle movements with hair cells from frog, turtle and rat, **we postulate that mechanosensitivity is based on similar physical principles across species.**

OBJECTIVES: Our plan is: (i) to investigate how the mechanical and electrical signatures of transduction-channel gating are modulated by the transepithelial potential, the hair cell's transmembrane potential and the extracellular calcium concentration near a hair bundle; (ii) to demonstrate that the observed transition between states of strong and weak gating force corresponds to a first-order phase transition in the transduction-channel protein complex; (iii) to monitor and modulate membrane viscosity in stereocilia of hair cells as a function of the dynamical state of the hair cell (i.e. quiescent vs. oscillatory, strong vs. weak gating force); (iv) to quantify entropy production and fluctuation-response relations in oscillatory hair bundles.

EXPECTED RESULTS: Our research is expected to significantly advance our fundamental understanding of hair-cell mechanosensitivity in several aspects:

- by demonstrating that the transduction-channel machinery is bistable, with an 'ON state' of high mechanosensitivity and an 'OFF state' of low sensitivity;
- by exploring the role of the lipid membrane in stereocilia as a target for mechanosensitivity control of the transduction channels and determining how active membrane modulation impacts hair-bundle mechanics;
- by showing that passive and active hair-bundle mechanosensitivity relies on the same physical principles in frog, an amphibian system, and rat, a mammalian system, thus in evolutionary distant vertebrate species;
- by providing a paradigmatic case study of nonequilibrium physics in neuroscience to show how recent tools of stochastic thermodynamics can quantify entropy production by oscillatory hair-cell bundles and help restoring fluctuation-response relations in this out-of-equilibrium system.

METHODS:

- micromanipulation of single cells;
- measurement of forces (1–100 pN) and movements (1–100 nm);
- iontophoresis of charged species (Ca^{2+}, drugs);
- application of currents, measurement of electrical potentials;
- electrophysiology (patch clamp);
- optical microscopy;
- theoretical modeling.

INTERNATIONAL COLLABORATION:

The project will be carried out in close collaboration with Tony Ricci's group (Stanford University, United States).

REQUIRED QUALIFICATION AND SKILLS:

- Strongly motivated physicist or biologist who is wishing to work at the interface between physics and biology.
- Demonstrated experience with quantitative approaches and experimental work is required. Previous experience in electrophysiology (patch clamp) or in cellular mechanics would be appreciated but is not mandatory.
- Ability to conduct independent research as well as work collaboratively within a multidisciplinary team.
- Strong scientific writing and communication skills in English.

REFERENCES:

1. Joliot A, Stickel L, Martin P (2026) Electrical Control of the Transduction Channels' Gating Force in Mechanosensory Hair Cells. Advanced Science:e09171.

2. Hudspeth AJ, Martin P (2023) Evolving critical oscillators for hearing. Nat Rev Phys 6:210–211.

3. Martin P, Hudspeth AJ (2021) Mechanical Frequency Tuning by Sensory Hair Cells, the Receptors and Amplifiers of the Inner Ear. Annu Rev Condens Matter Phys 12:29–49.

4. Tobin M, Chaiyasitdhi A, Michel V, Michalski N, Martin P (2019) Stiffness and tension gradients of the hair cell's tip-link complex in the mammalian cochlea Wu DK, King AJ, Ricci AJ, eds. eLife 8:e43473.

5. Bormuth V, Barral J, Joanny J-F, Jülicher F, Martin P (2014) Transduction channels' gating can control friction on vibrating hair-cell bundles in the ear. Proc Natl Acad Sci USA 111:7185–7190.

6. Martin P, Hudspeth AJ (1999) Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli. Proc Natl Acad Sci U S A 96:14306–14311.