Fluctuations and Response in Non-reciprocal Biophysical Models

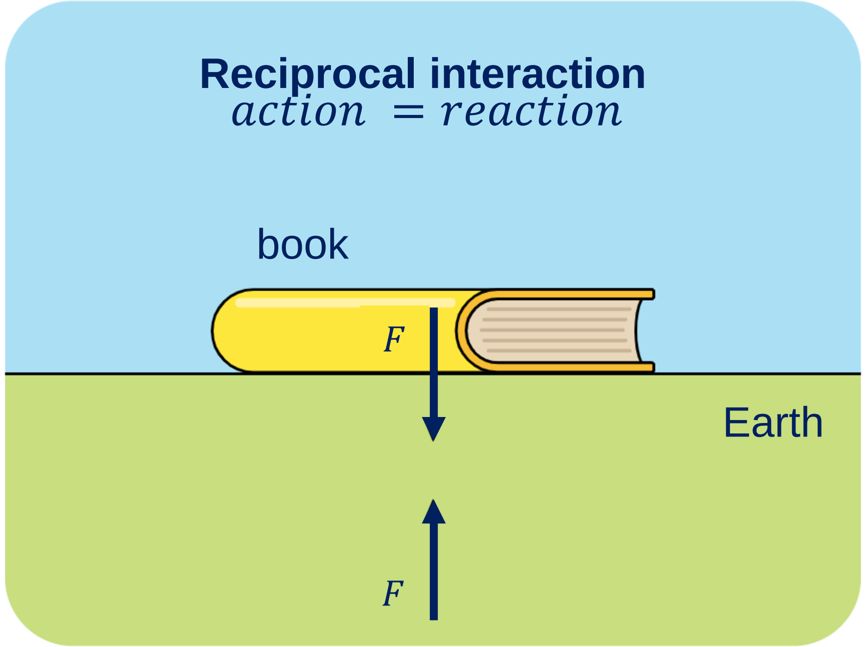
Kristian Angeli Pajanonot

Advisers: Dr. Edgar Roldan
Dr. Sarah Loos

Non-reciprocal interactions

Introduction

Physical interactions between particles that are coupled are typically reciprocal



There is gravitational force on the book due to Earth and the gravitational force of the book on Earth (action = reaction)

Image from: Nagwa.com, "Lesson Explainer: Newton's Third Law of Motion," 2022. [Online]. Available: https://www.nagwa.com/en/explainers/923174389174/

Non-reciprocal interactions

Introduction

However, reciprocal interactions are often broken in models of many complex living systems

Non-reciprocal interactions

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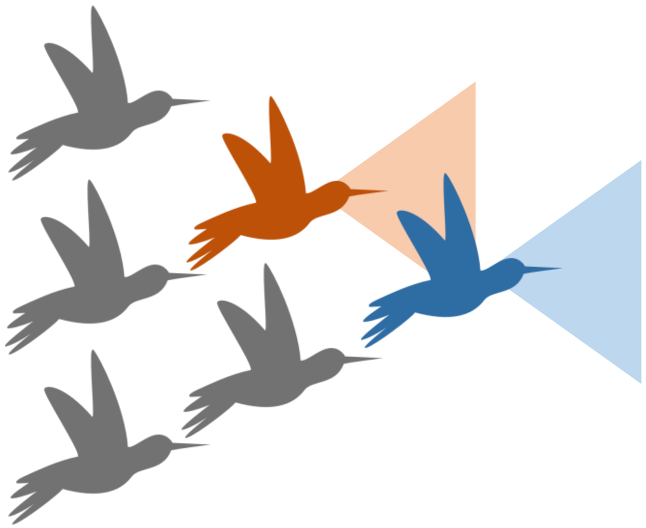
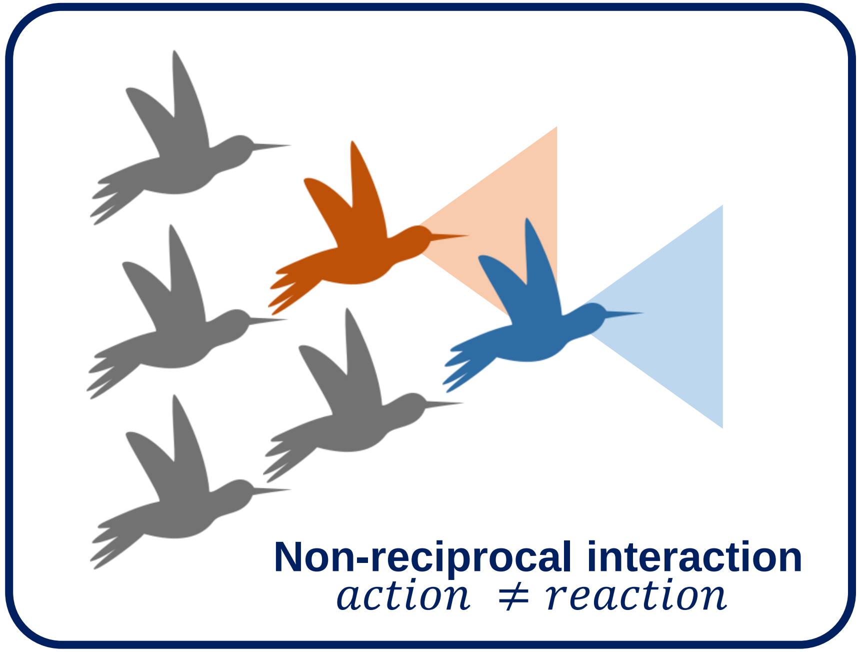


Non-reciprocal interactions

Introduction

However, reciprocal interactions are often broken in models of many complex living systems

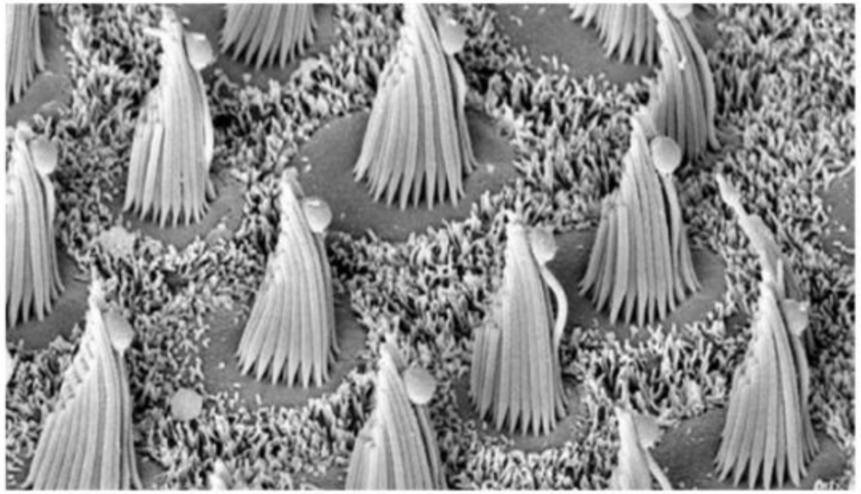
Birds in flocks demonstrate how easy the law can be broken since they alter their flying patterns in reaction to the birds in front of them, but not vice versa.



Non-reciprocal interactions in small-scale systems

Introduction

(a) Hair bundle



(b) Cellular sensor

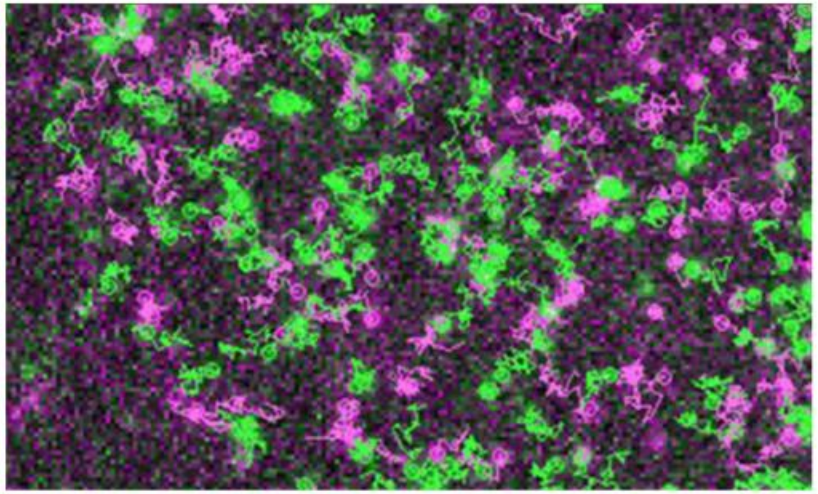


Image from: (a) T. Reichenbach and A. Hudspeth, “The physics of hearing: fluid mechanics and the active process of the inner ear,” *Reports on Progress in Physics*, vol. 77, no. 7, p. 076601, 2014.

(b) T. Sungkaworn, M.-L. Jobin, K. Burnecki, A. Weron, M. J. Lohse, and D. Calebiro, “Single-molecule imaging reveals receptor–g protein interactions at cell surface hot spots,” *Nature*, vol. 550, no. 7677, pp. 543–547, 2017.

Non-reciprocal interactions in small-scale systems

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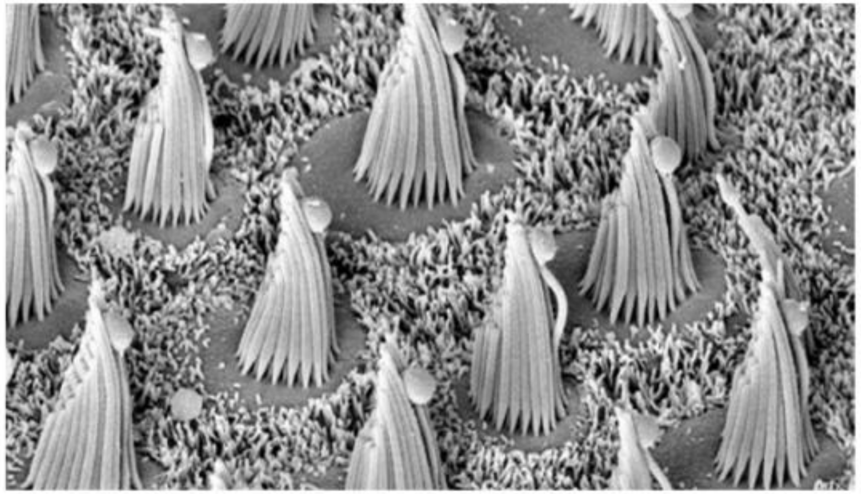

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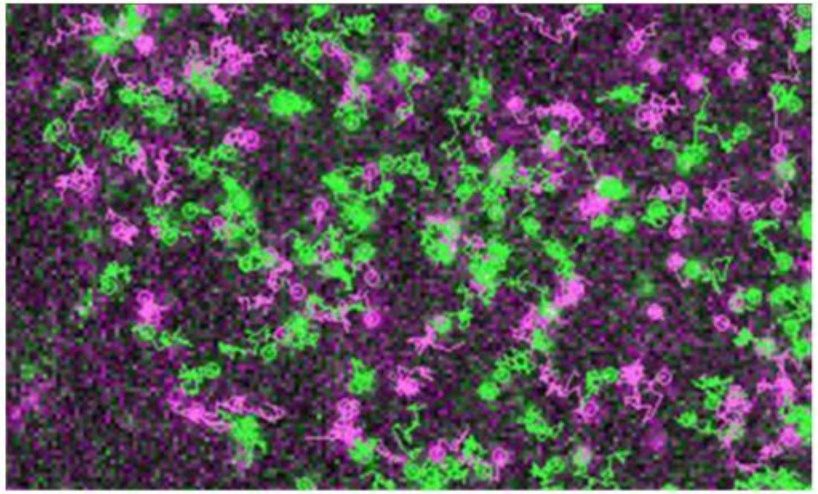

What are the thermodynamic implications of systems that exhibit non-reciprocal interactions?

Image from: (a) T. Reichenbach and A. Hudspeth, "The physics of hearing: fluid mechanics and the active process of the inner ear," *Reports on Progress in Physics*, vol. 77, no. 7, p. 076601, 2014.

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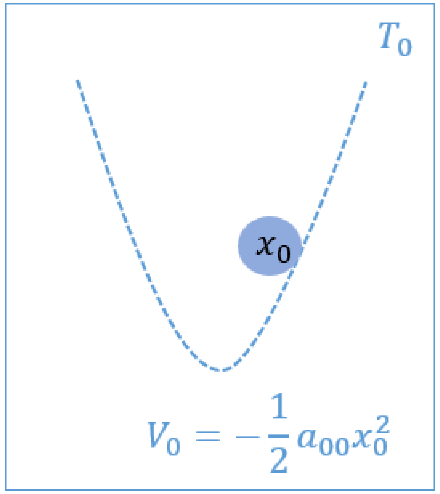
Theory

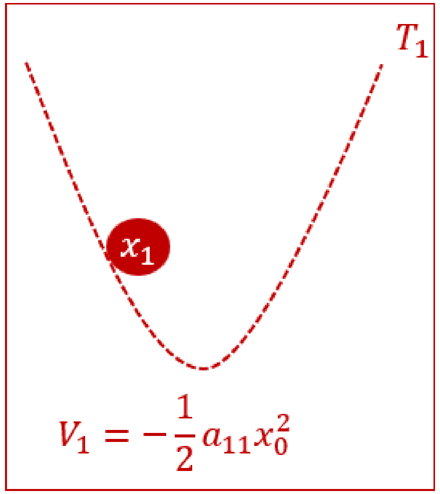
2-Dimensional Overdamped Langevin Equation

Theory

Case 1: Two uncoupled systems

$$\begin{aligned}\gamma_0 \dot{x}_0 &= a_{00} x_0 + \sqrt{2 k_B T_0}\,\xi_0 \\ \gamma_1 \dot{x}_1 &= a_{11} x_1 + \sqrt{2 k_B T_1}\,\xi_1\end{aligned} \tag{2}$$





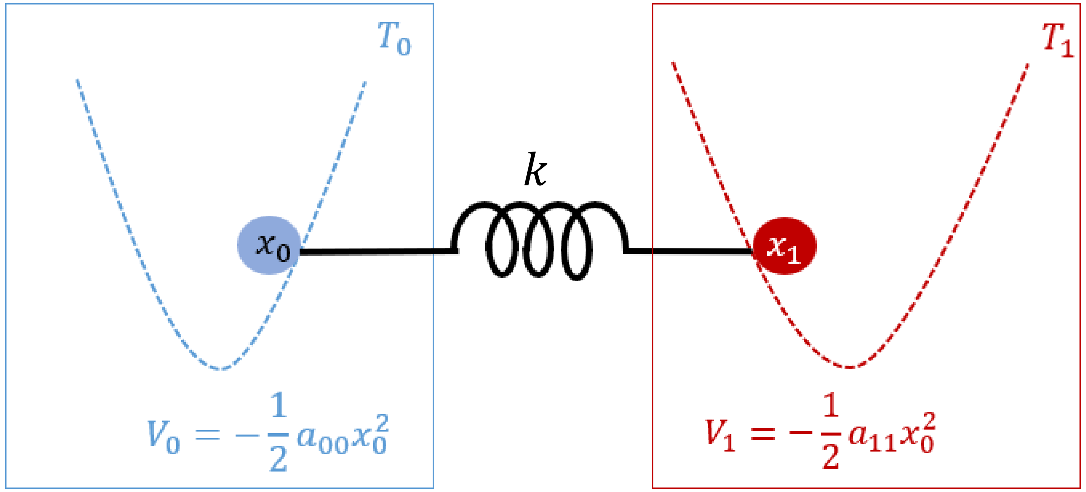
$a_{00} < 0, a_{11} < 0$

2-Dimensional Overdamped Langevin Equation

Theory

Case 2: Two systems coupled by a spring (coupling is reciprocal)

$$\begin{aligned} \gamma_0 \dot{x}_0 &= a_{00} x_0 - k x_1 + \sqrt{2 k_B T_0}\,\xi_0 \\ \gamma_1 \dot{x}_1 &= -k x_0 + a_{11} x_1 + \sqrt{2 k_B T_1}\,\xi_1 \end{aligned} \tag{3}$$



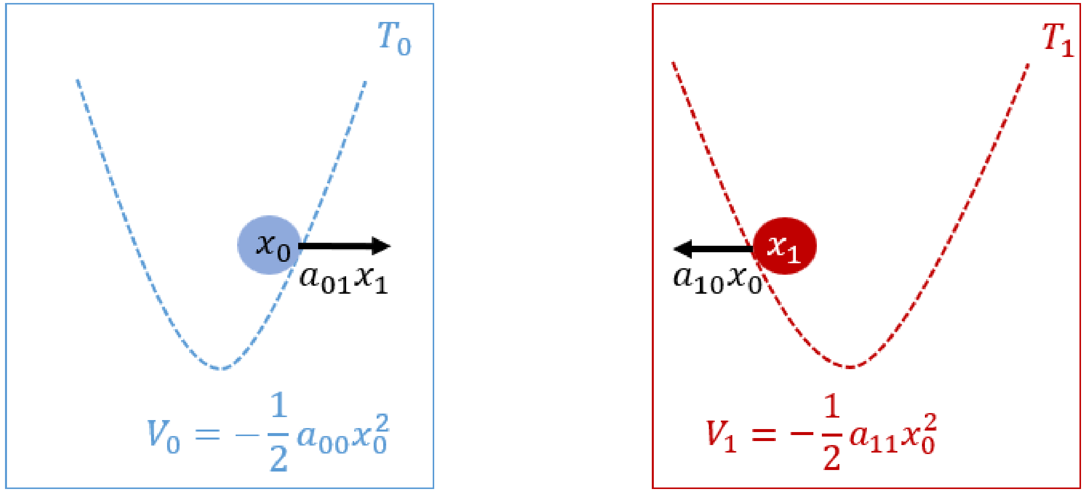
$a_{00} < 0, a_{11} < 0$

2-Dimensional Overdamped Langevin Equation

Theory

Case 3: Two systems with non-reciprocal coupling

$$\begin{aligned} \gamma_0 \dot{x}_0 &= a_{00}x_0 + a_{01}x_1 + \sqrt{2k_B T_0}\xi_0 \\ \gamma_1 \dot{x}_1 &= a_{10}x_0 + a_{11}x_1 + \sqrt{2k_B T_1}\xi_1 \end{aligned} \tag{4}$$



$$a_{00} < 0, a_{11} < 0, a_{10} < 0, a_{01} < 0$$

Reciprocal vs. Non-reciprocal Coupling

Theory

When $a_{10} = a_{01}$, the coupling is reciprocal

$$\begin{aligned} \gamma_0 \dot{x}_0 &= a_{00} x_0 + a_{01} x_1 + \sqrt{2 k_B T_0} \xi_0 \\ \gamma_1 \dot{x}_1 &= a_{10} x_0 + a_{11} x_1 + \sqrt{2 k_B T_1} \xi_1 \end{aligned} \quad (4)$$

Equation (4) can be rewritten as:

$$\begin{aligned} \gamma_0 \dot{x}_0 &= \frac{-\partial V}{\partial x_0} + \sqrt{2 k_B T_0} \xi_0 \\ \gamma_1 \dot{x}_1 &= \frac{-\partial V}{\partial x_1} + \sqrt{2 k_B T_1} \xi_1 \end{aligned} \quad (5)$$

When $a_{10} \neq a_{01}$, the coupling is non-reciprocal

Equation (4) becomes:

$$\begin{aligned} \gamma_0 \dot{x}_0 &= \frac{-\partial V}{\partial x_0} + f_{nc} + \sqrt{2 k_B T_0} \xi_0 \\ \gamma_1 \dot{x}_1 &= \frac{-\partial V}{\partial x_1} + f_{nc} + \sqrt{2 k_B T_1} \xi_1 \end{aligned} \quad (6)$$

Non-reciprocal interactions appear as non-conservative forces in our equations of motion

Non-conservative Force

Theory

Conservative force

$$\oint F \circ dx = \int -\partial_x V \circ dx = 0 \tag{7}$$

Non-conservative force

$$\oint F \circ dx = \underbrace{\int -\partial_x V \circ dx}_{=0} + \int f_{nc} \circ dx \neq 0 \tag{8}$$

System is at non-equilibrium → energy dissipation

Measures of Non-equilibrium

Theory

1. Heat rate

2. Violation of Fluctuation-Dissipation Theorem (FDT)

1. Heat rate

Theory: Measures of Non-equilibrium

Stochastic Heat[1] – the energy exchanged between the system and the thermal environment

$$0 = -\gamma \dot{x}_t + \underbrace{V'(x(t)) + f(x(t))}_{\text{total force}, F(x(t))} + \sqrt{2k_B T\gamma}\xi \quad (9)$$

forces exerted by the thermal environment on the particle

The energy transfer from the environment to the particle:

$$\delta Q = (-\gamma \dot{x} + \sqrt{2k_B T\gamma}\xi) \circ dx \quad (10)$$

cannot be measured experimentally in the laboratory

$$\boxed{\begin{aligned} \delta Q &= -F(x(t)) \circ dx \\ \delta Q &= -(V'(x(t)) + f(x(t))) \circ dx \end{aligned}} \quad (11)$$

[1] K. Sekimoto, *Stochastic energetics.* Springer, 2010, vol. 799.

1. Heat rate

Theory: Measures of Non-equilibrium

$$\begin{aligned} \gamma_0 \dot{x}_0 &= a_{00} x_0 + a_{01} x_1 + \sqrt{2 k_B T_0} \xi_0 \\ \gamma_1 \dot{x}_1 &= a_{10} x_0 + a_{11} x_1 + \sqrt{2 k_B T_1} \xi_1 \end{aligned} \tag{4}$$

Stochastic Heat dissipated for particle x_0 and x_1 in $[t, t+dt]$

$$\begin{aligned} \delta Q_0 = -(a_{00} x_0 + a_{01} x_1) \circ dx_0 \\ \delta Q_1 = -(a_{10} x_0 + a_{11} x_1) \circ dx_1 \end{aligned} \tag{12}$$

Heat rate

Numerical simulation

$$\left\langle \dot{Q} \right\rangle = \lim_{t \to \infty} \frac{\langle Q(t) \rangle}{t} \tag{13}$$

Analytical solution[2]

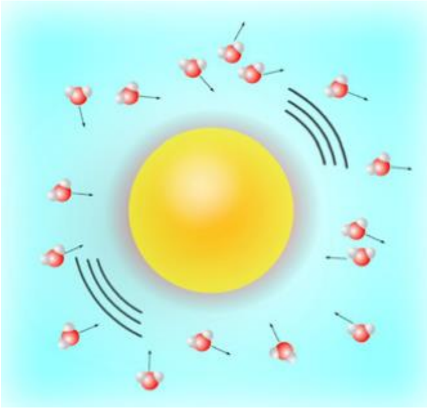
$$\begin{aligned} \left\langle \dot{Q}_0 \right\rangle = k_B \frac{a_{01}(a_{10} T_0 - a_{01} T_1)}{a_{00}\gamma_1 + a_{11}\gamma_0} \\ \left\langle \dot{Q}_1 \right\rangle = k_B \frac{a_{10}(a_{01} T_1 - a_{10} T_0)}{a_{00}\gamma_1 + a_{11}\gamma_0} \end{aligned} \tag{14}$$

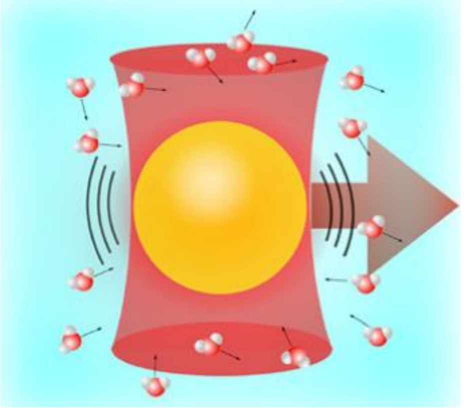
[2] S. A. Loos and S. H. Klapp, "Irreversibility, heat and information flows induced by non-reciprocal interactions," *New Journal of Physics*, vol. 22, no. 12, p. 123051, 2020.

2. Violation of FDT

Theory: Measures of Non-equilibrium

Fluctuation-Dissipation Theorem[3] (FDT) – relates the fluctuation of the system in the absence of external forces, and the response of a given system to an external force





Fluctuations are characterized by the autocorrelation function $C_x(t)$:

$$\boxed{C_x(t) = \langle x(t)x(t+\tau)\rangle} \quad (15)$$

Position autocorrelation function

Response is characterized by a response function $R_x(t)$:

$$\boxed{\langle x(t)\rangle = \int_0^t R_x(t-t')F(t')dt'} \quad (16)$$

$\langle x(t)\rangle$ denotes the value of x at time t when the force F is applied

[3] R. Kubo, "The fluctuation-dissipation theorem," *Reports on progress in physics*, vol. 29, no. 1, p. 255, 1966.

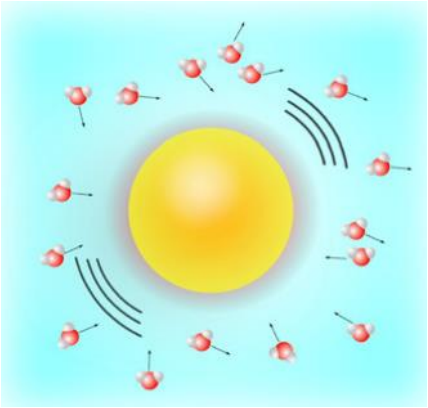
Image from: F. S. Gnesotto, F. Mura, J. Gladrow, and C. P. Broedersz, "Broken detailed balance and non-equilibrium dynamics in living systems: a review," *Reports on Progress in Physics*, vol. 81, no. 6, p. 066601, 2018.

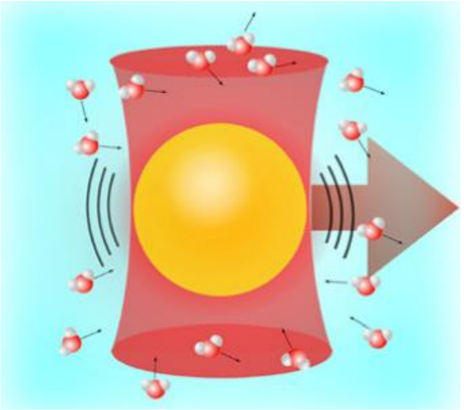
2. Violation of FDT

Theory: Measures of Non-equilibrium

$$\boxed{C_x(t) = \langle x(t)x(t+\tau)\rangle}$$

$$\boxed{\langle x(t)\rangle = \int_0^t R_x(t-t')F(t')dt'}$$





$$\boxed{\tilde{C}_x(\omega)} = \frac{2k_BT}{\omega}\boxed{\tilde{R}''_x(\omega)} \qquad (17)$$

Fluctuation-Dissipation Theorem (FDT)

holds for systems at thermal equilibrium

Image from: F. S. Gnesotto, F. Mura, J. Gladrow, and C. P. Broedersz, “Broken detailed balance and non-equilibrium dynamics in living systems: a review,” *Reports on Progress in Physics*, vol. 81, no. 6, p. 066601, 2018.

Measures of Non-equilibrium: Violation of FDT

Theory: Measures of Non-equilibrium

Energy dissipation from the violation of FDT (Harada-Sasa equality)[4]

$$\langle J \rangle = \gamma \int_{-\infty}^{+\infty} \frac{d\omega}{2\pi} \left(\omega^2 \tilde{C}_x(\omega) - 2 k_B T \omega \tilde{R}''_x(\omega) \right) \tag{18}$$

For an equilibrium system: $\langle J \rangle = 0$
For a non-equilibrium system: $\langle J \rangle \neq 0$

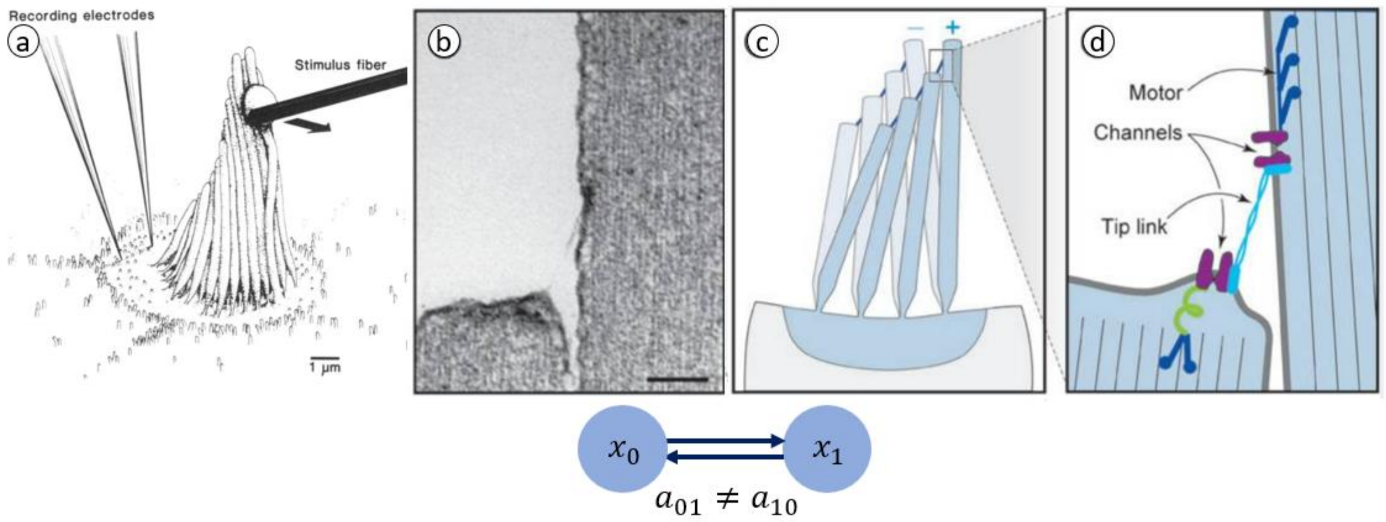
[4] T. Harada and S.-i. Sasa, "Equality connecting energy dissipation with a violation of the fluctuation-response relation," *Physical review letters*, vol. 95, no. 13, p. 130602, 2005.

Results

Biophysical Model 1: Hair bundle oscillations

Results

Hair bundle oscillations



X_0 = position of the hair bundle (x)
X_1 = active force generated by the molecular motors inside the hair bundle (F)

$$\begin{bmatrix} \gamma & 0 \\ 0 & \lambda \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{F} \end{bmatrix} = \begin{bmatrix} -k & 1 \\ -\bar{k} & -1 \end{bmatrix} \begin{bmatrix} x \\ F \end{bmatrix} + \begin{bmatrix} \eta_x \\ \eta_F \end{bmatrix}$$

Image from [5-6]

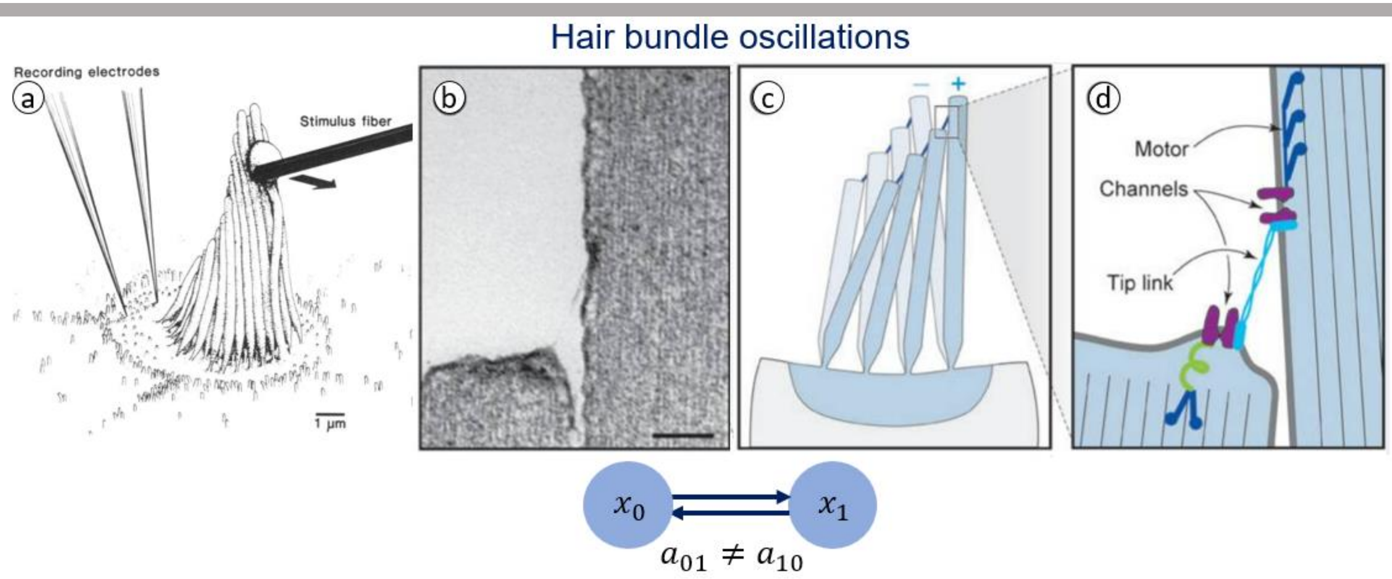
[5] A. Hudspeth, "Making an effort to listen: Mechanical amplification in the ear," *Neuron*, vol. 59, 2008.
[6] M. A. Vollrath, K. Y. Kwan, and D. P. Corey, "The micromachinery of mechanotransduction in hair cells," *Annual review of neuroscience*, vol. 30, p. 339, 2007.

Model from:

F. Berger and A. Hudspeth, "Violation of the fluctuation-response relation from a linear model of hair bundle oscillations," *bioRxiv*, 2022.

Biophysical Model 1: Hair bundle oscillations

Results



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Uncoupled case: Equilibrium limit

Image from [5-6]

[5] A. Hudspeth, "Making an effort to listen: Mechanical amplification in the ear," *Neuron*, vol. 59, 2008.
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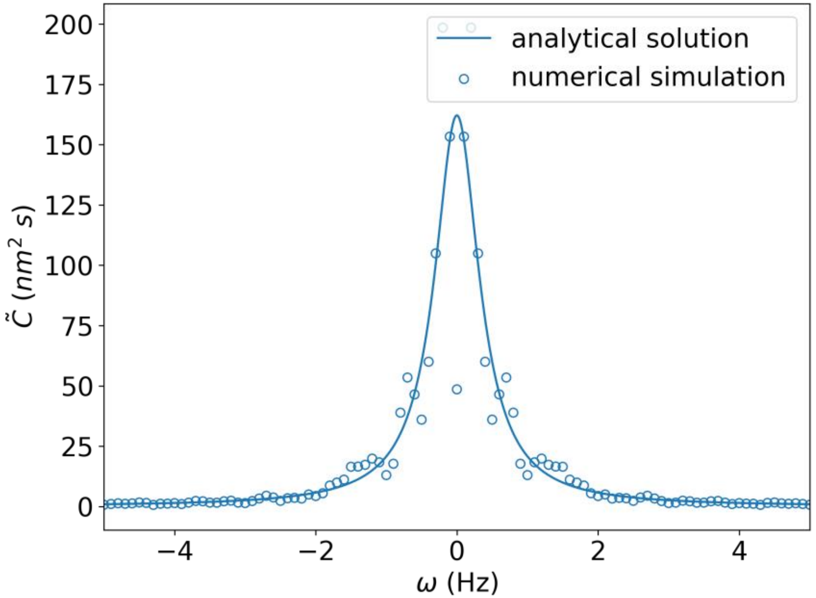
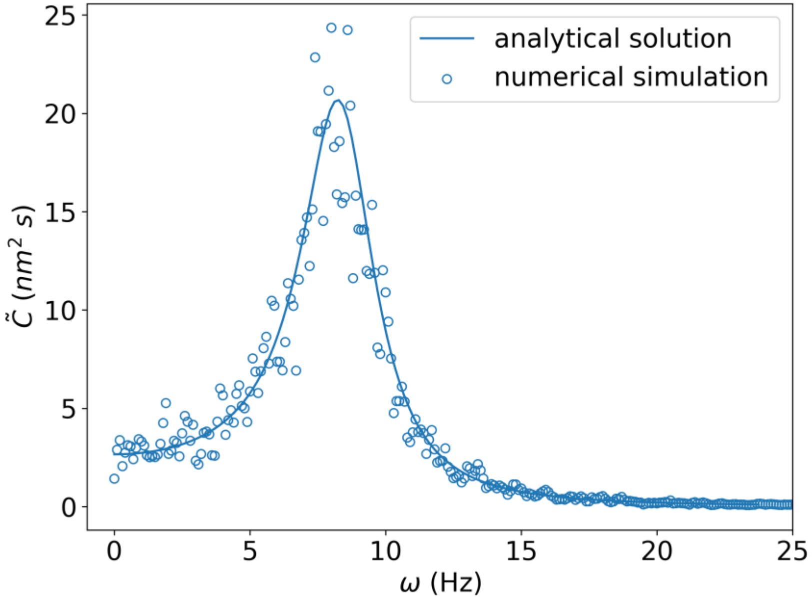
Autocorrelation function – Numerics vs. Analytical Solution

Results: Hair bundle oscillations

$$\text{coupling matrix} \begin{bmatrix} -k & 0 \\ 0 & -1 \end{bmatrix} \qquad \begin{bmatrix} -k & 1 \\ -\bar{k} & -1 \end{bmatrix}$$



(a) Equilibrium case



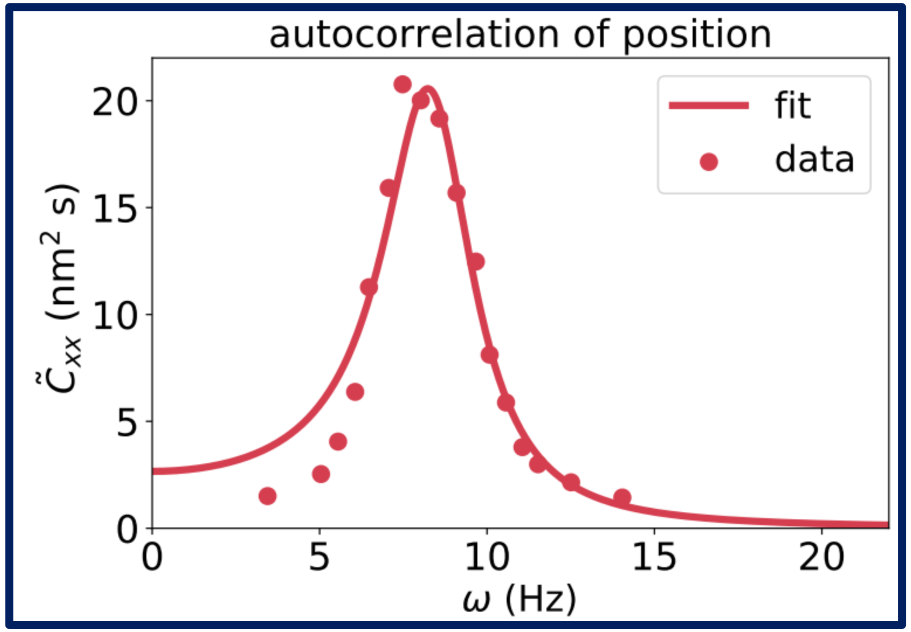
(b) Non-equilibrium case

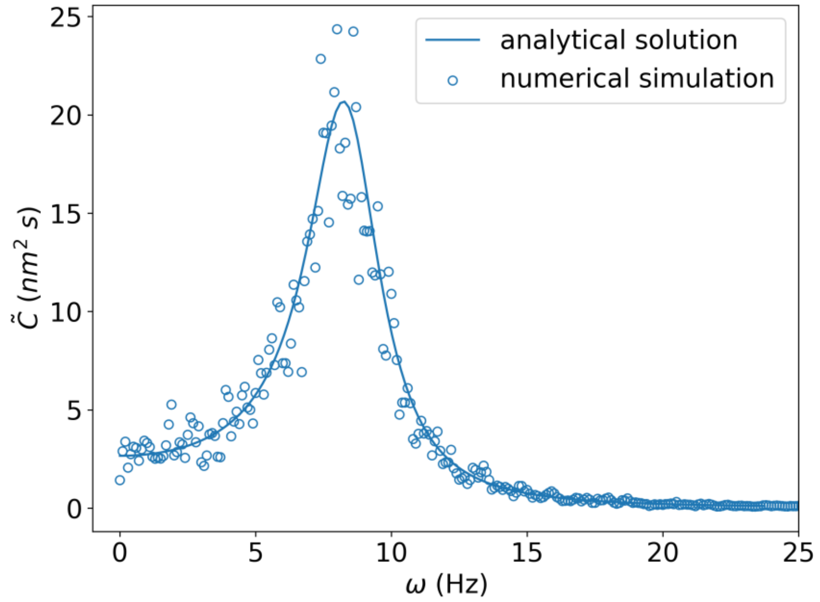
Non-equilibrium case shows a peak at 8 Hz

Autocorrelation function – Numerics vs. Analytical Solution

Results: Hair bundle oscillations

In agreement with results from Berger, et.al[7]





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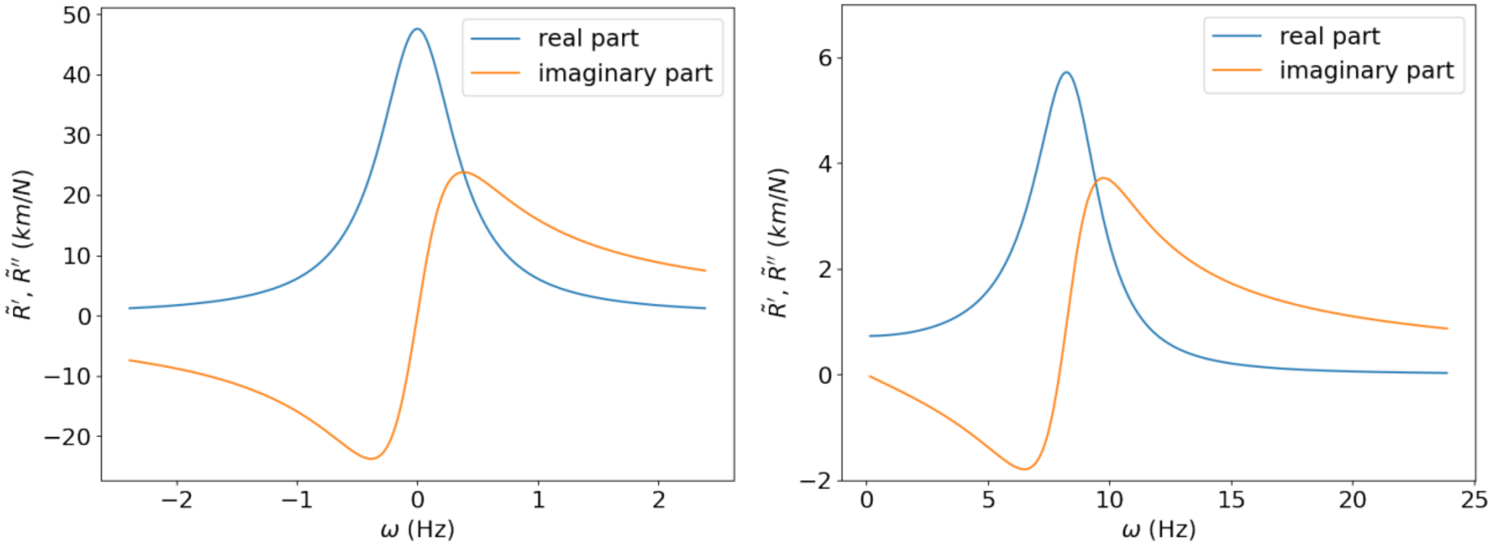
[7] F. Berger and A. Hudspeth, "Violation of the fluctuation-response relation from a linear model of hair bundle oscillations," *bioRxiv*, 2022.

Response function – Analytical solution

Results: Hair bundle oscillations



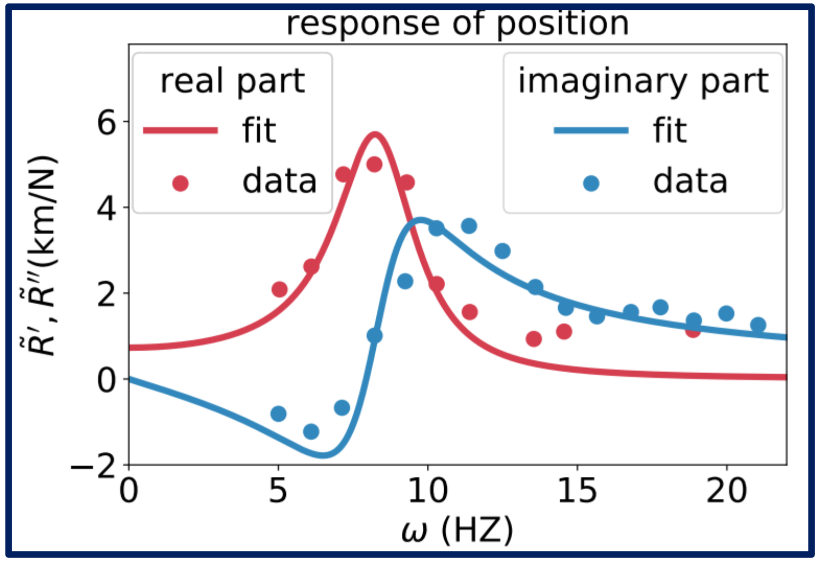
(a) Equilibrium: Response of position x (b) Non-equilibrium: Response of position x

Non-equilibrium: shows a peak at 8 Hz (real part), and a sign change at 8 Hz (imaginary part)

Response function – Analytical solution

Results: Hair bundle oscillations

In agreement with results from Berger, et.al[7]



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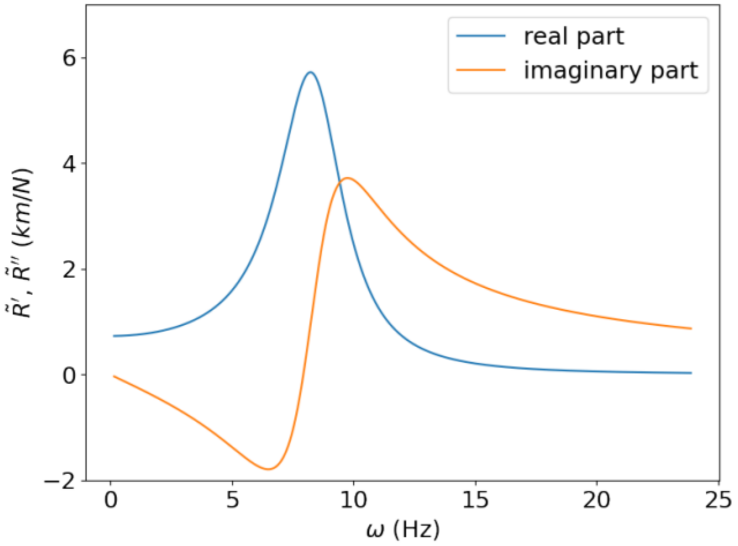


(b) Non-equilibrium: Response of position x

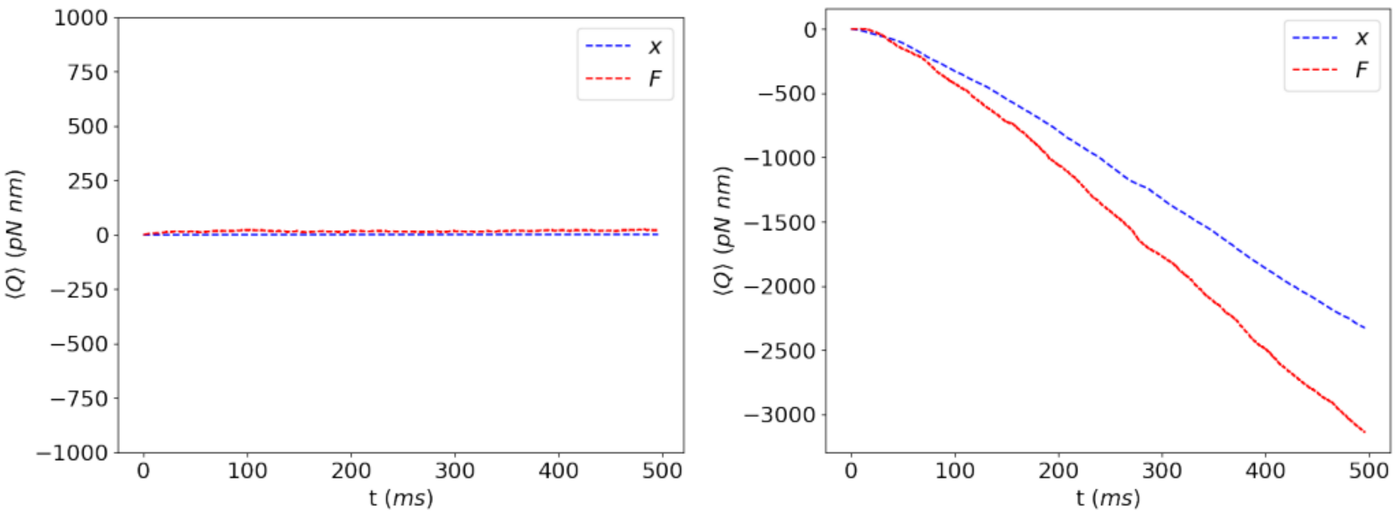
Non-equilibrium: shows a peak at 8 Hz (real part), and a sign change at 8 Hz (imaginary part)

[7] F. Berger and A. Hudspeth, "Violation of the fluctuation-response relation from a linear model of hair bundle oscillations," *bioRxiv*, 2022.

Heat rate (Numerics)

Results: Hair bundle oscillations

Average Cumulative Stochastic Heat



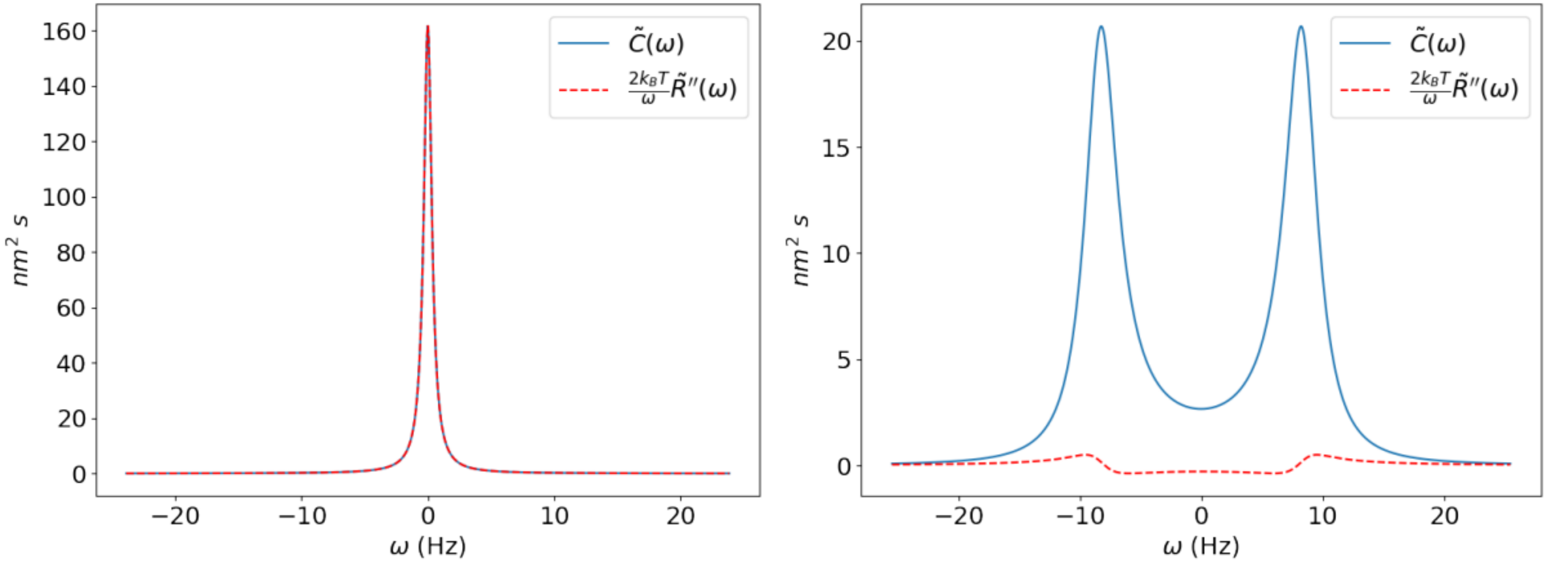
(a) Equilibrium case (b) Non-equilibrium case

Heat rate	System at equilibrium	System at non-equilibrium
$\left\langle \dot{Q}_x \right\rangle$	0.00	4.98 pN nm/ms
$\left\langle \dot{Q}_F \right\rangle$	0.02	6.72 pN nm/ms
$\left\langle \dot{Q}_x \right\rangle + \left\langle \dot{Q}_F \right\rangle$	0.02	11.70 pN nm/ms

Non-zero heat rate for non-equilibrium system

Energy dissipation from violation of FDT (Analytical solution)

Results: Hair bundle oscillations

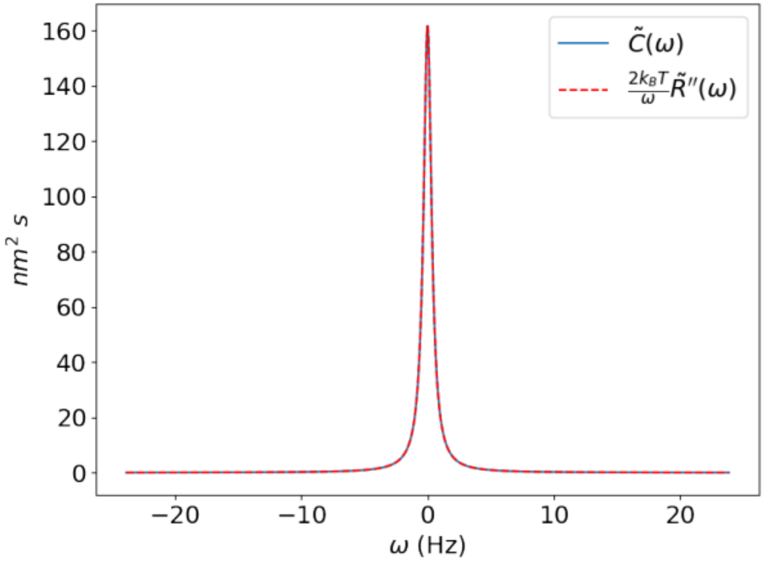


(a) Equilibrium case

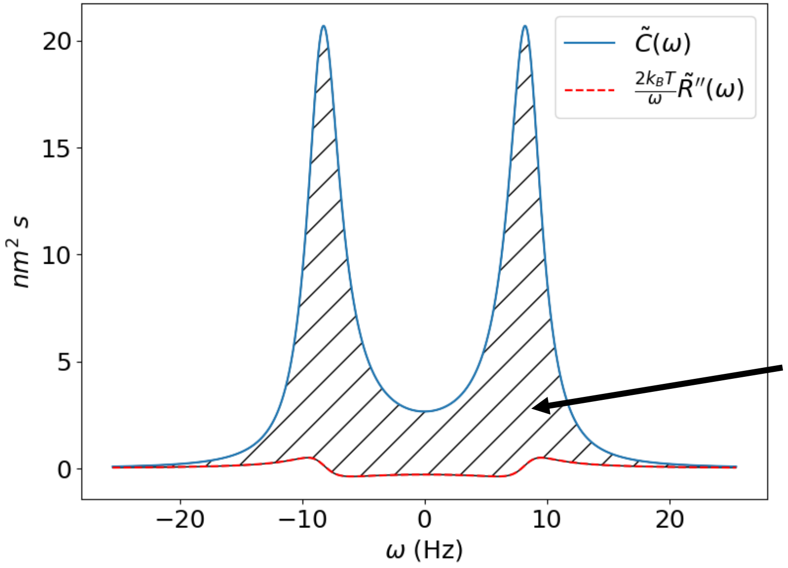
(b) Non-equilibrium case

Energy dissipation from violation of FDT (Analytical solution)

Results: Hair bundle oscillations



(a) Equilibrium case



(b) Non-equilibrium case

dissipation $\langle J \rangle$

$$\langle J\rangle = \gamma \int_{-\infty}^{+\infty} \frac{d\omega}{2\pi} \left(\omega^2 \tilde{C}_x(\omega) - 2k_B T \omega \tilde{R}''_x(\omega)\right)$$

System	Energy dissipation $\langle J\rangle$
Equilibrium	0
Non-equilibrium	4.97 pN nm/ms

Non-zero $\langle J \rangle$ for non-equilibrium system

Results

For a 1-dimensional system:

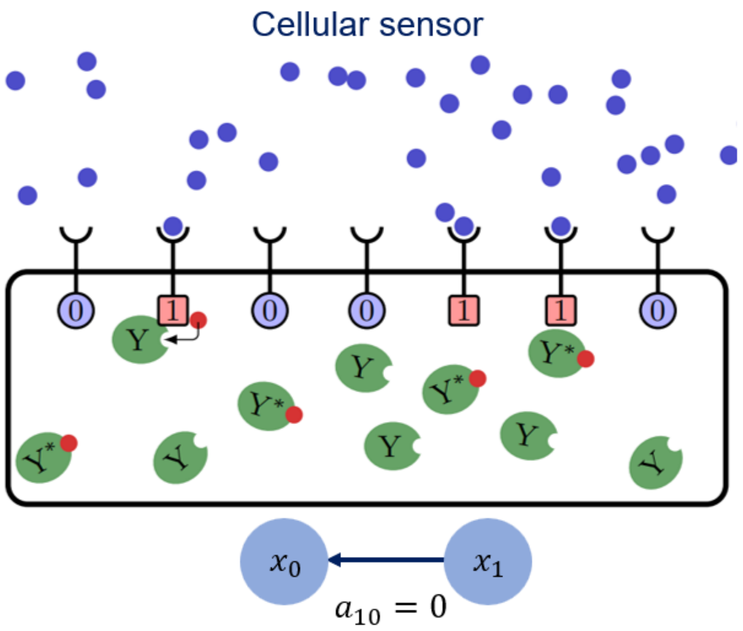
$$\langle J \rangle = \langle \dot{Q}_0 \rangle$$

Does this relationship hold when we have a 2-dimensional system exhibiting non-reciprocal interactions?

$$\langle J \rangle = \langle \dot{Q}_0 \rangle? \quad \text{or} \quad \langle J \rangle = \langle \dot{Q}_0 + \dot{Q}_1 \rangle?$$

Biophysical Model 2: Cellular sensor model

Results



X_0 = receptor sensing the signal (r)
X_1 = external ligand concentration (x)

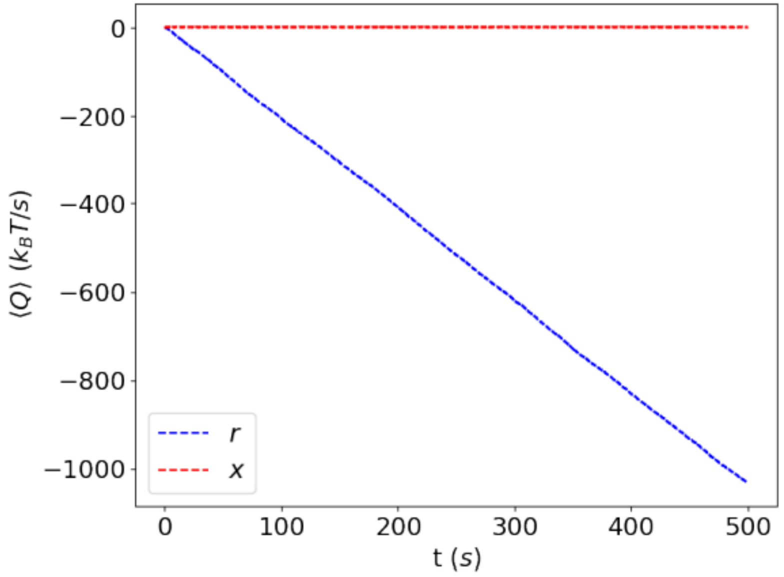
$$\begin{bmatrix} \gamma_0 & 0 \\ 0 & \gamma_1 \end{bmatrix} \begin{bmatrix} \dot{r} \\ \dot{x} \end{bmatrix} = \begin{bmatrix} -\omega_r & \omega_r \\ 0 & -\omega_x \end{bmatrix} \begin{bmatrix} r \\ x \end{bmatrix} + \begin{bmatrix} \xi_r \\ \xi_x \end{bmatrix}$$

Unidirectional coupling

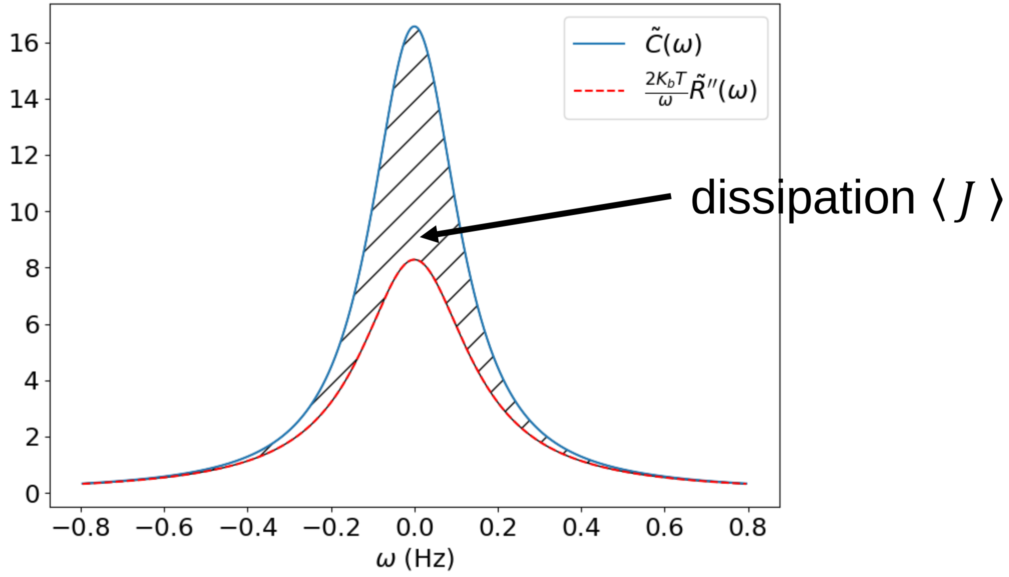
D. Hartich, A. C. Barato, and U. Seifert, "Sensory capacity: an information theoretical measure of the performance of a sensor," *Physical Review E*, vol. 93, no. 2, p. 022116, 2016.

Heat Rate and Energy Dissipation from violation of FDT

Preliminary Results: Cellular Sensor Model



(a) Average cumulative stochastic heat



(b) $\tilde{C}(\omega)$ and $\tilde{R}''(\omega)$ as a function of ω

Parameters	$\langle \dot{Q} \rangle$ (numerical simulation)	$\langle \dot{Q} \rangle$ (analytical solution)	$\langle J \rangle$
r	$2.08\ k_B T/s$	$2.07\ k_B T/s$	$2.07\ k_B T/s$
x	0.00	0.00	-

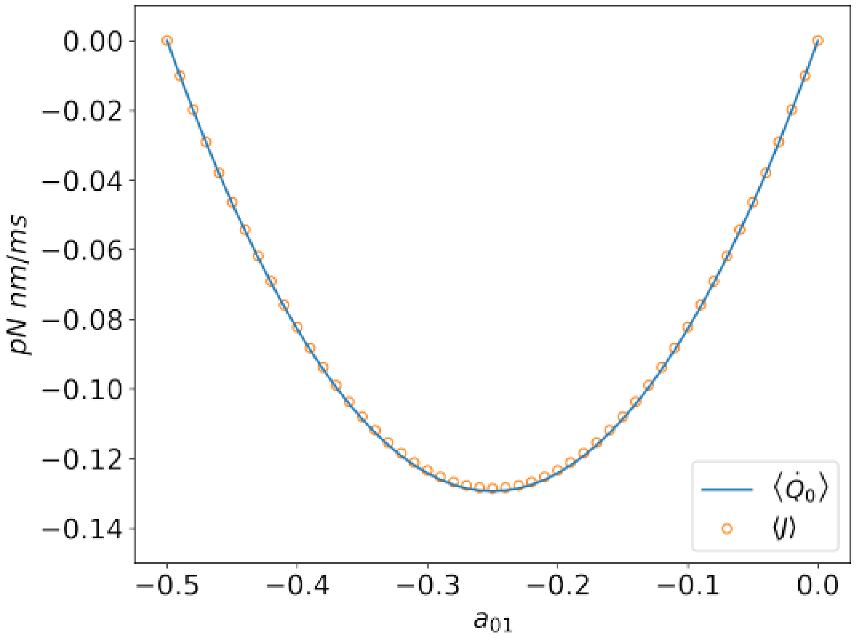
Since r is unidirectionally coupled to x, then r is at non-equilibrium characterized with a non-zero heat rate and energy dissipation

Different Degrees of Reciprocity: Isothermal conditions

Results: Heat rate for x_0 and Energy dissipation

$$\begin{aligned} \gamma_0 \dot{x_0} &= a_{00}x_0 + a_{01}x_1 + \sqrt{2k_BT_0}\xi_0 \\ \gamma_1 \dot{x_1} &= a_{10}x_0 + a_{11}x_1 + \sqrt{2k_BT_1}\xi_1 \end{aligned} \tag{4}$$

Setting $a_{10} = -0.5$, we vary a_{01} from -0.5 to 0. Isothermal condition ($\boldsymbol{T_0 = T_1}$)



Case 1: When $a_{01} = -0.5$, the system is:

$$\begin{aligned} \dot{x_0} &= -x_0 - 0.5x_1 + \sqrt{2k_BT_0}\xi_0 \\ \dot{x_1} &= -0.5x_0 - x_1 + \sqrt{2k_BT_1}\xi_1 \end{aligned}$$

system has reciprocal coupling

Case 2: When $a_{01} = 0$, the system becomes:

$$\begin{aligned} \dot{x_0} &= -x_0 + \sqrt{2k_BT_0}\xi_0 \\ \dot{x_1} &= -0.5x_0 - x_1 + \sqrt{2k_BT_1}\xi_1 \end{aligned}$$

x_0 is uncoupled to x_1

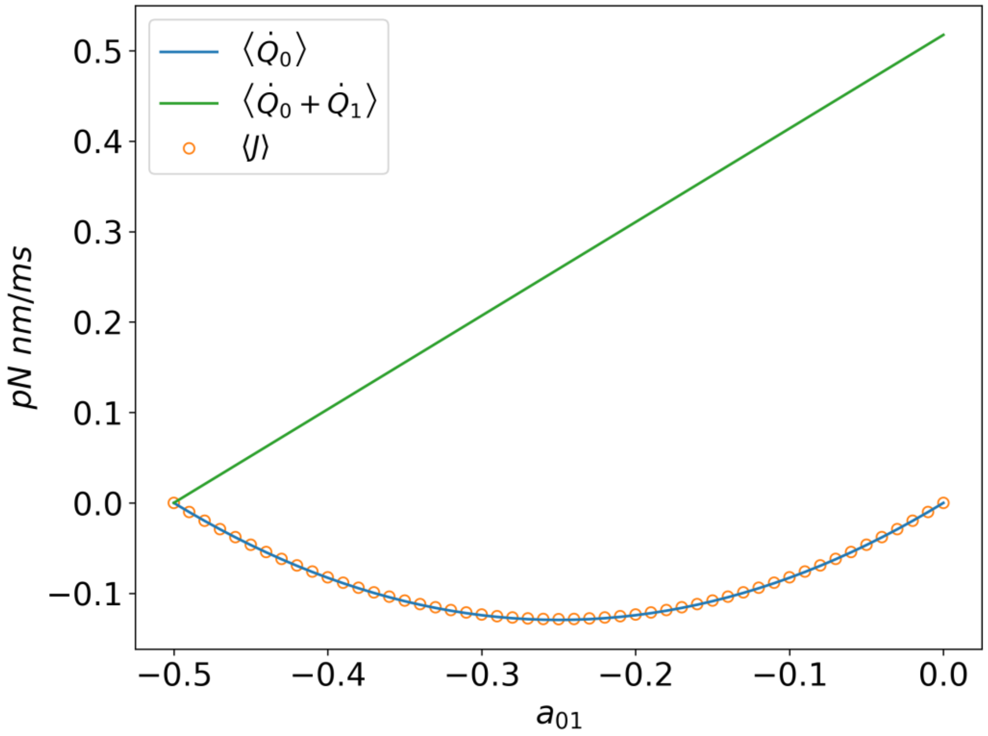
Case 3: When $-0.5 < a_{01} < 0$,

system has non-reciprocal coupling

Different Degrees of Reciprocity: Isothermal conditions

Results: Heat rate for x_0 and Energy dissipation

Setting $a_{10} = -0.5$, we vary a_{01} from -0.5 to 0. Isothermal condition ($\boldsymbol{T_0} = \boldsymbol{T_1}$)

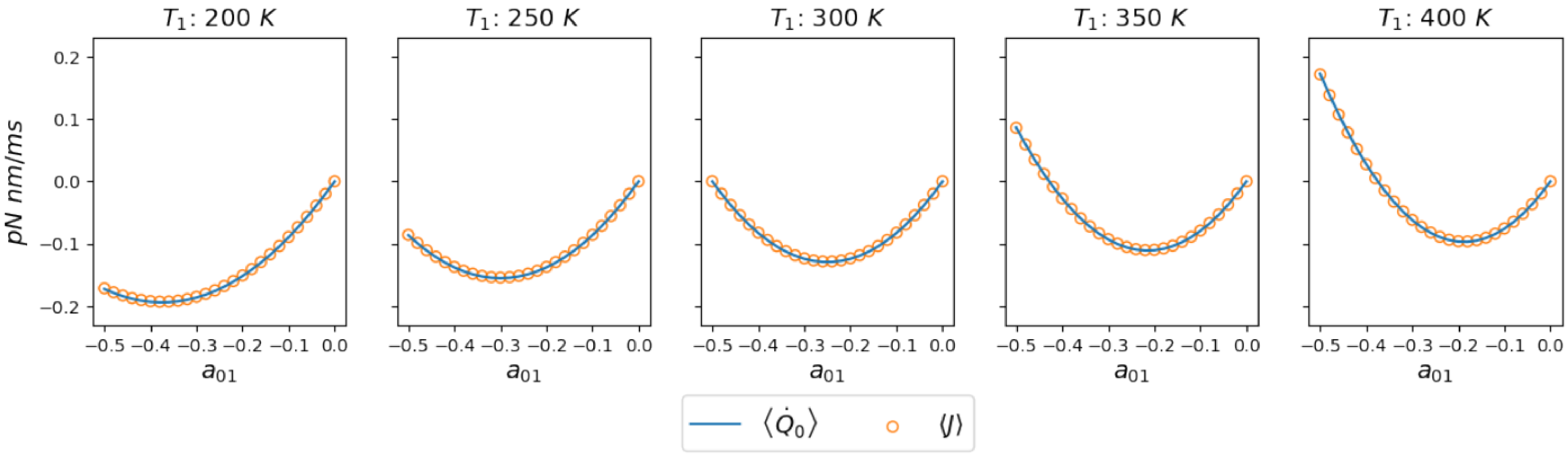


Then $\langle J \rangle = \langle \dot{Q}_0 \rangle$

Different Degrees of Reciprocity: Non-isothermal conditions

Results: Heat rate for x_0 and Energy dissipation

Setting $a_{10} = -0.5$ and $T_0 = 300K$, we vary a_{01} from -0.5 to 0 and T_1 from $200K$ to $400K$



Can thermal equilibrium exist when there is non-reciprocal coupling?
Loos, et.al[8] showed that there is a special case, where a temperature gradient is introduced in the system:

$$a_{10}T_0 = a_{01}T_1 \qquad (19)$$

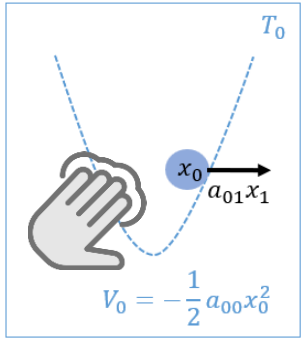
Plot is symmetric with respect to the point of $\boldsymbol{a_{01}}$ at

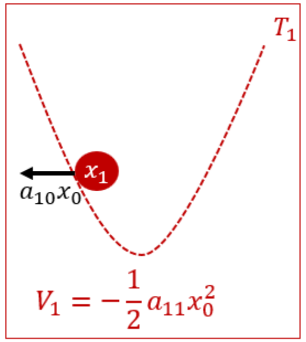
$$a_{01} = 0.5\left(a_{10}\frac{T_0}{T_1}\right) \qquad (20)$$

[8] S. A. Loos and S. H. Klapp, "Irreversibility, heat and information flows induced by non-reciprocal interactions," *New Journal of Physics*, vol. 22, no. 12, p. 123051, 2020.

Conclusions

- The value of $\langle J \rangle = \langle \dot{Q}_o \rangle$





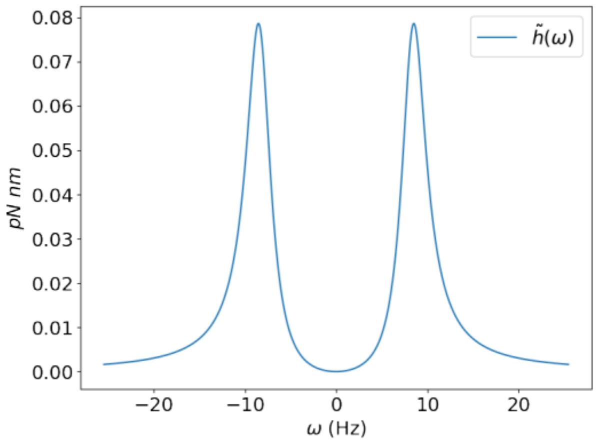
- Hair bundle oscillations show that the system is out of equilibrium. The frequency that contributes the highest to the energy dissipation is at 8 Hz, the bundle's frequency of spontaneous oscillation.

- Cellular sensor model shows that the system is out of equilibrium. The frequency that contributes the highest to the energy dissipation is at 0 Hz.

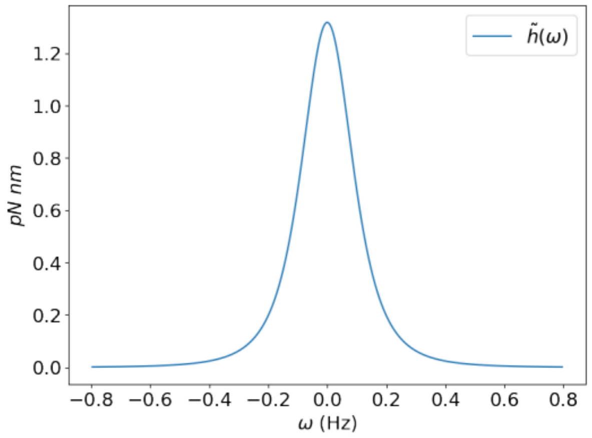
Violation function:

$$\tilde{h}(\omega) = \frac{\gamma}{2\pi}\left(\omega^2 \tilde{C}_x(\omega) - 2k_B T \omega \tilde{R}''_x(\omega)\right)$$

Hair bundle model

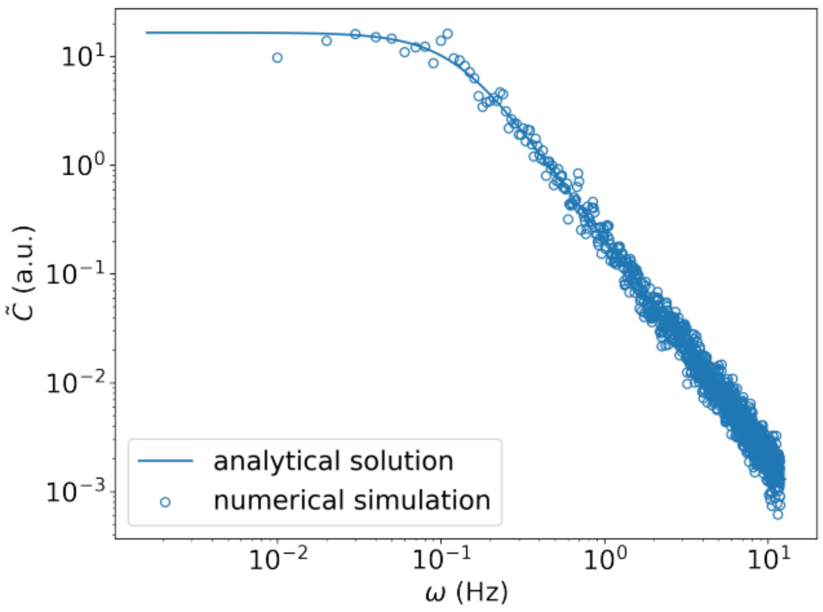


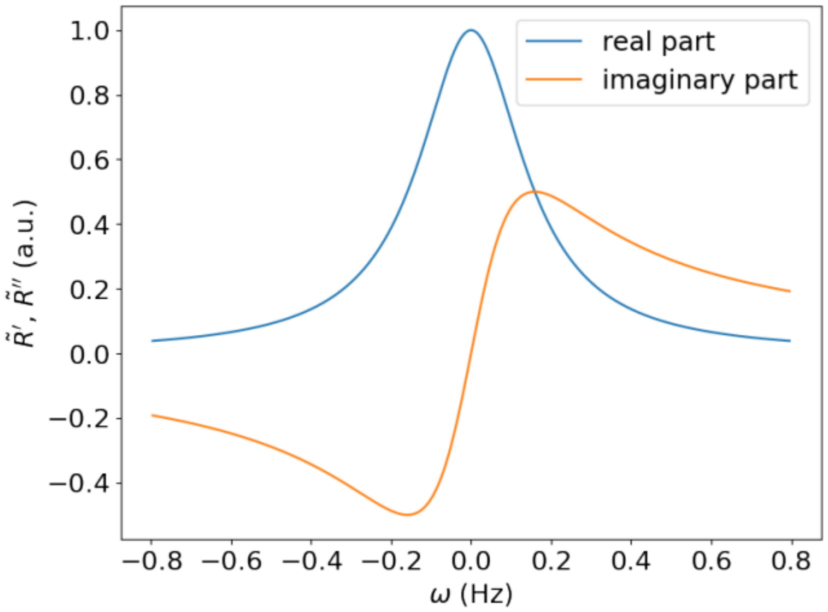
Cellular sensor model



Autocorrelation and Response function

Preliminary Results: Cellular Sensor Model

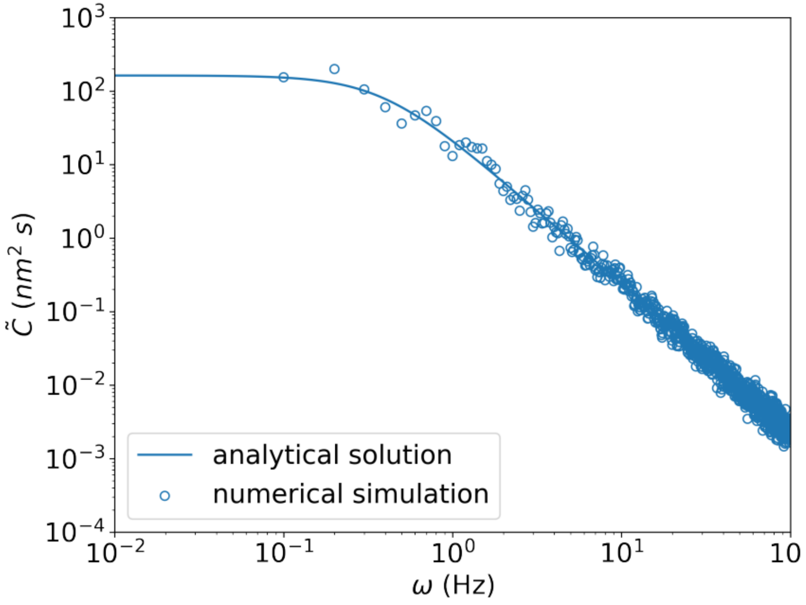




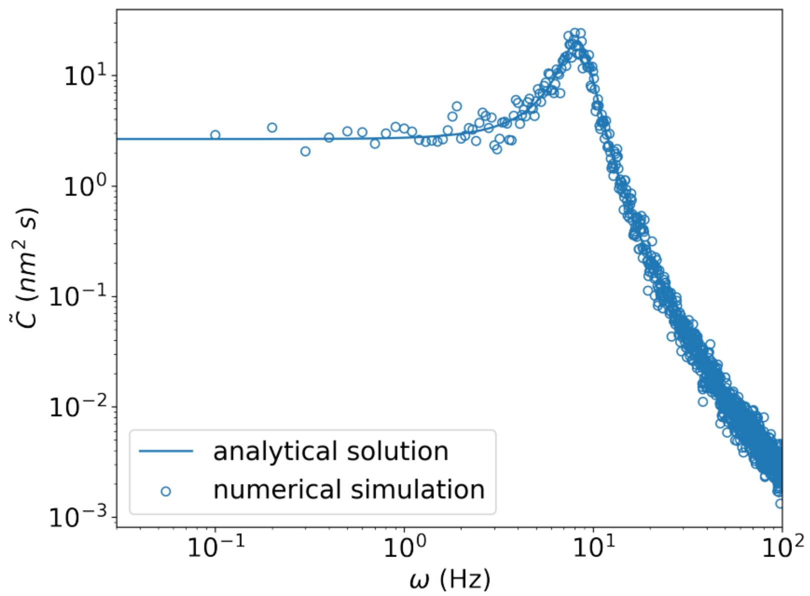
Autocorrelation function – Numerics vs. Analytical Solution

Results: Hair bundle oscillations

coupling matrix $\begin{bmatrix} -k & 0 \\ 0 & -1 \end{bmatrix}$ $\qquad$ $\begin{bmatrix} -k & 1 \\ -\bar{k} & -1 \end{bmatrix}$



(a) Equilibrium case



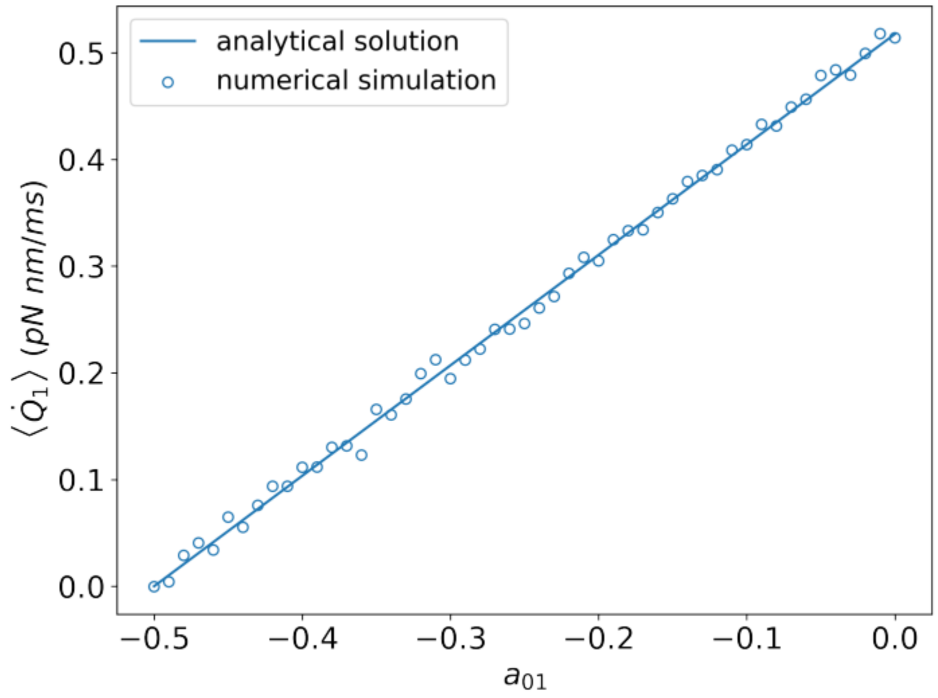
(b) Non-equilibrium case

Equilibrium: follows a Lorentzian function
Non-equilibrium: shows a peak at 8 Hz

Different Degrees of Reciprocity: Isothermal conditions

Results: Heat rate for x_1

Setting $a_{10} = -0.5$, we vary a_{01} from -0.5 to 0. Isothermal condition ($\boldsymbol{T_0 = T_1}$)



Case 1: When $a_{01} = -0.5$, the system is:

$$\begin{aligned} \dot{x}_0 &= -x_0 - 0.5x_1 + \sqrt{2k_B T_0}\xi_0 \\ \dot{x}_1 &= -0.5x_0 - x_1 + \sqrt{2k_B T_1}\xi_1 \end{aligned}$$

system has reciprocal coupling and $\boldsymbol{a_{10}T_0 = a_{01}T_1}$

Case 2: When $a_{01} = 0$, the system becomes:

$$\begin{aligned} \dot{x}_0 &= -x_0 + \sqrt{2k_B T_0}\xi_0 \\ \dot{x}_1 &= -0.5x_0 - x_1 + \sqrt{2k_B T_1}\xi_1 \end{aligned}$$

$\boldsymbol{x_1}$ is unidirectionally coupled to $\boldsymbol{x_0}$

Case 3: When $-0.5 < a_{01} < 0$,

system has non-reciprocal coupling and $\boldsymbol{a_{10}T_0 \neq a_{01}T_1}$