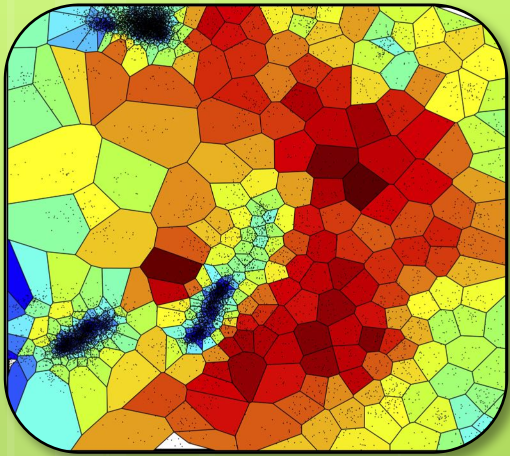

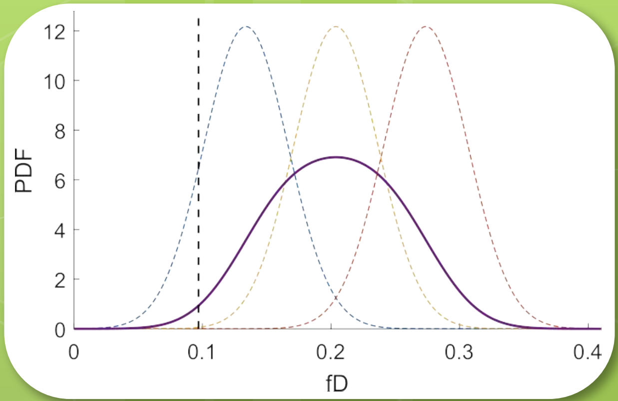

September 18–22, 2017

The Itô-Stratonovich Dilemma and the Inverse Problem for the Overdamped Langevin Equation: A Bayesian Approach

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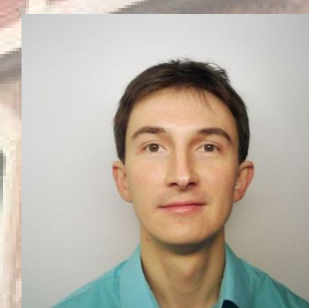
Mohamed El Beheiry



Me

https://research.pasteur.fr/en/team/decision-and-bayesian-computation/

Outline

1. Decision and Bayesian Computation Lab

1.1. Drosophila larvae behavior,

1.2. Escale: A data exchange solution,

1.3. DIVA: Big data in virtual and augmented reality,

2. TRamWAy (Inference MAP) Project

2.1. What and why?

2.2. Christian: Inference Without Tracking,

2.3. François: Space Tessellation,

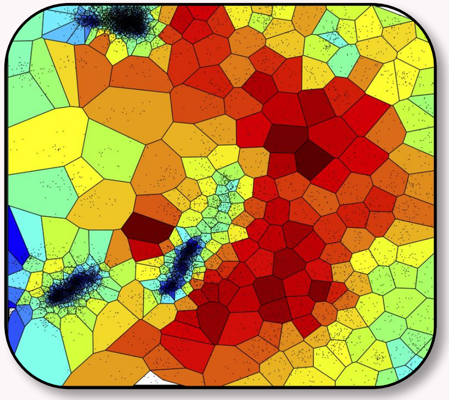
2.4. The Overdamped Langevin equation & the Itô-Stratonovich dilemma,

2.5. The inverse problem,

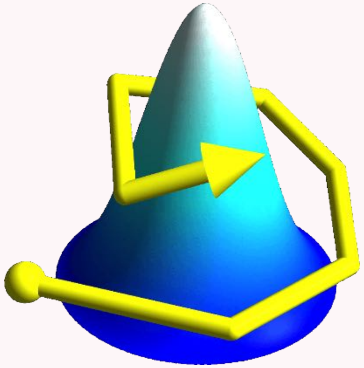
2.6. A Bayesian solution,

2.7. Statistical properties,

3. Conclusions.



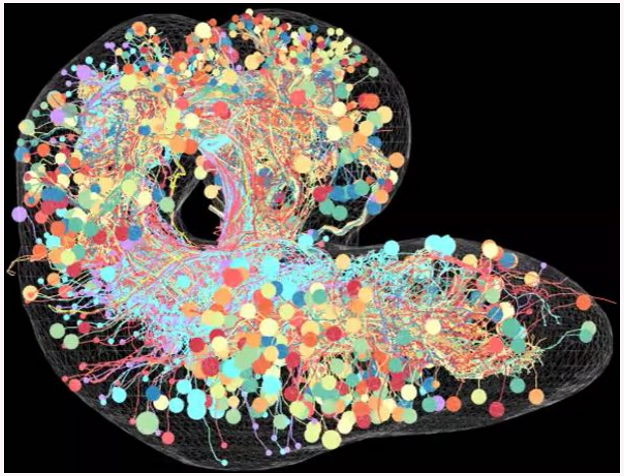
Intracellular diffusivity map



TRamWAy project

Drosophila Larvae Project

From Brain Structure to Behavior



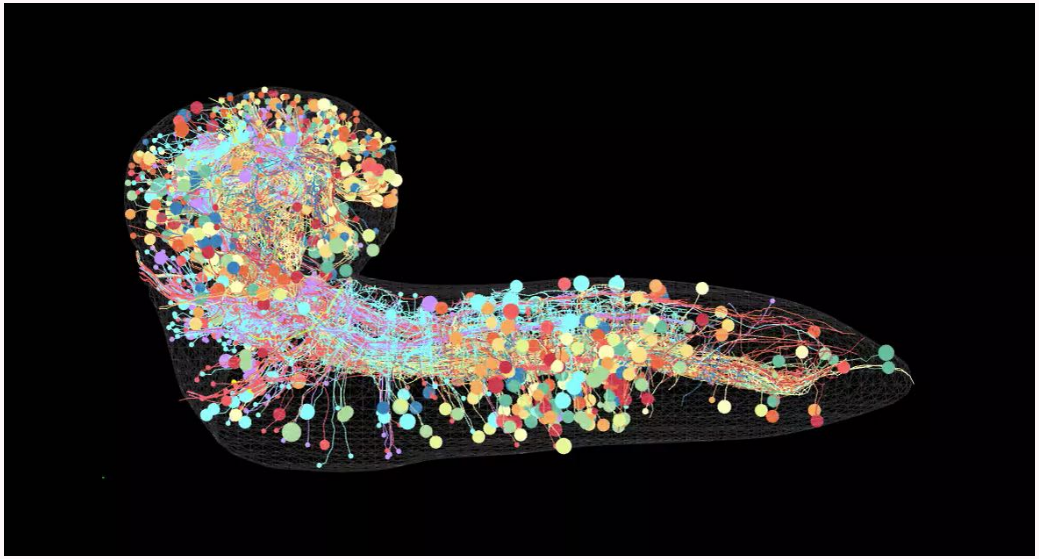
From Brain Structure to Behavior

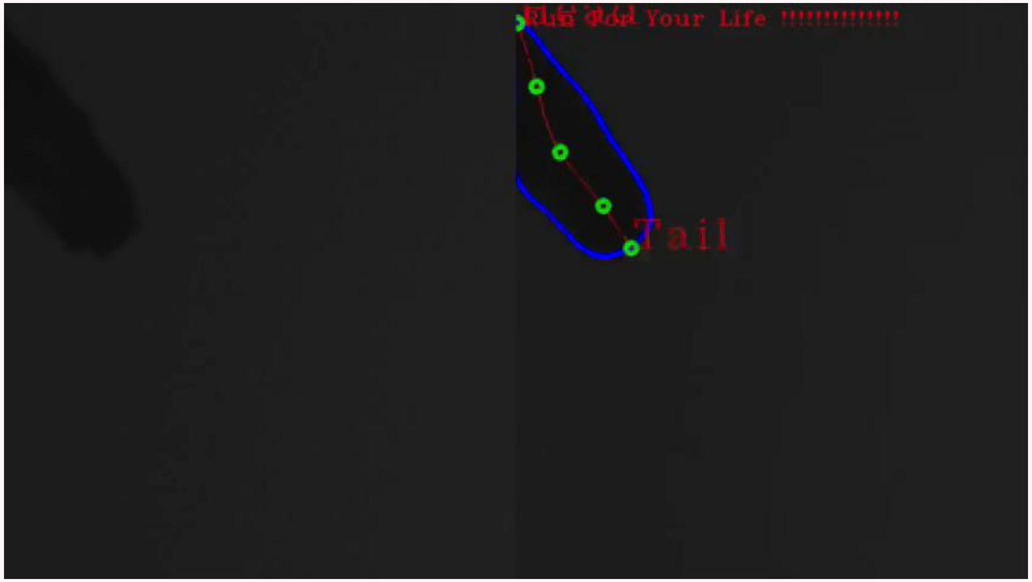
We have access to:

- the full **connectome** of the *Drosophila* larvae brain (10k neurons),
- annotated videos of larvae **behavior** under optogenetic or sensory **stimuli**.

Challenge:

Identify function of individual neurons or neural circuits.





Decision making as a multi-armed bandit game

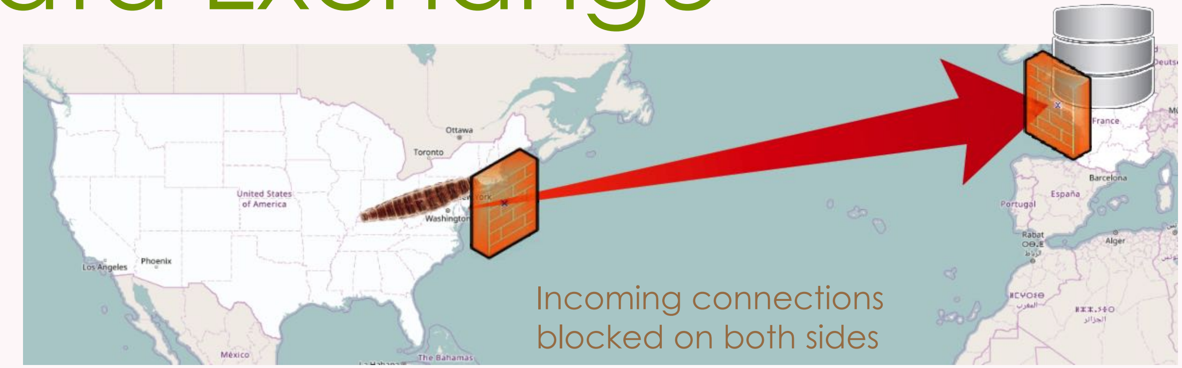
Jean-Baptiste Masson

In collaboration with Janelia Research Campus, USA

hhmi janelia Research Campus

François: Data Exchange

The **problem:** file synchronization between clients **behind firewalls.**



Solution (Escale):

- Exchange via **a cloud service,**
- **Remove** data from the cloud right after transfer,
- Automatically **manage size quotas** and **encryption**,
- Support **Dropbox, Google Drive, Yandex.Disk** (and other WebDAV services), Amazon Cloud Storage, Amazon S3, FTP, Google Cloud Storage, Microsoft OneDrive, etc.
- **Easy install** (available in standard python repository): `pip install escale`

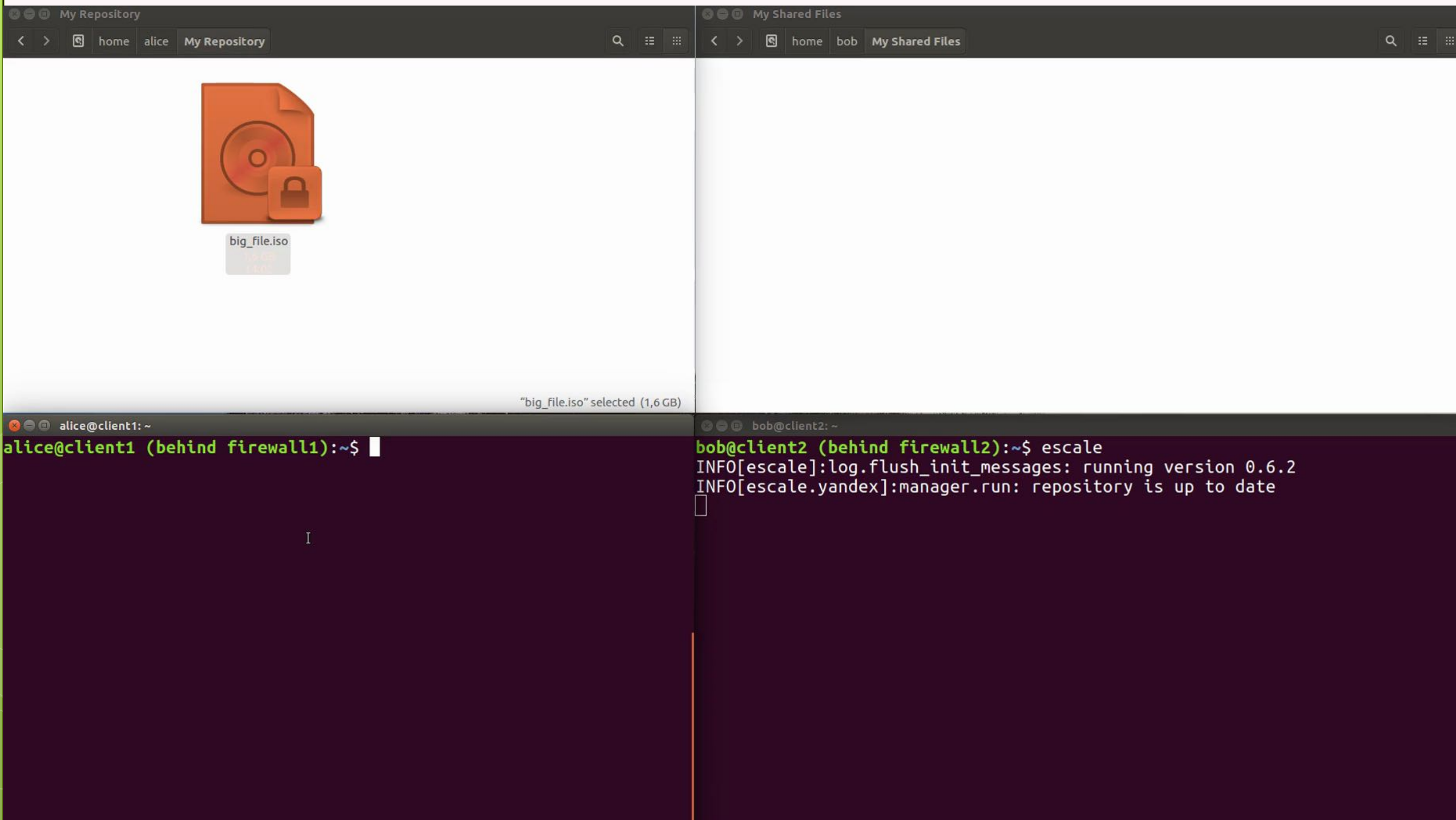
François Laurent

Check out Escale (free and open source):

https://github.com/francoislaurent/escale

Escale: Demonstration

Escale is very **easy** to install and use:

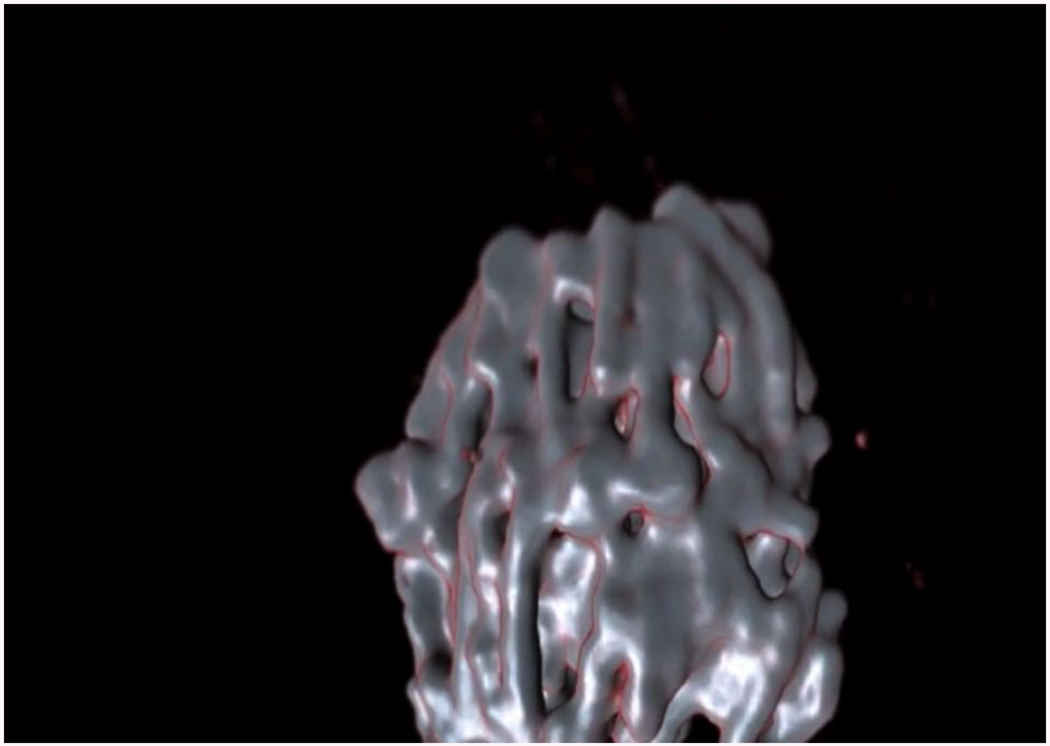


https://github.com/francoislaurent/escale

DIVA Project

Big Data to Virtual and Augmented Reality

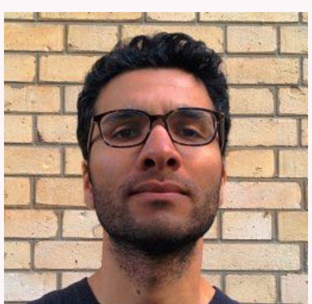
Startup: Big Data to Virtual and Augmented Reality (DIVA)



A new tool to work with data:

- **visualize** 3D data in real time,
- provide an **interactive environment**,
- simplify data **analysis** and **interpretation**.

chromosome separation in mitosis in HeLa Cells [1]



Mohamed El Beheiry

Maxime Dahan

Check out the project:

https://tinyurl.com/DIVA-Pasteur

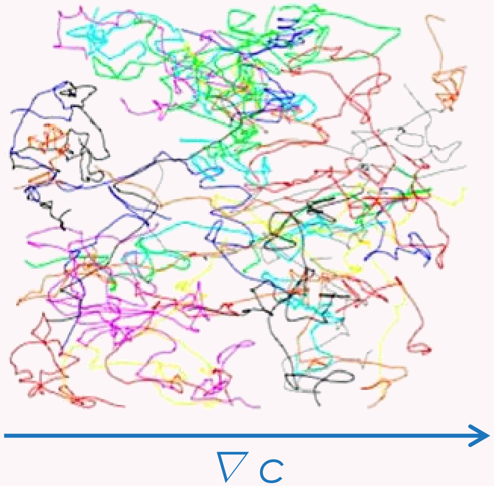
1. Chen et al., *Science* **346**, 6208 (2014)

TRamWAy Project

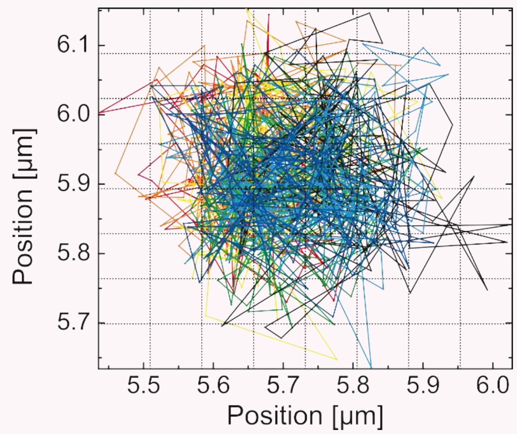
Aka "Inference MAP”.

Funding: TRamWAy ANR (2017).

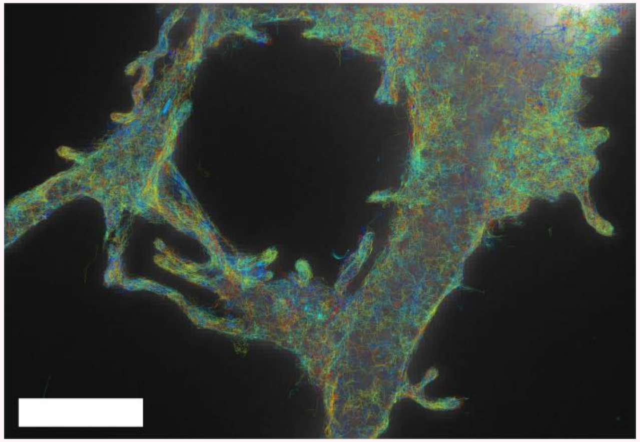
Random Walk as a Probe



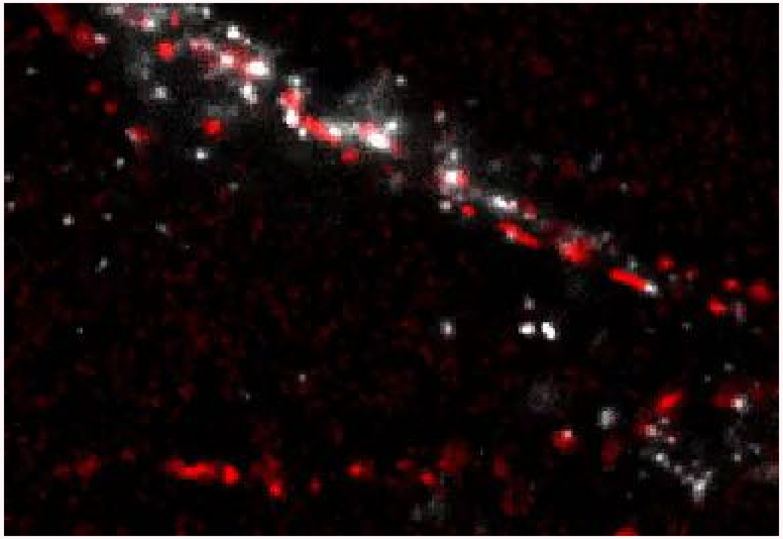
Chemotaxis in *E. coli*
(51 tracks) [2]



Receptor on a kidney cell membrane (1 track) [1]



Glycine **receptor** in a mouse hippocampal neuron (9453 tracks) [3]



Structure of the **cell surface**.

Intracellular **transport**.

How to extract information from these data?

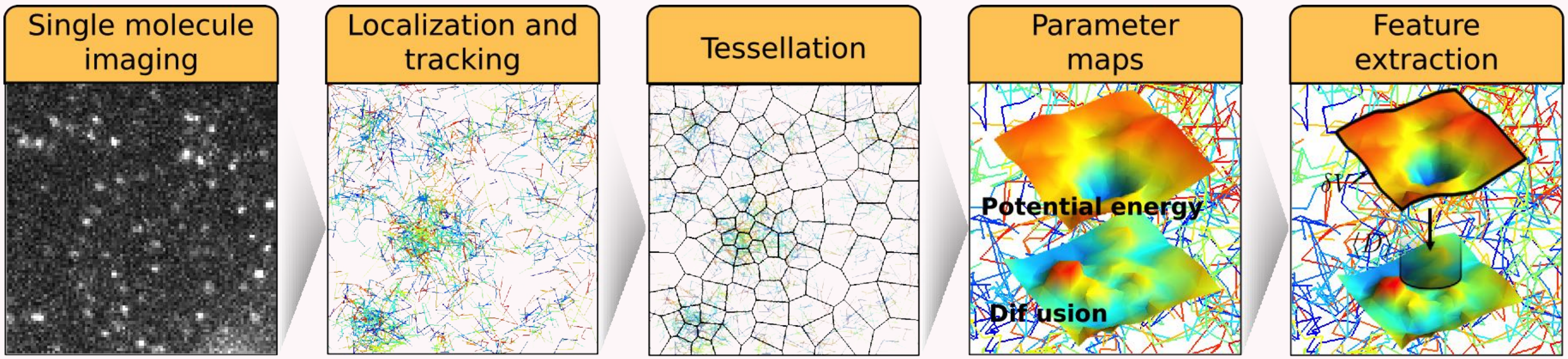
Glycine **receptor** (white) interaction with gephyrin scaffold (red) [4 – 5]

1. Masson et al., *Phys. Rev. Lett.* **102**, 048103 (2009)
2. Masson et al., *PNAS* **109**, 5 (2012)
3. El Beheiry et al., *Nat. Meth.* **12**, 7 (2015)
4. Masson et al, *Nat. Meth.* (2015)
5. Masson et al, *Biophys. J.* (2013)

TRamWAy Project

Easy to use: All steps combined in **a single piece of software.**

TRamWAy (Inference MAP) [1] pipeline as originally proposed in 2015:



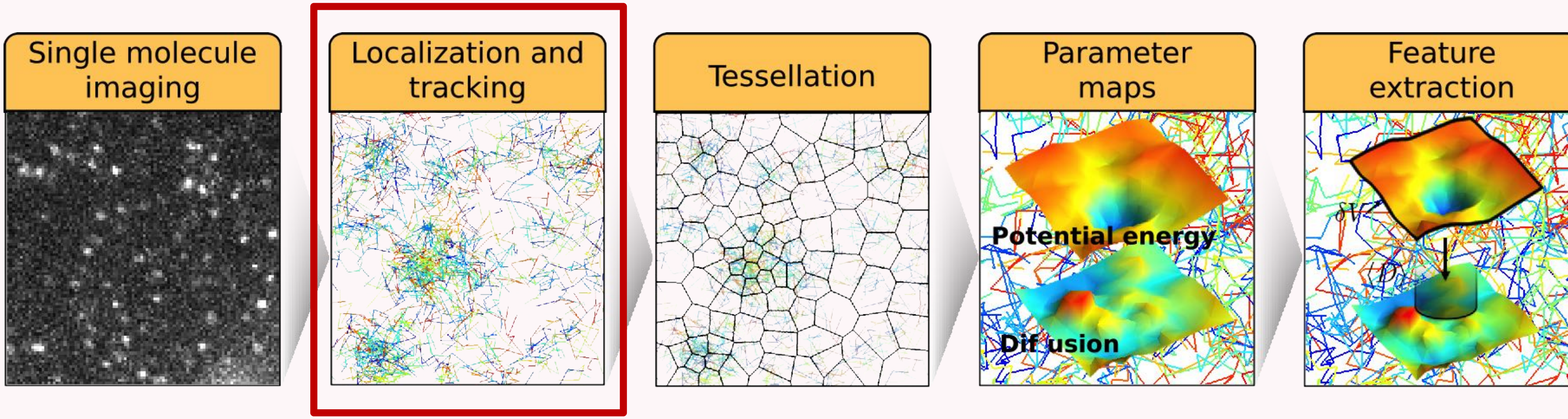
General: All kinds of **random walks**, not only biomolecules.

Free & **open source** (have a look at **GitHub**):
https://github.com/DecBayComp/TRamWAy

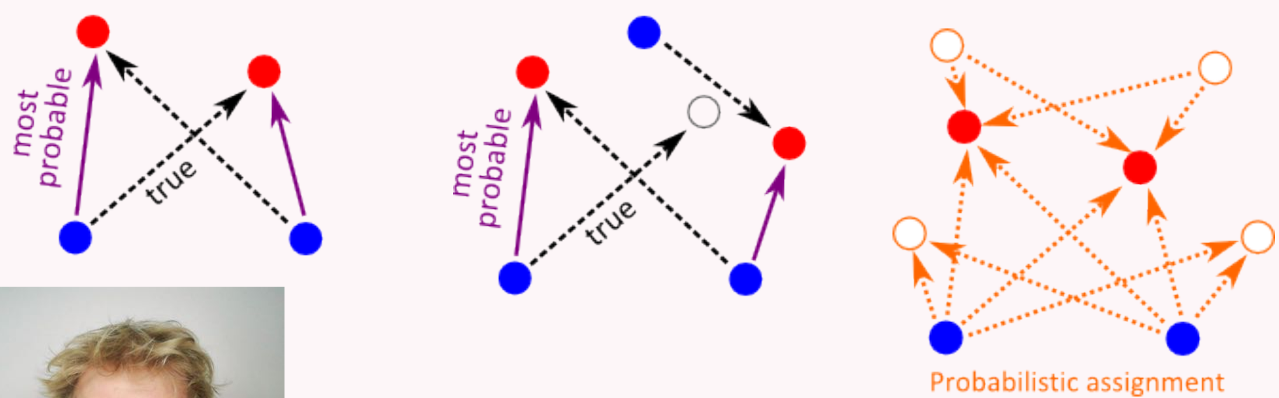
Several steps can be improved.

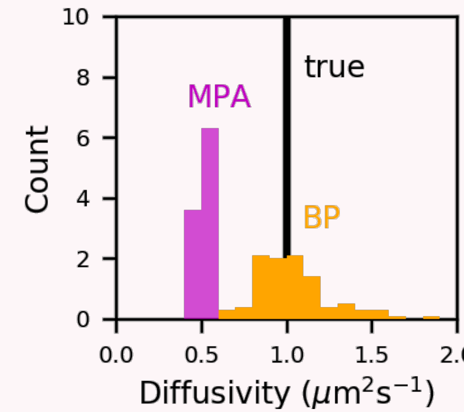
1. El Beheiry et al., *Nat. Meth.* **12**, 7 (2015)

Christian: Inference Without Tracking



At **high particle density** and **low temporal resolution**, diffusivity **estimate is biased** towards lower values:





BP = Belief propagation

MPA = most probable assignment

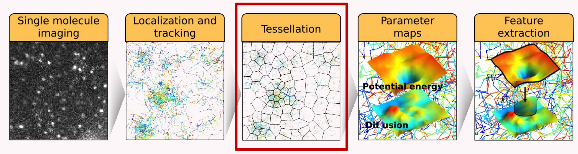
Christian Vestergaard

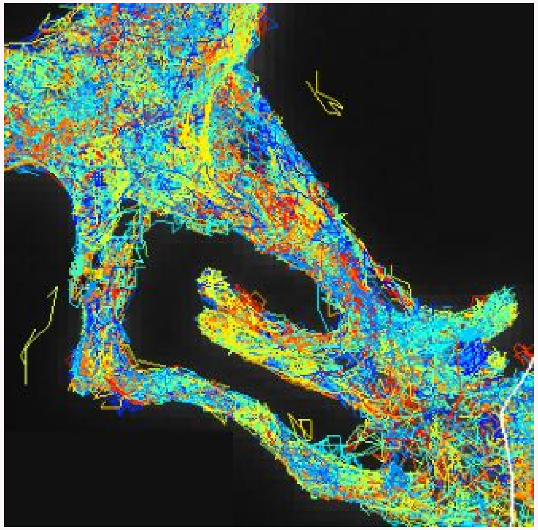
Solution:

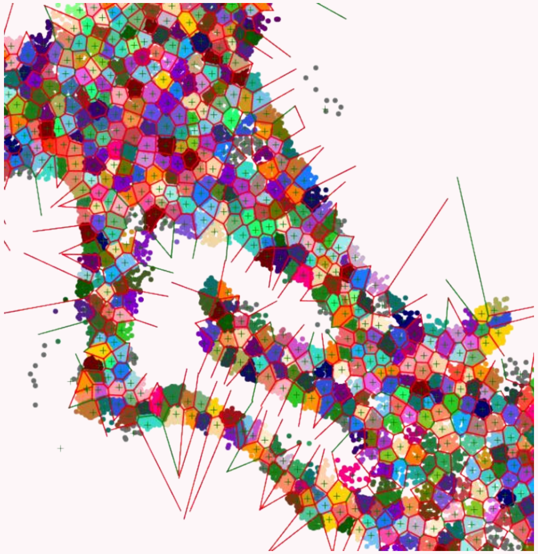
A probabilistic description taking into account all possible trajectories

François: Space Tessellation

Particles do **not** sample the environment **uniformly.**







Cell size should be **optimized**:

- choose a correct physical scale (be **reasonable**),
- minimize cell area (be **accurate**),
- reduce estimate confidence interval (be **precise**),
- parallelize computations (be **fast**).

Used algorithm:

Self-organizing GWR graph (Grow When Required).

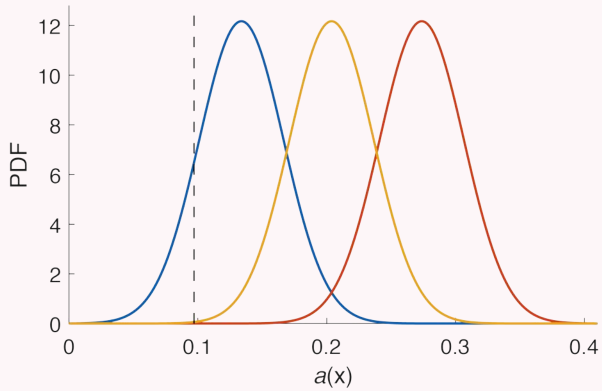
François Laurent

Soon available in TRamWAy:

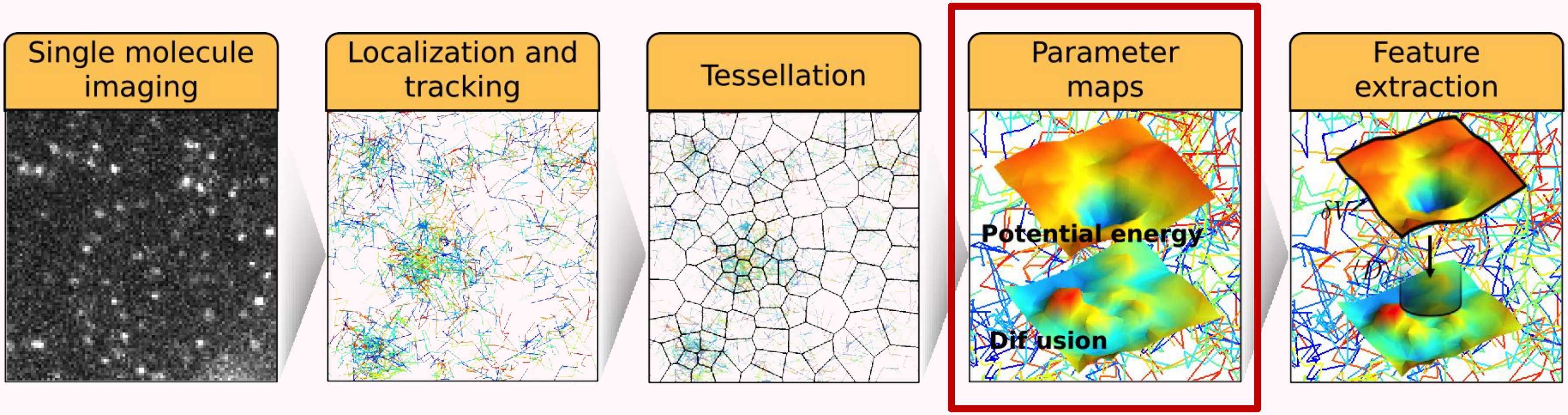
https://github.com/DecBayComp/TRamWAy

The Itô-Stratonovich Dilemma

The Inverse Problem



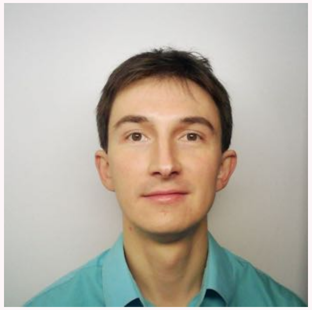
Inference: Ambiguous Force Maps



TRamWAy uses the **Overdamped Langevin equation** to perform inference.

The inferred forces allow **different interpretations.**

This is the **Itô-Stratonovich dilemma** for the inverse problem.



Me

Main question:

How to overcome this ambiguity?

Overdamped Langevin Equation

The **Overdamped Langevin Equation**:

local force

time step

white noise

overdamped: no inertial term

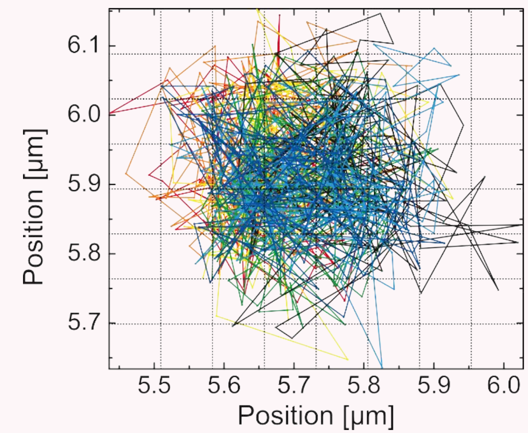
$$dX_t = \frac{f(X_t)}{\gamma(X_t)}dt + \sqrt{2D(X_t)} \circ dW_t.$$

particle jump at time t

viscous drag

local diffusivity

Masson et al. (2009)



Note:

The white noise is a zero-mean uncorrelated Wiener process: $W_t \sim \mathcal{N}(0, t)$.

In biology, the **parameters *D*, *f*** and γ often **depend on location.**

This equation is ambiguous regarding stochastic integration ($\circ$).

1. Masson et al., *Phys. Rev. Lett.* **102**, 048103 (2009)

Itô-Stratonovich Dilemma

In a general notation:

integration convention

white noise

spatial coordinate

$$dX_t = a(X_t)dt + b(X_t) \circ dW_t$$

drift

diffusivity

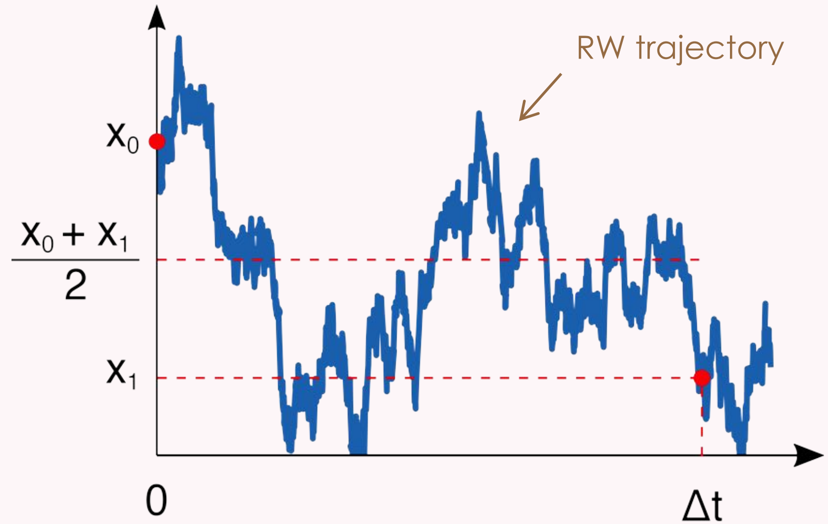
Unclear:

At which point X_t should $a(X_t)$ and $b(X_t)$ be evaluated?

In **deterministic PDEs**, the trajectory does not depend on the choice.

Dilemma: with the OLE, the choice changes the statistical properties of the trajectory.

Consider one time step Δt: $x_0 \longrightarrow x_1$



Common choices (conventions):

- Starting point (**Itô**): $a(x_0)$,
- End point (**Hänggi**): $a(x_1)$,
- Mid-point in space (**Stratonovich**): $a\left(\frac{x_0+x_1}{2}\right)$,

Note that in general, $\frac{x_0+x_1}{2} \neq X\left(\frac{\Delta t}{2}\right)$.

Direct Problem

In general, consider **an arbitrary choice** of x within the interval $x_0 \leq x \leq x_1$:

$$x = (1-\lambda)x_0 + \lambda\, x_1 \qquad \text{with} \qquad 0 \leq \lambda \leq 1.$$

If the noise has zero mean, $\langle \Delta W \rangle = 0$, then, **on the average**

$$\langle a(x)\Delta t \rangle = a(x_0)\Delta t + O(\Delta t^2),$$

where averaging is performed over different realizations of the stochastic trajectory.

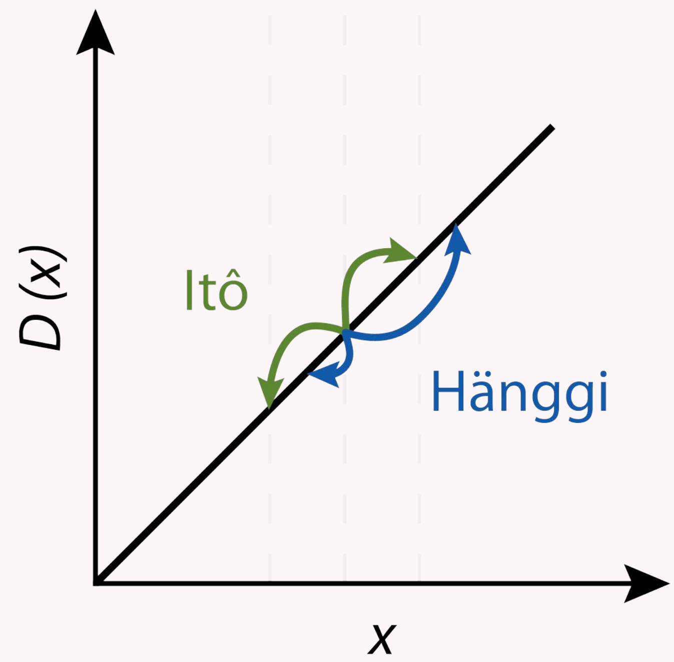
The force term $\propto \Delta t$ does not depend on λ.

But

$$\langle b(x)\Delta W \rangle = \boxed{\lambda b(x_0)b'(x_0)\Delta t} + O(\Delta t^2).$$

This noise term adds **spurious drift** $\propto \lambda\Delta t$.

$$x_1 - x_0 = a(x)dt + b(x) \circ dW_t$$



there is a preferential jump direction

The chosen convention changes the equilibrium distribution.

Distinguish a Spurious Force

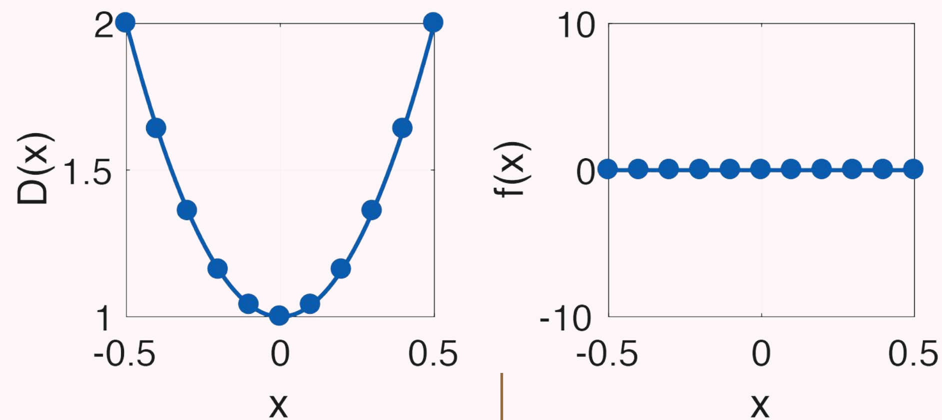
In a real (biological) experiment, **there is a difference** between **spurious** and **non-spurious** forces.

The main difference is seen **in equilibrium**:

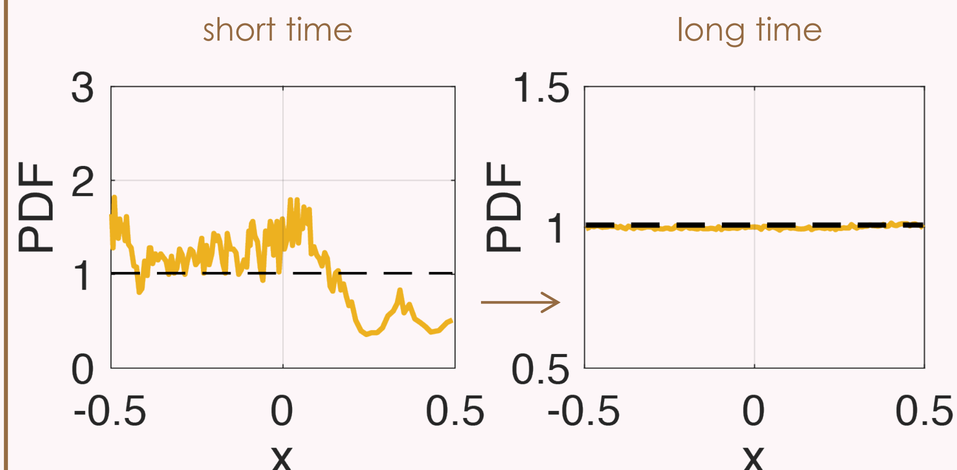
- **Local forces** define the equilibrium distribution of particle locations,
- **Spurious forces** do not influence the equilibrium distribution [1].

Only Hänggi convention gives correct physical equilibrium!

Given diffusivity and force:



Expected equilibrium **particle density**:



1. van Kampen, *Stochastic Processes in Physics and Chemistry* (1992)

Other Equilibrium Distributions

Hänggi gives the physical **equilibrium** distribution [1].

Other conventions may be good for **non-physical systems** (e.g., economics).

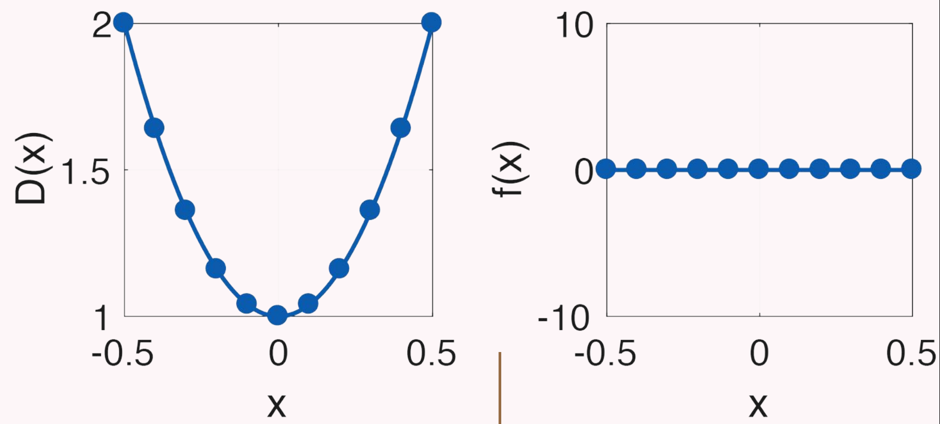
Dilemma resolved!

This result does not apply to **out-of-equilibrium** systems.

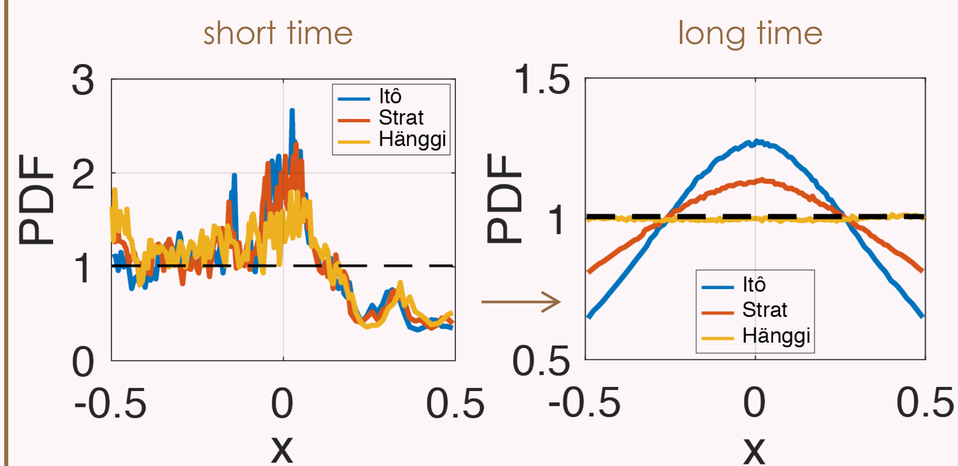
Biological systems are intrinsically out of equilibrium…

Which convention should one use for the inverse problem in out-of-equilibrium systems?

Given diffusivity and force:



Simulated particle density:



1. van Kampen, *Stochastic Processes in Physics and Chemistry* (1992)

Out-of-Equilibrium λ Is Unknown

What one sees in experiment:

$$dX_t = \boxed{a_\lambda(X_t)}\,dt + \boxed{b(X_t)}\,dW_t,$$

where

$$a_\lambda(x) = a_0(x) + \lambda\, b(x) b'(x).$$

?

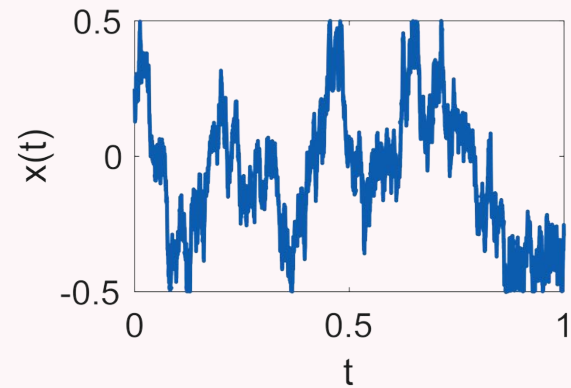
Given a random trajectory, one can **infer**:

- $a_\lambda(x)$ from the **drift**,
- $b(x)$ from the **fluctuations**,

but there is **no information** about λ.

Basically, we have access to the **total force** $a_\lambda(x)$, but we do not know its **composition**.

The contribution of the spurious force is unknown, but bounded.



The inverse problem summary:

- No difference if $b(x) = \mathrm{Const}(x)$,
- All λ conventions provide **statistically equivalent descriptions**,
- **Physics** behind is **different**,
- One knows $b(x)$.

Interval of Local Force Values

Assume for a given trajectory, the local force $a_0(x)$ is correctly calculated from the total force $a(x)$ by using λ^*:

$$dX_t = a(X_t)\,dt + b(X_t)\,dW_t,$$

with

$$\underbrace{a_0(x)}_{\text{local force}} = a(x) - \underbrace{\lambda^*\, b(x)b'(x)}_{\text{spurious force}}.$$

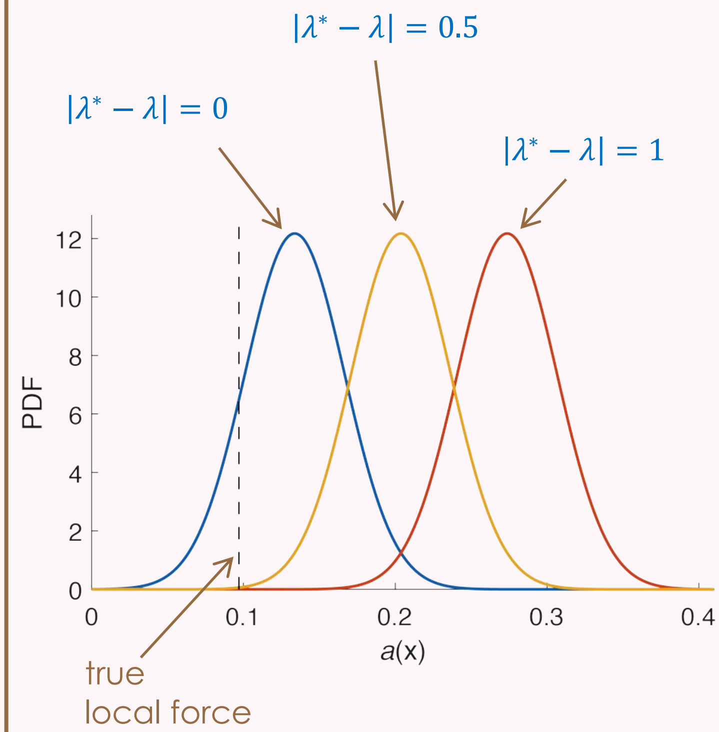
By inferring the force with a different λ, one constructs an estimate:

$$\hat{a}_0(x) = a(x) - \lambda\, b(x)b'(x).$$

This estimate introduces a bias:

$$\delta a(x) \equiv \hat{a}_0(x) - a_0(x) = \boxed{(\lambda^* - \lambda)\, b(x)b'(x)}$$

Example (for a fixed x):



But

$$0 \le |\lambda - \lambda^*| \le 1$$

because

$$0 \le \lambda, \lambda^* \le 1.$$

Even better: a Bayesian method that marginalizes over λ.

Bayesian Statistics

The Bayesian approach is based on **the Bayes rule [1]**:

$$p(\theta|\, x) = \frac{p(x|\, \theta)\, \pi(\theta)}{p(x)}.$$

It describes the **change in belief** (probability) of a hypothesis given observations x.

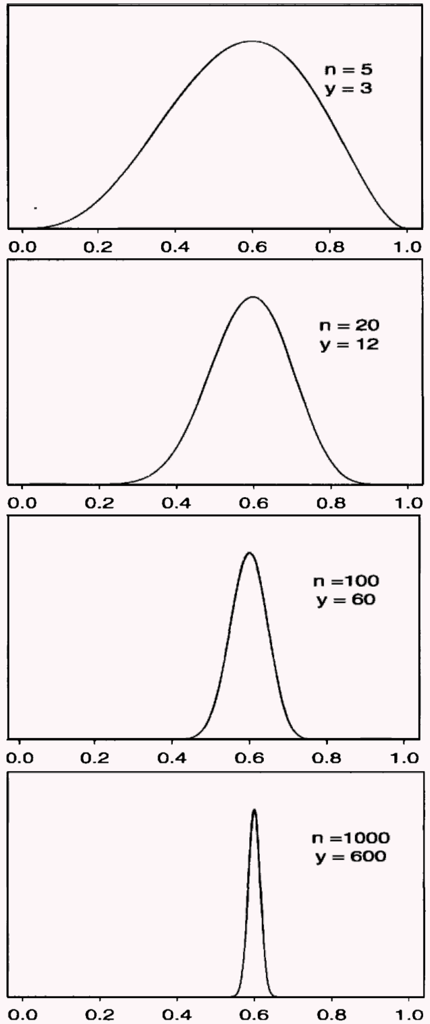
Here:

- θ are model **parameters** (e.g., diffusivity, force),
- $p(x|\, \theta)$ is the **likelihood** of observing data x given parameters θ,
- $\pi(\theta)$ is the **prior information** about model parameters,
- $p(x)$ is a **normalization factor** independent of the hypothesis,
- $p(\theta|x)$ is the **posterior** distribution (updated belief).

Advantage:

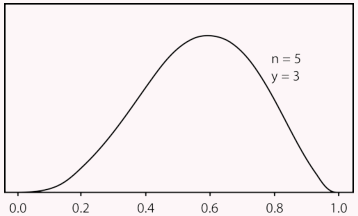
- correctly **incorporate prior information,**
- **regularize** solution (e.g. penalize strong gradients).

Example [1]
(binomial distribution):



1. Gelman et al., *Bayesian Data Analysis* (2004)

Choosing a Prior



Informative priors

- **Population** interpretation:

  Specify a possible **range** of parameters θ (a **uniform prior**),

- **State of knowledge:**

  Reflect what is known (expected) from **previous experiments**.

Non-informative (reference) priors

"Let the data speak for themselves".
Prior plays the **minimal role** possible in the posterior distribution.

- **Jeffreys prior** (invariant to reparametrization):

$$\pi(\theta) = \sqrt{\mathrm{E}\left[\left(\frac{d\log p(x|\,\theta)}{d\theta}\right)^2\right]}.$$

"Convenient" priors

A **conjugate prior** provides **posterior in the form of the prior** and simplifies interpretation.

In any case, information contained in the evidence should outweigh the prior.

1. Gelman et al., *Bayesian Data Analysis* (2004)

Dilemma: The Bayesian Solution

For a given trajectory, $a(x)$ and $b(x)$ are known, so one could write down **an interval of values** of the local force $a_0(x)$:

$$|a_0(x) - a(x)| \leq |b(x)b'(x)|.$$

But if all λ values are **equiprobable**, **not** all values from this interval are **equally likely** (no information).

A correct way to **account for** this **uncertainty** in λ is by using a Bayesian approach.

It allows one to **assign probability** to different local force values.

If **other information** is available, it can be incrorporated by using a **different prior**.

To get the PDF, one integrates over λ:

$$p(\theta|\, x) = \int_0^1 \frac{p(x|\, \theta, \lambda)\, \pi(\theta, \lambda)}{p(x)} d\lambda,$$

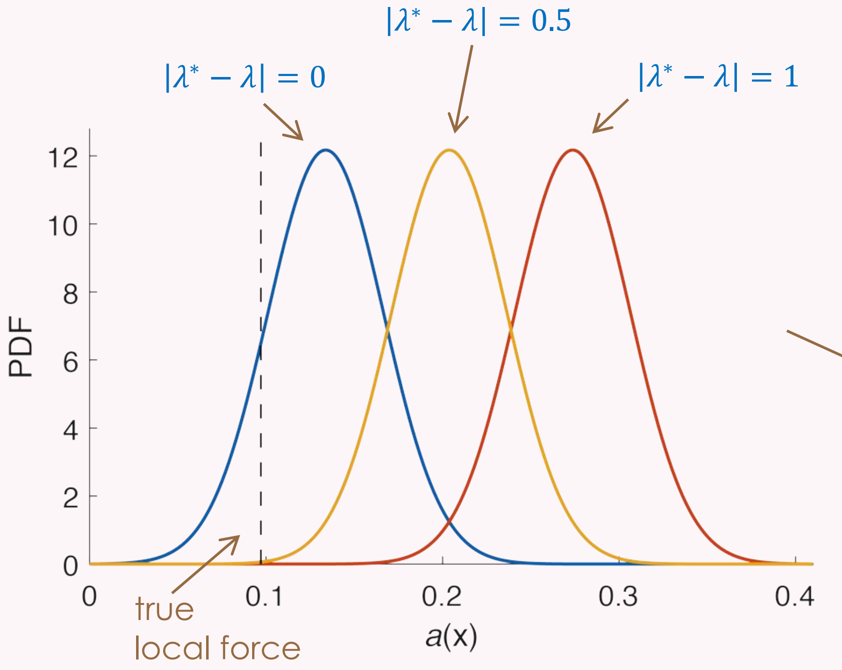
where

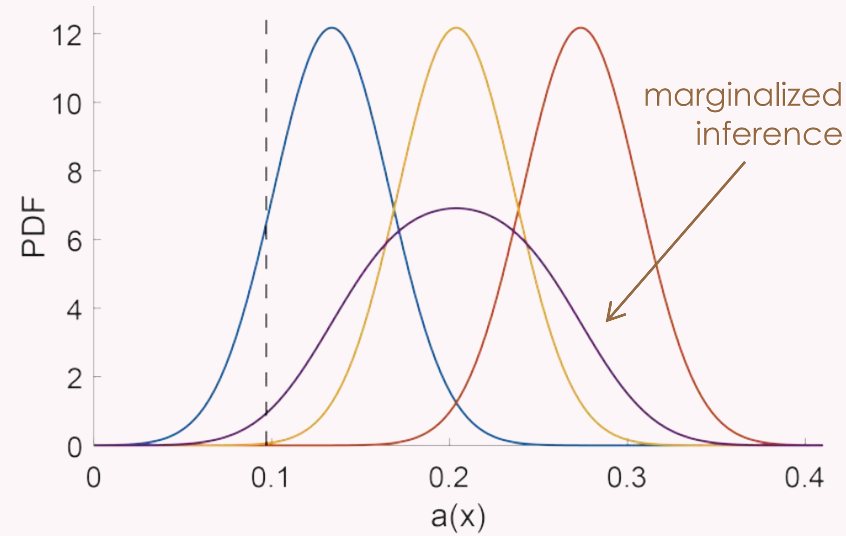
- $\theta = (a(x), b(x))$ are the **drift** and **diffusivity** of the OLE,
- $p(x|\theta)$ is the **likelihood** of the trajectory given parameters θ,
- $\pi(\theta, \lambda)$ is the **prior** distribution,
- $p(x)$ is a **normalization factor** independent of λ or θ.

The proposed method takes into account the uncertainty in the estimate of λ.

Posterior Distribution

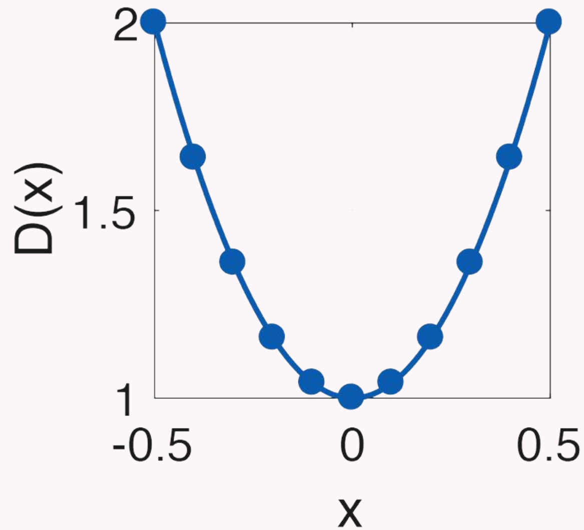
The distributions marginalized over λ are wider than fixed λ distributions

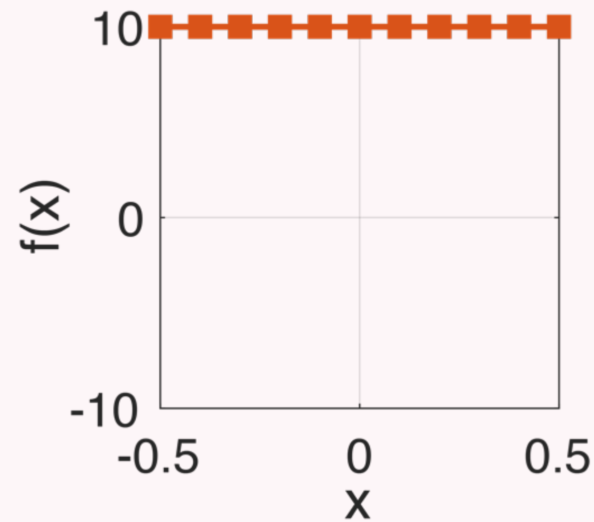




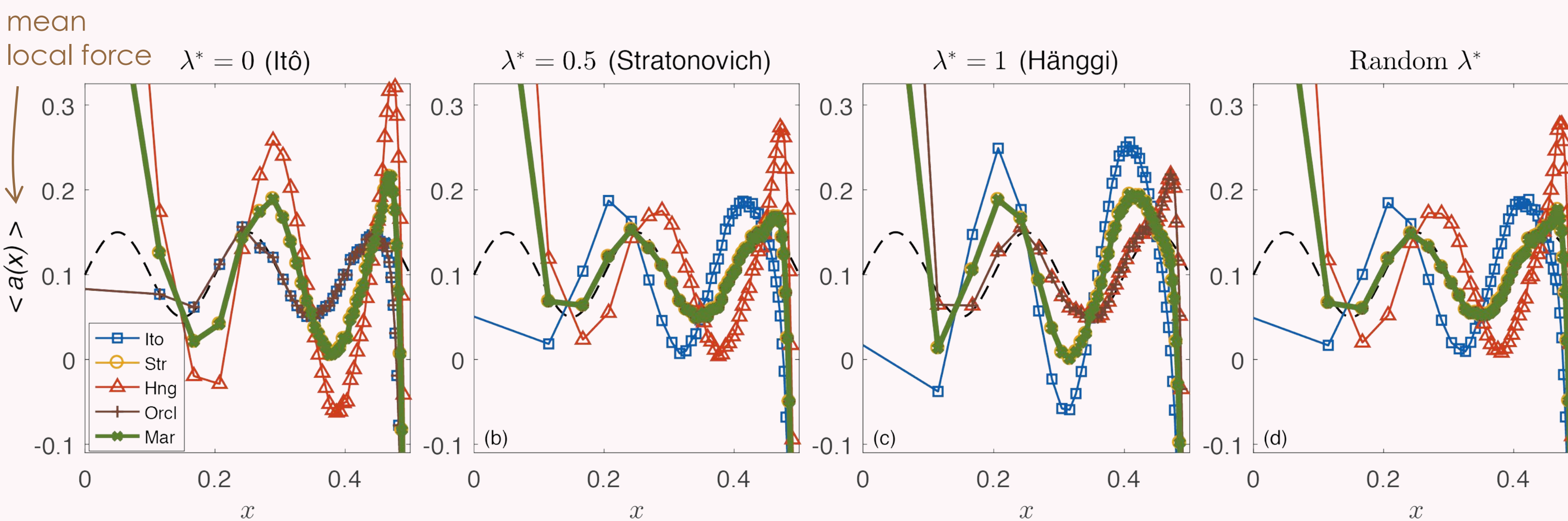
Accuracy of the Method

An **example** of varying diffusivity and uniform force:



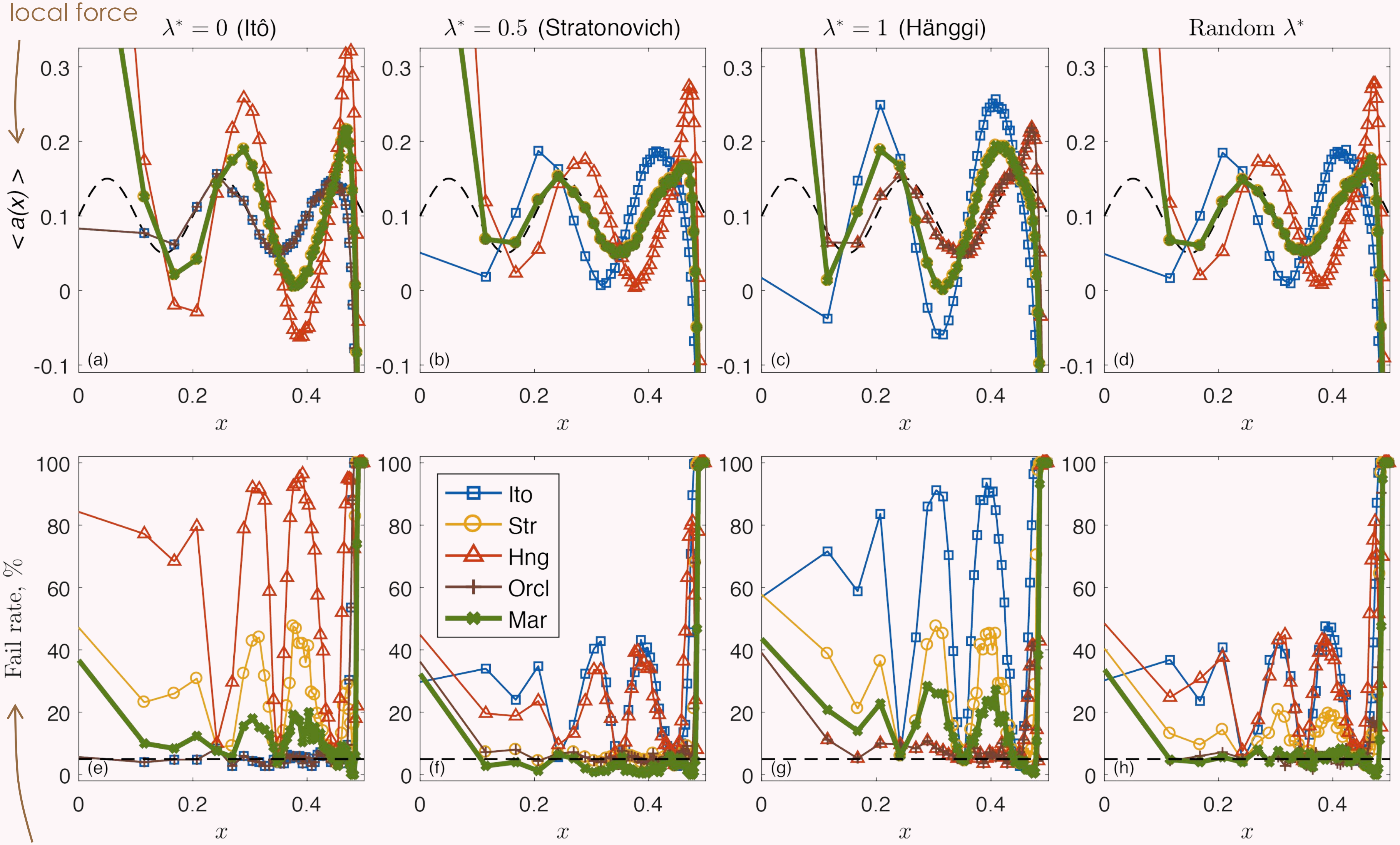


On the average, the method is **accurate**:



Precision of the Method

mean
local force



fail rate for the 95% confidence interval

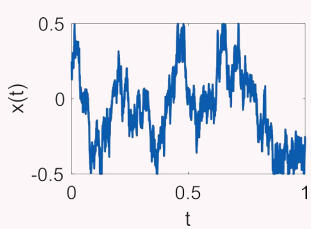
Conclusions & Open Questions

Conclusions:

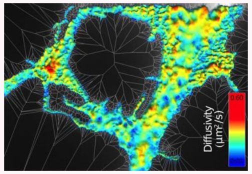
- One **cannot directly estimate** the local force,
- **Range** of possible spurious force contributions **is known,**
- Our **Bayesian approach** takes into account the uncertainty in λ,
- It **assigns probability** to the values of the local force.

Advantages:

- **Smaller bias** than fixed-λ methods,
- More robust **confidence intervals**.



Questions:



Practical:

- **Incorporate** the method into TRamWAy,
- Identify local forces in **real experimental data.**

General:

- For systems with more information, a **non-uniform λ prior** can be used.
- Which value of λ^* does **Nature use** in out-of-equilibrium systems?
- This result can be applied **outside biology** (economics, hydrodynamics or molecular dynamics simulations).

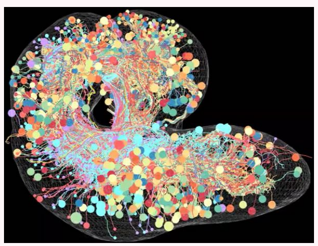
Thank you for your attention!

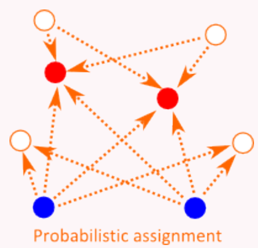
More details → Serov et al., 2017 (in preparation)

Open Positions in the DBC Lab

Brain connectome, behavior, networks:

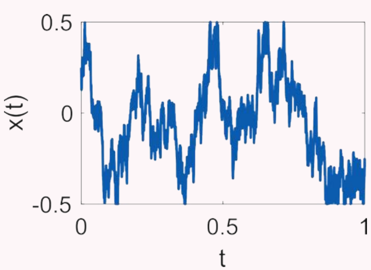
- The Virtual *C. Elegans*: Reinforcement Learning (a 3-6 months **internship**);
- From Brain Structure to Behavior (**a Ph.D. project**).

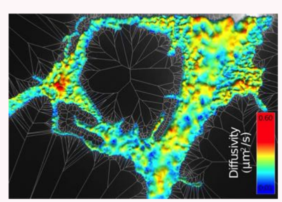




Random walks, dynamics inference:

- Variational Inference of Neuroreceptor Dynamics in Synapses (**a Postdoctoral project**, funding: ANR TRamWAy).





DIVA, augmented and virtual reality:

- Augmented Reality Intern (a 3-6 months **internship**);
- Machine Learning Intern (a 3-6 months **internship**).