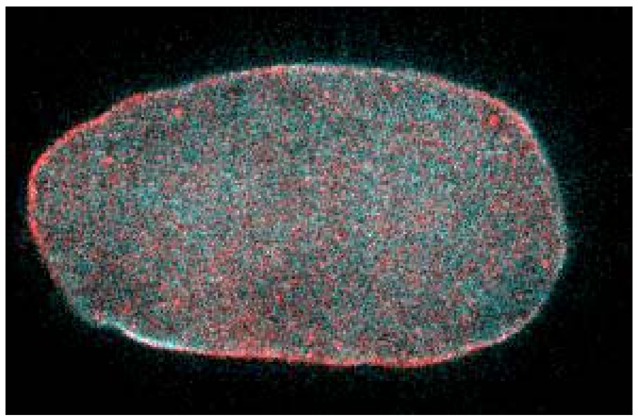
Enabling data-driven discovery in biology: Statistical learning of *interpretable* mathematical models from microscopy videos

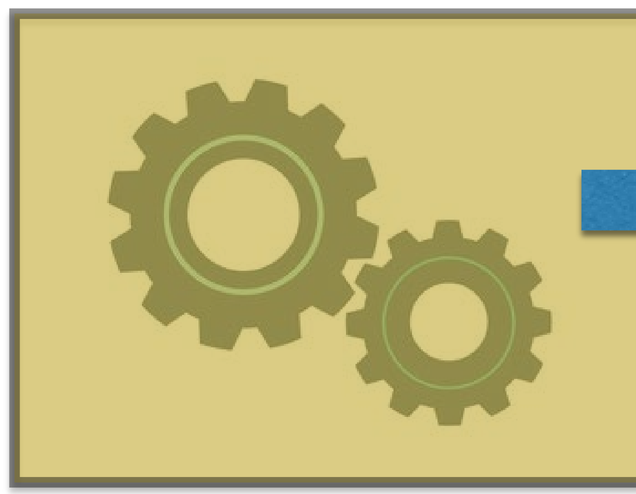
Suryanarayana Maddu, Bevan Cheeseman, Ivo F. Sbalzarini, Christian Mueller



Grill lab (MPI-CBG)

DATA

Drescher lab, MPI for terrestrial microbiology



Inference box

ODE/PDE

$$\frac{dy}{dt} = ty^2 + c$$

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + \frac{\partial^4 u}{\partial x^4} + u\frac{\partial u}{\partial x}$$

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FLATIRON INSTITUTE Center for Computational Mathematics

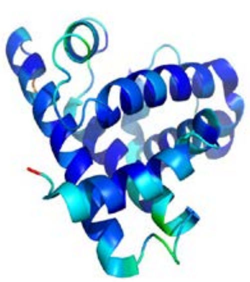
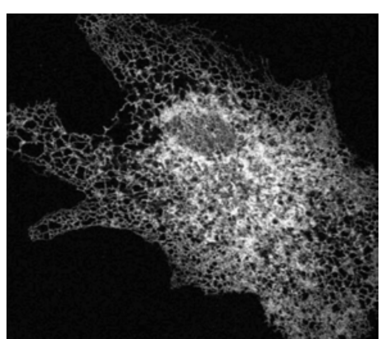
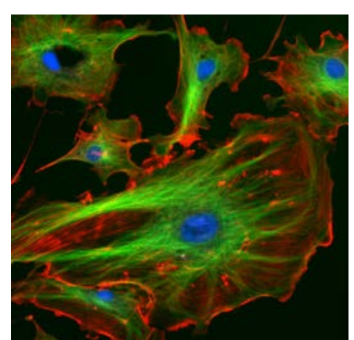
CBG Max Planck Institute of Molecular Cell Biology and Genetics

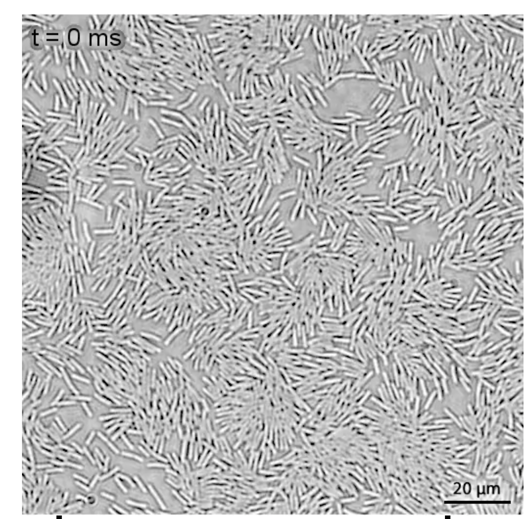
Life in a nutshell

- Highly organized
- Regulated
- Complex shapes
- Non-equilibrium
- Non-linear
- Coupled

Images: Wikipedia

Life at different scales

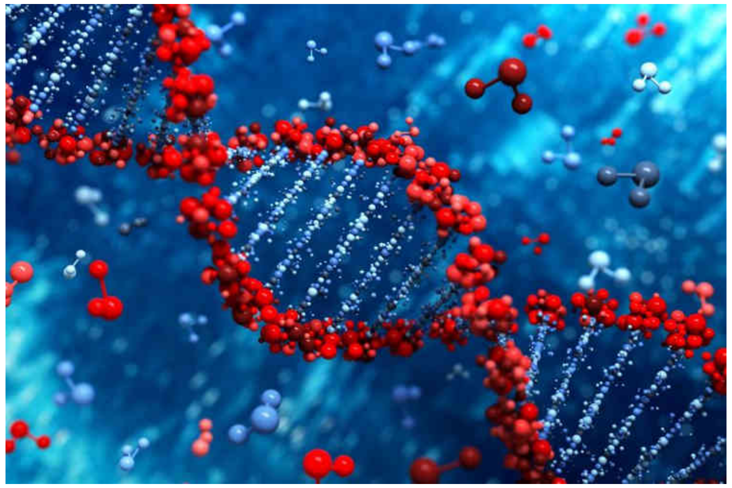




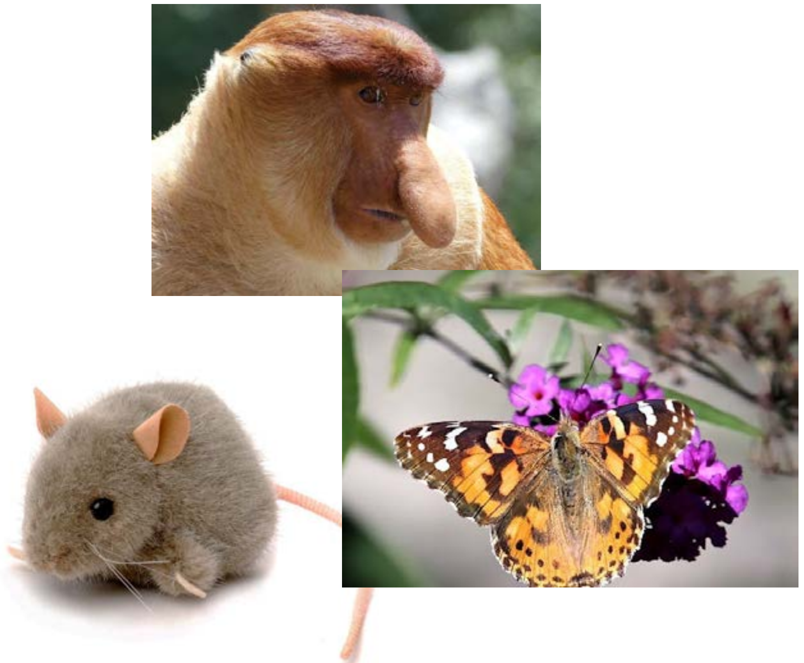


Molecules — Sub-cellular — Cells — tissue/organs — Organisms — Ecosystems

The big question(s) in biology

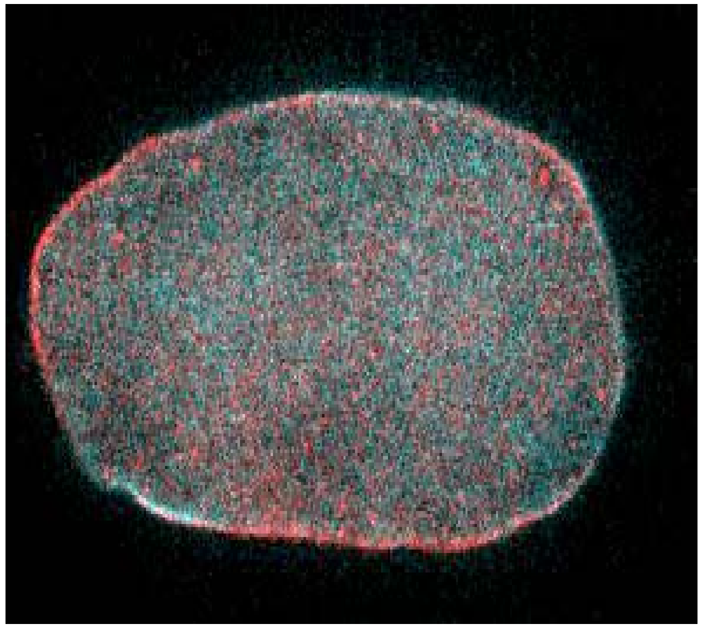
Genotype - Phenotype ?



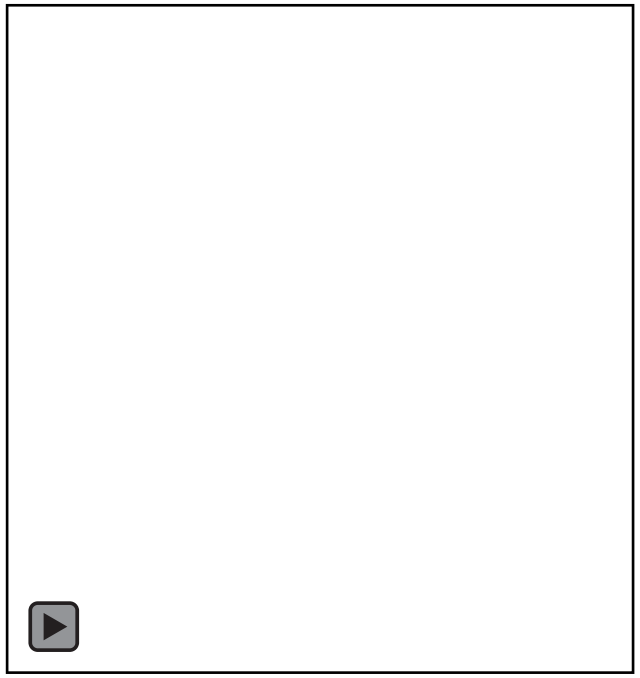


Images: Wikipedia

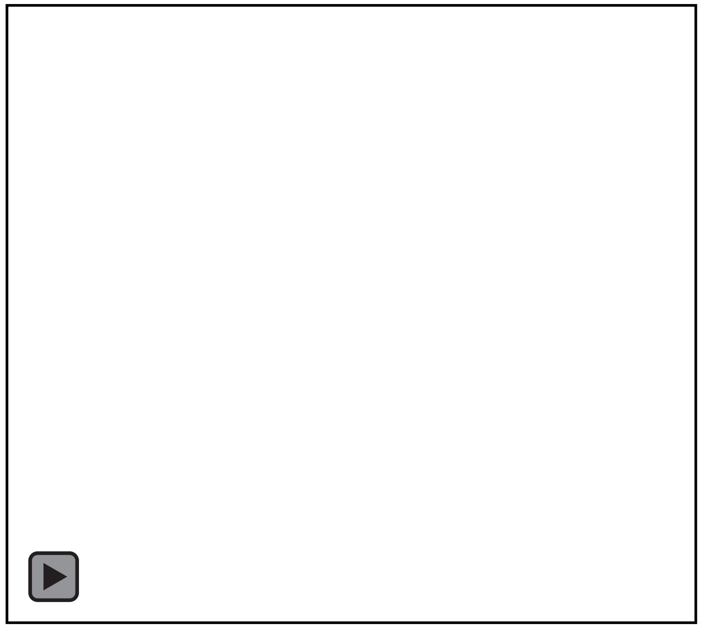
Individual interactions —> emergent dynamics ?



Cellular scale
(Grill lab,MPI-CBG)



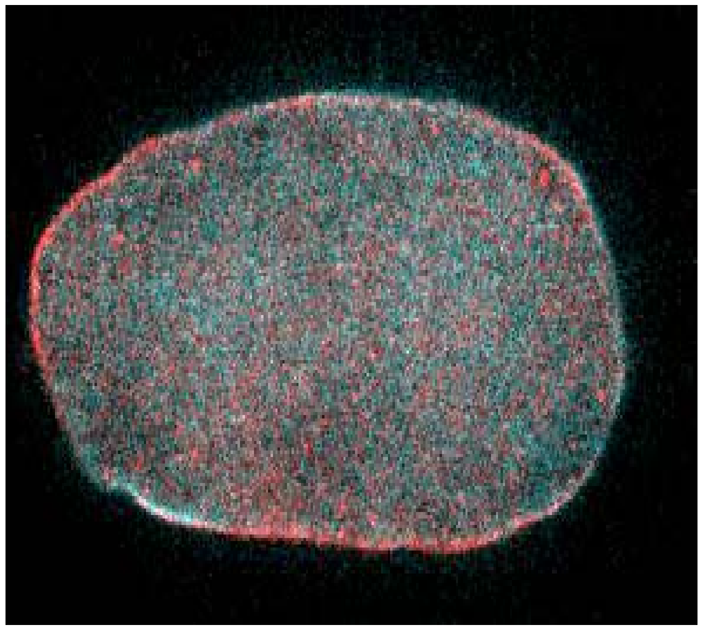
Tissue scale
(Tomancak lab, MPI-CBG)



Eco-systems scale
Drescher lab (MPI-terMic)

Mathematical models for emergent dynamics

Individual interactions —> emergent dynamics ?



Cellular scale
(Grill lab,MPI-CBG)

Tissue scale
(Tomancak lab, MPI-CBG)

Eco-systems scale
Drescher lab (MPIterMic)

- Spatial organisation
- Temporal dynamics
- Environmental influences
- Physics of interactions
- Regulatory mechanism

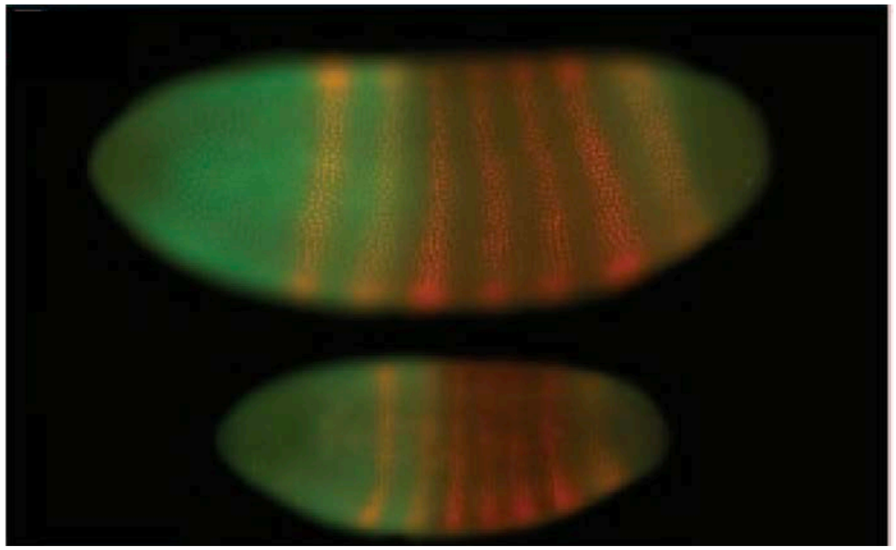
PDE

→ u, $\mathbf{x}$, t

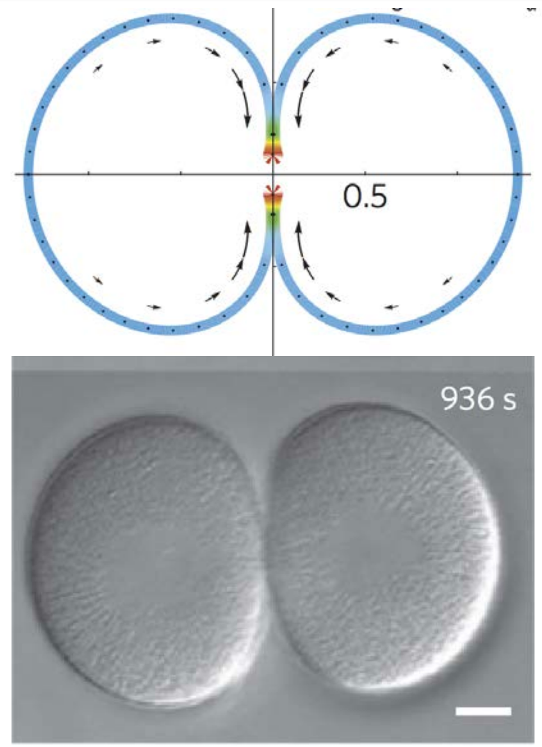
→ Initial/boundary Conditions

→ PDE components

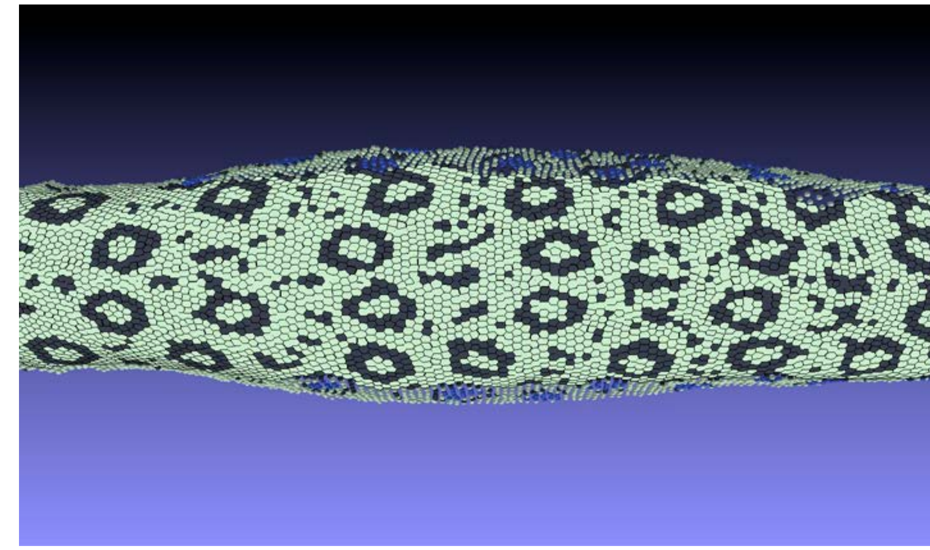
Modeling emergent dynamics : PDE success



Gregor et al, PNAS 2005

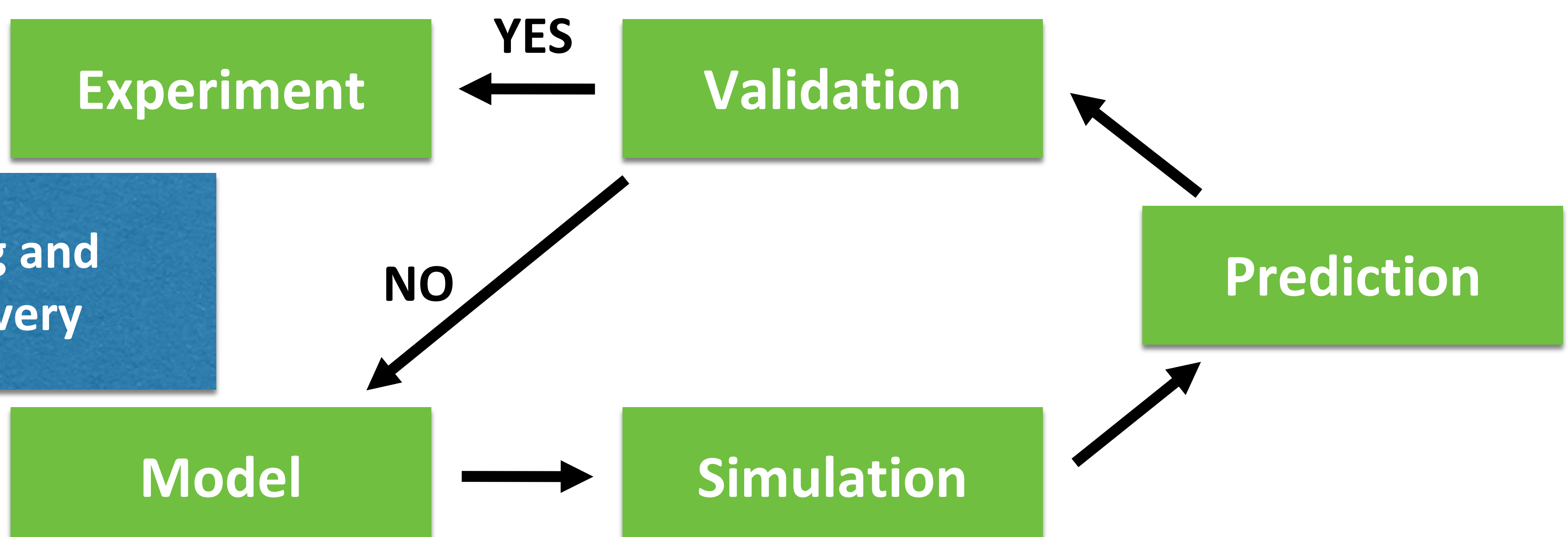


J Prost et al, Nature 2015



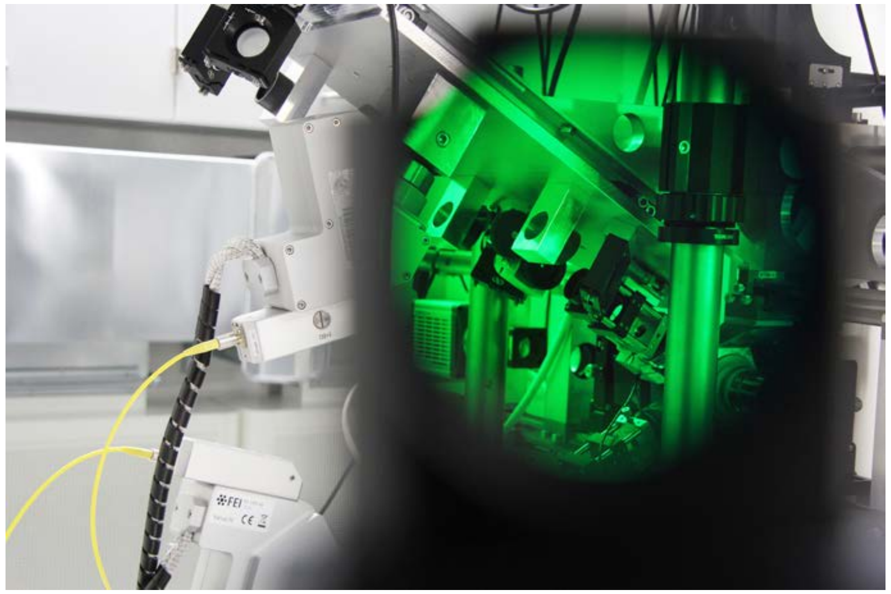
L Manukyan et al, Nature 2017

Hypothesis testing and Knowledge discovery



new paradigm

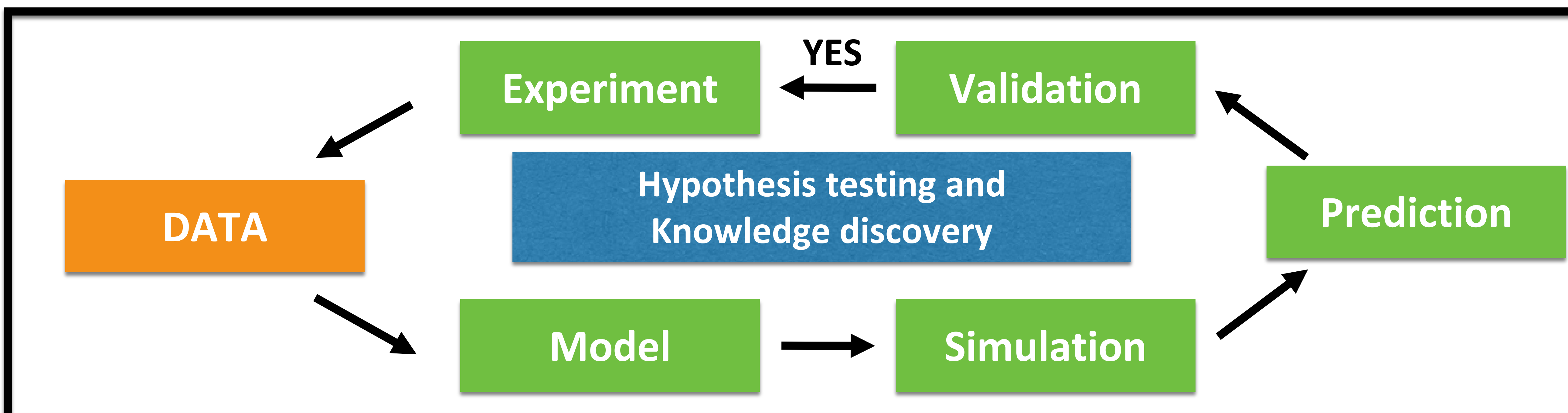
Biological microscopy data ERA



Self-driving light sheet microscope
- MPI-CBG/CSBD

BIOLOGICAL DATA-SETS

- long-term imaging of single molecules - **fluorescence microscopy**
- simultaneous measurements of multiple biosensors - **live cell microscopy**
- development of entire organisms - **lattice light-sheet microscopy, SPIM**



Microscopy data —> mathematical models PDE/ODEs

Formal definition of data-driven PDE inference

Generic non-linear, space time-dependent, parametric systems

State-variable

Parameters

$$\frac{\partial u}{\partial t} = \mathcal{N}\left(\left[u, u^2, u_{xx}, uu_x, \ldots\right], x, t, \Theta, \Sigma\right)$$

Dynamics

Stochastic effects

$$\frac{\partial u}{\partial t} = \beta_0 + \beta_1 u + \beta_2 u \frac{\partial u}{\partial x} + \beta_3 u^2 + \ldots.. + \beta_k u^3 \frac{\partial^2 u}{\partial x^2} + \ldots.,$$

Data and measurement model

State-variable measurements

$$v\left(x_m, t_n\right) = \mathcal{F}\left(u_{m,n}, x_m, t_n, \Xi\right)$$

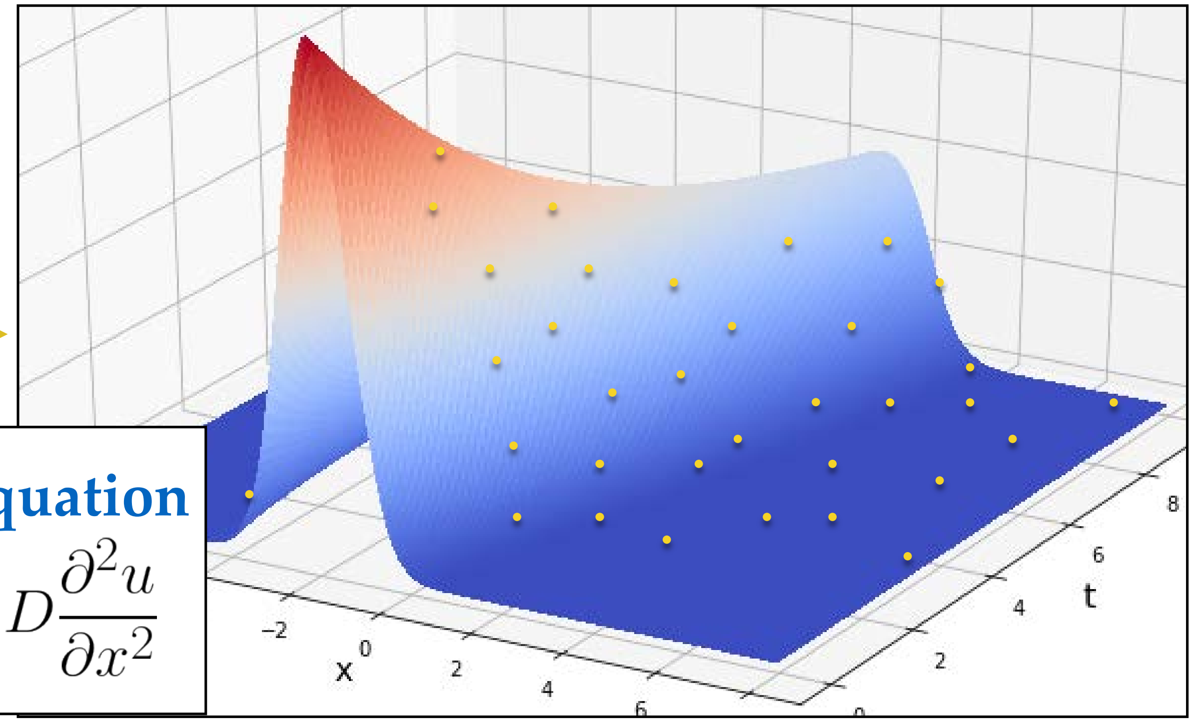
Measurement model

Measurement noise

Given data $u_{m,n}$ and $v\left(x_m, t_n\right) \approx \frac{\partial u}{\partial t}$, build $\mathcal{F}(\cdot) \approx \mathcal{N}(\cdot)$?

CASE STUDY: 1D BURGERS EQUATION inference

$u_{m,n}$



urgers Equation

$$u\frac{\partial u}{\partial x} = D\frac{\partial^2 u}{\partial x^2}$$

Representative microscopy data

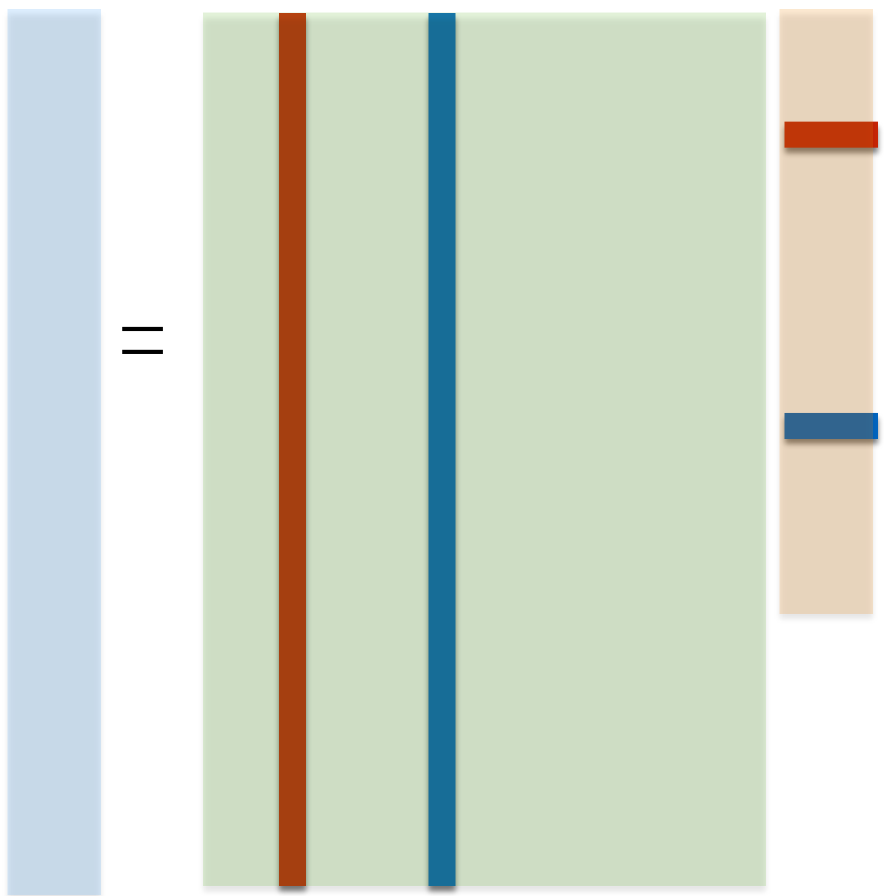
$$\begin{bmatrix} u_t(x_0,t_0) \\ u_t(x_1,t_0) \\ u_t(x_2,t_0) \\ \vdots \\ u_t(x_{n-1},t_m) \\ u_t(x_n,t_m) \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & u(x_0,t_0) & u_x(x_0,t_0) & \dots & u^5u_{xxx}(x_0,t_0) \\ 1 & u(x_1,t_0) & u_x(x_1,t_0) & \dots & u^5u_{xxx}(x_1,t_0) \\ 1 & u(x_2,t_0) & u_x(x_2,t_0) & \dots & u^5u_{xxx}(x_2,t_0) \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & u(x_{n-1},t_m) & u_x(x_{n-1},t_m) & \dots & u^5u_{xxx}(x_{n-1},t_m) \\ 1 & u(x_n,t_m) & u_x(x_n,t_m) & \dots & u^5u_{xxx}(x_n,t_m) \end{bmatrix}}_{\text{Example dictionary for state variable u in one spatial dimension}} \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \cdot \\ \cdot \\ \beta_p \end{bmatrix}$$

$U_t(N \times 1)$ $\Theta(N \times p)$ $\beta(p \times 1)$

N - #points sampled, p - dictionary size

The belief system - SPARSITY

Sparse - regression



$U_t(N \times 1)$ $\Theta(N \times p)$ $\beta(p \times 1)$

Least-squares formulation

$$\hat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} ||U_t - \Theta\beta||_2^2$$

- Linear-least square solution (N>p)

Sparse regression formulation

$$\hat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} ||U_t - \Theta\beta||_2^2 + \lambda||\beta||_0$$

data fitting term

Sparsity

- NP hard - heuristic algorithms exist

Rudy et al, Sci Advances (2017)

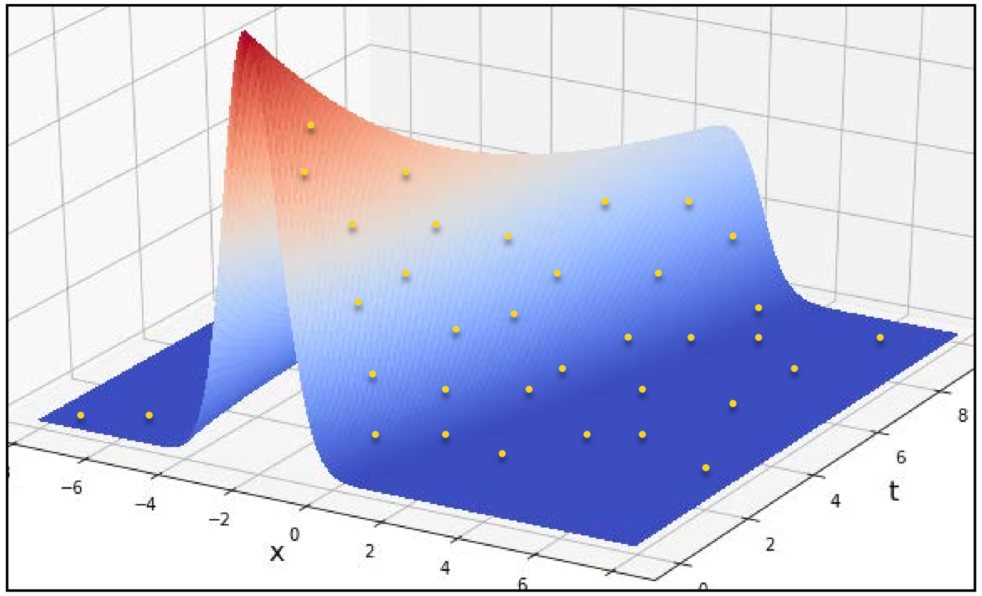
Relaxed sparse regression form

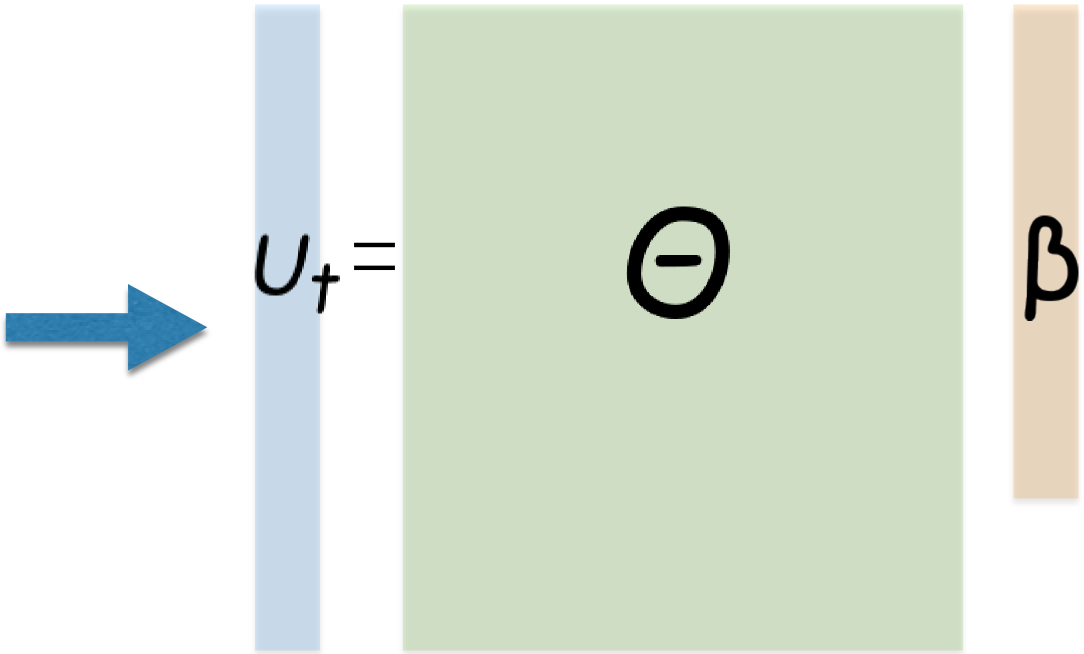
$$\hat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} ||U_t - \Theta\beta||_2^2 + \lambda||\beta||_{1,2}$$

- Lasso, Randmized Lasso, Elastic Net

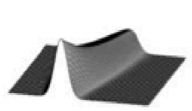
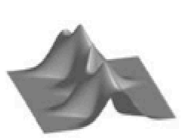
H Schaeffer et al, Royal Society (2016)

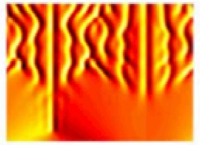
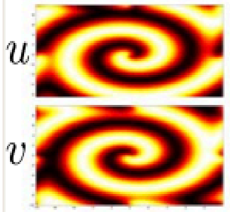
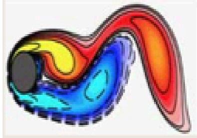
Success with sparse regression for PDE inference





$$\hat{\beta} = \arg\min_{\beta} \| U_t - \Theta\beta \|_2^2 + \lambda \|\beta\|_0$$

PDE		Form
	KdV	$u_t + 6uu_x + u_{xxx} = 0$
	Burgers	$u_t + uu_x - \epsilon u_{xx} = 0$
	Schrödinger	$iu_t + \frac{1}{2}u_{xx} - \frac{x^2}{2}u = 0$

	KS	$u_t + uu_x + u_{xx} + u_{xxxx} = 0$
u, v 	Reaction Diffusion	$u_t = 0.1\nabla^2 u + \lambda(A)u - \omega(A)v$ $v_t = 0.1\nabla^2 v + \omega(A)u + \lambda(A)v$ $A^2 = u^2 + v^2, \omega = -\beta A^2, \lambda = 1 - A^2$
	Navier-Stokes	$\omega_t + (\mathbf{u} \cdot \nabla)\omega = \frac{1}{Re}\nabla^2\omega$

Rudy et al, Sci Advances (2017)

Barriers to cross for application to real experimental data

$$\hat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} \|U_t - \Theta\beta\|_2^2 + \lambda\|\beta\|_0$$

data fitting term

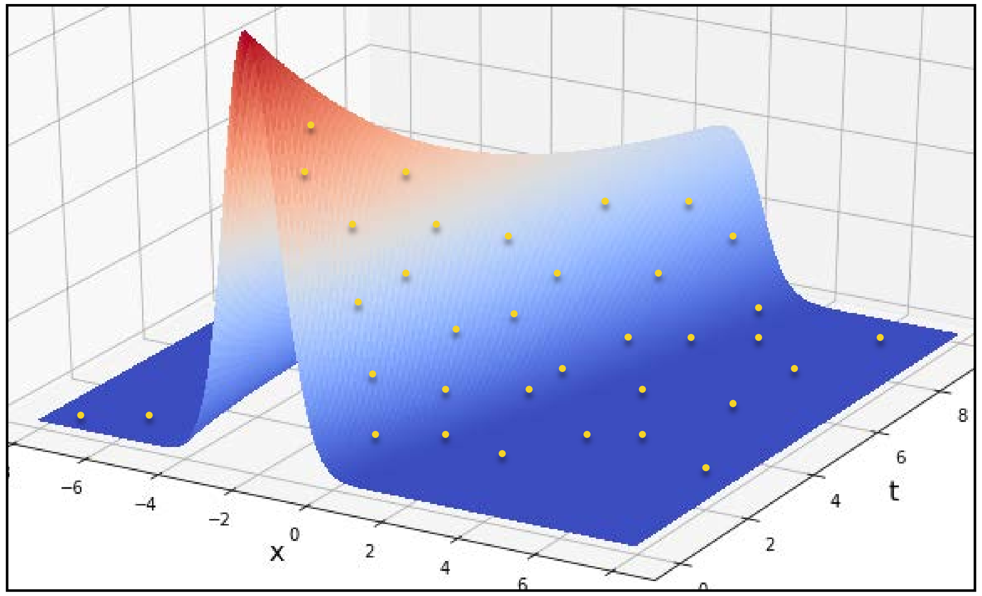
Sparsity

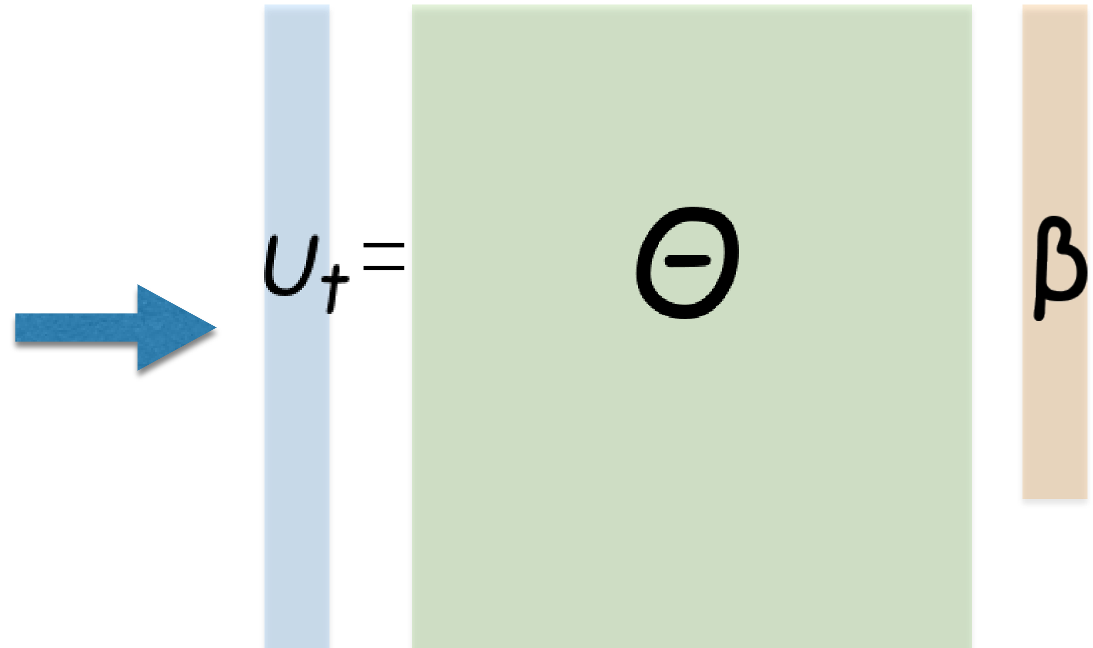
- Parametric dependency of the algorithm with change in design, What is the right **complexity parameter** lambda ?
- Does the algorithm always give the right support ? Is this the best way to solve the hard L_0 problem ?
- How can we compare between algorithms ? Can we guarantee consistency for varying design's ?

- Derivative computation from noisy data
- Noise performance (1%)

parameter dependence

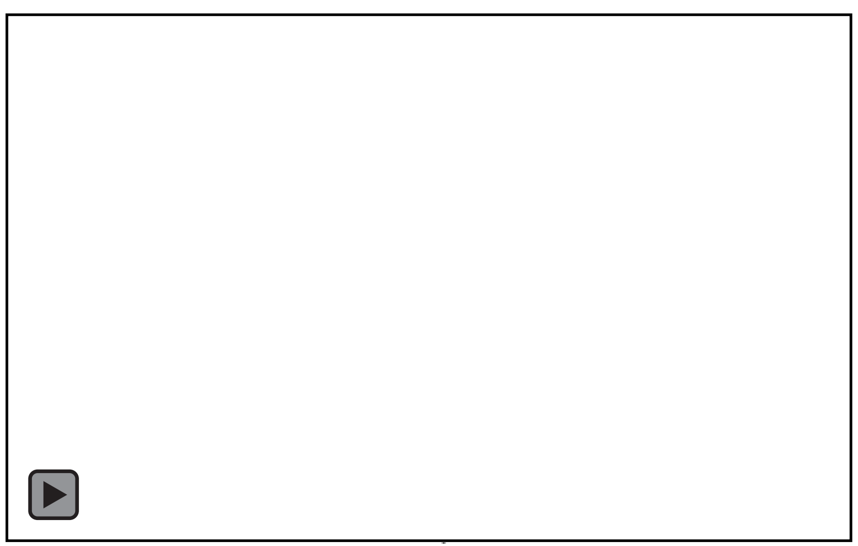
Regularization paths for 1D BURGERS EQUATION inference





$$\hat{\beta} = \arg\min_{\beta} \|U_t - \Theta\beta\|_2^2 + \lambda\|\beta\|_1$$

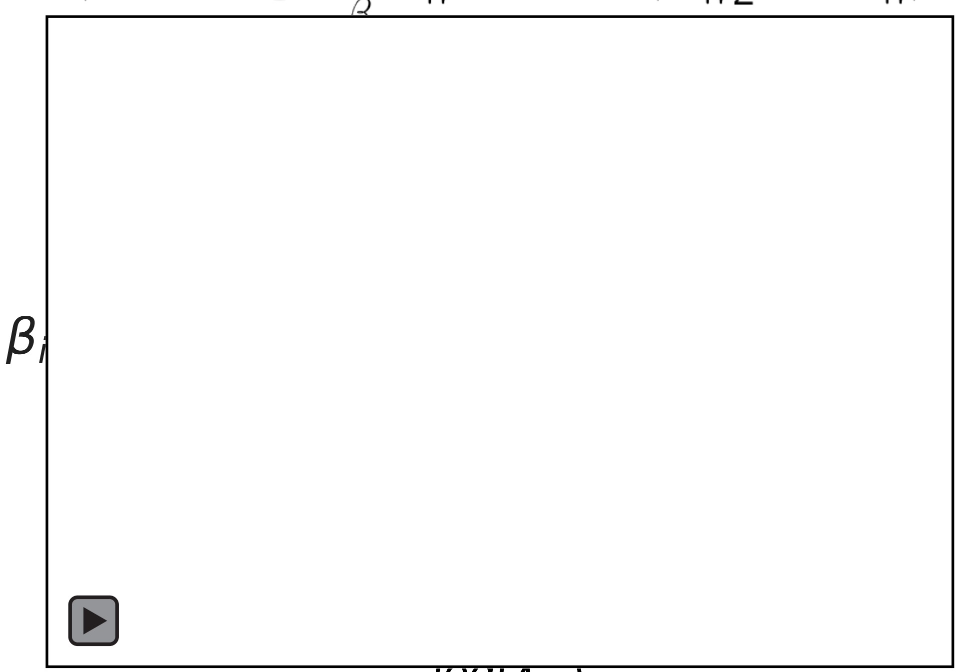
β_i



$-log(\lambda^*)$

$$\hat{\beta} = \arg\min_{\beta} \|U_t - \Theta\beta\|_2^2 + \lambda\|\beta\|_0$$

β_i

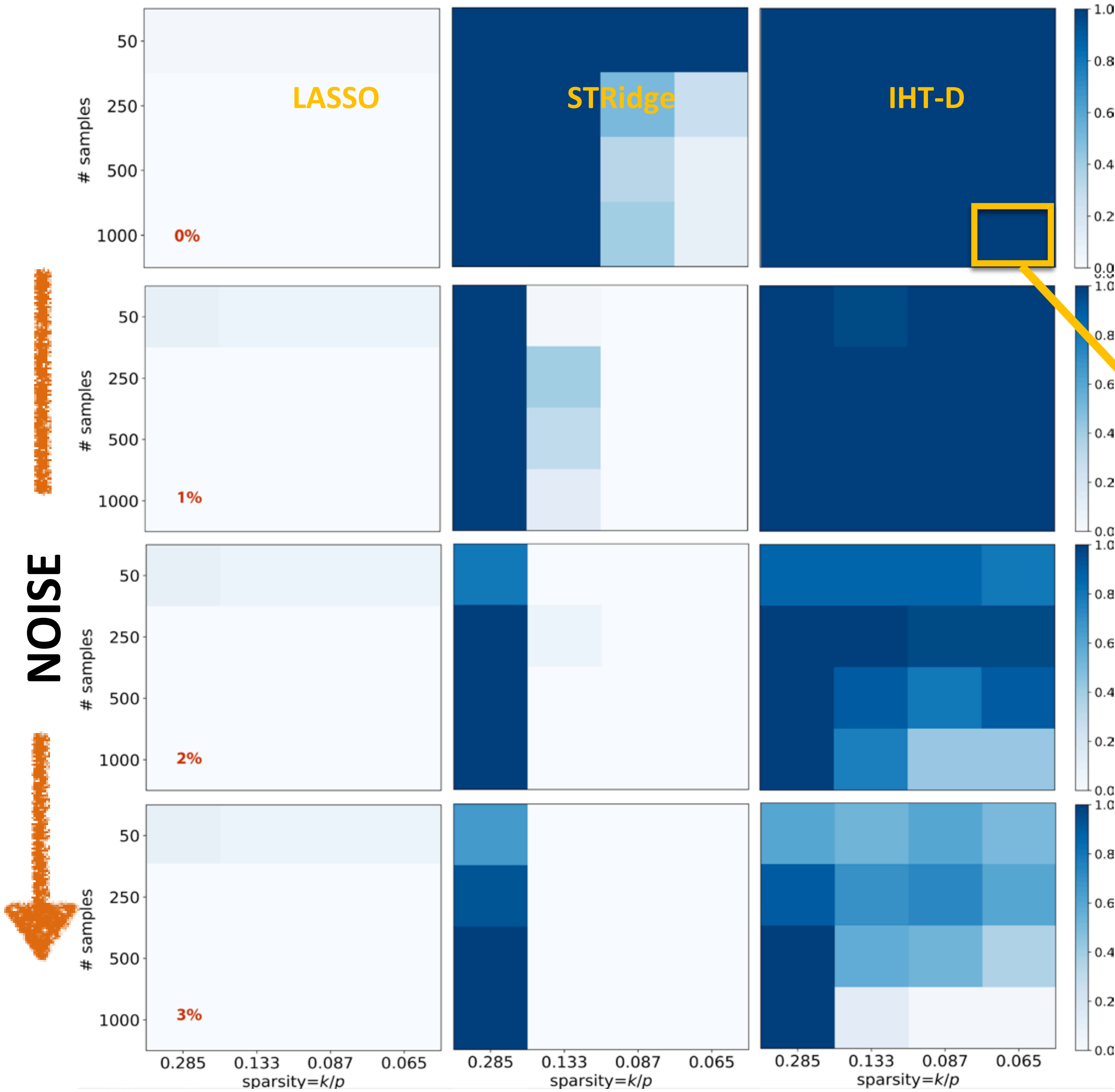


$-log(\lambda^*)$

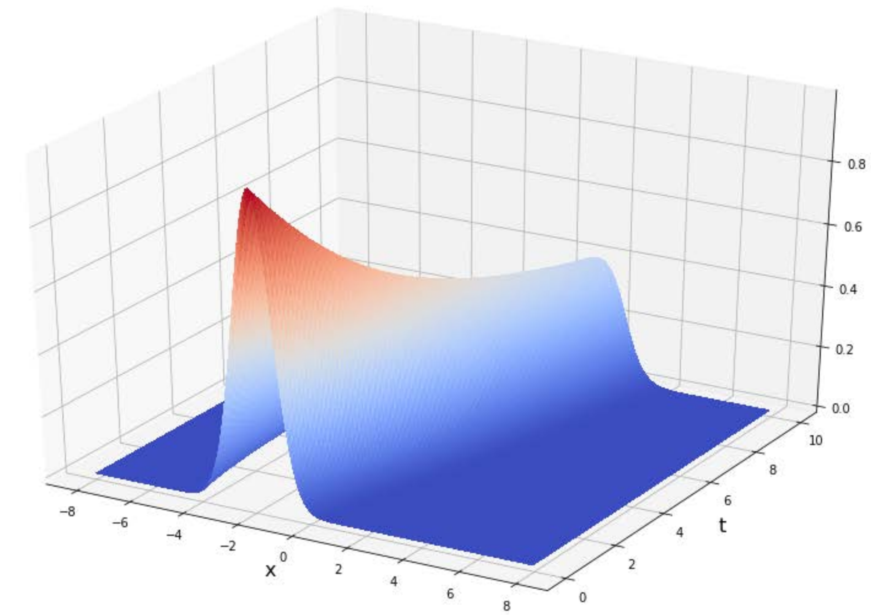
But which algorithm has the best recoverability?

Best sparsity-promoter

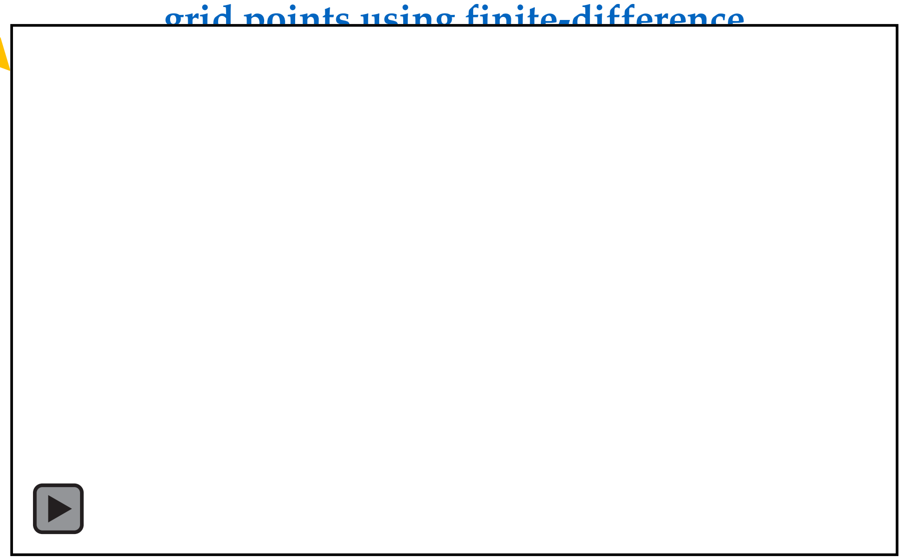
Which sparsity promoter ?



Success probability through oracle lambda for noise = 0-3%



Numerical simulation of 1D Burgers on 128 space grid points using finite-difference



k = # true components
p = dictionary size
STRidge parameter = 1e-5
Polynomial differentiation

IHT-D shows better performance in comparison to STRidge and LASSO

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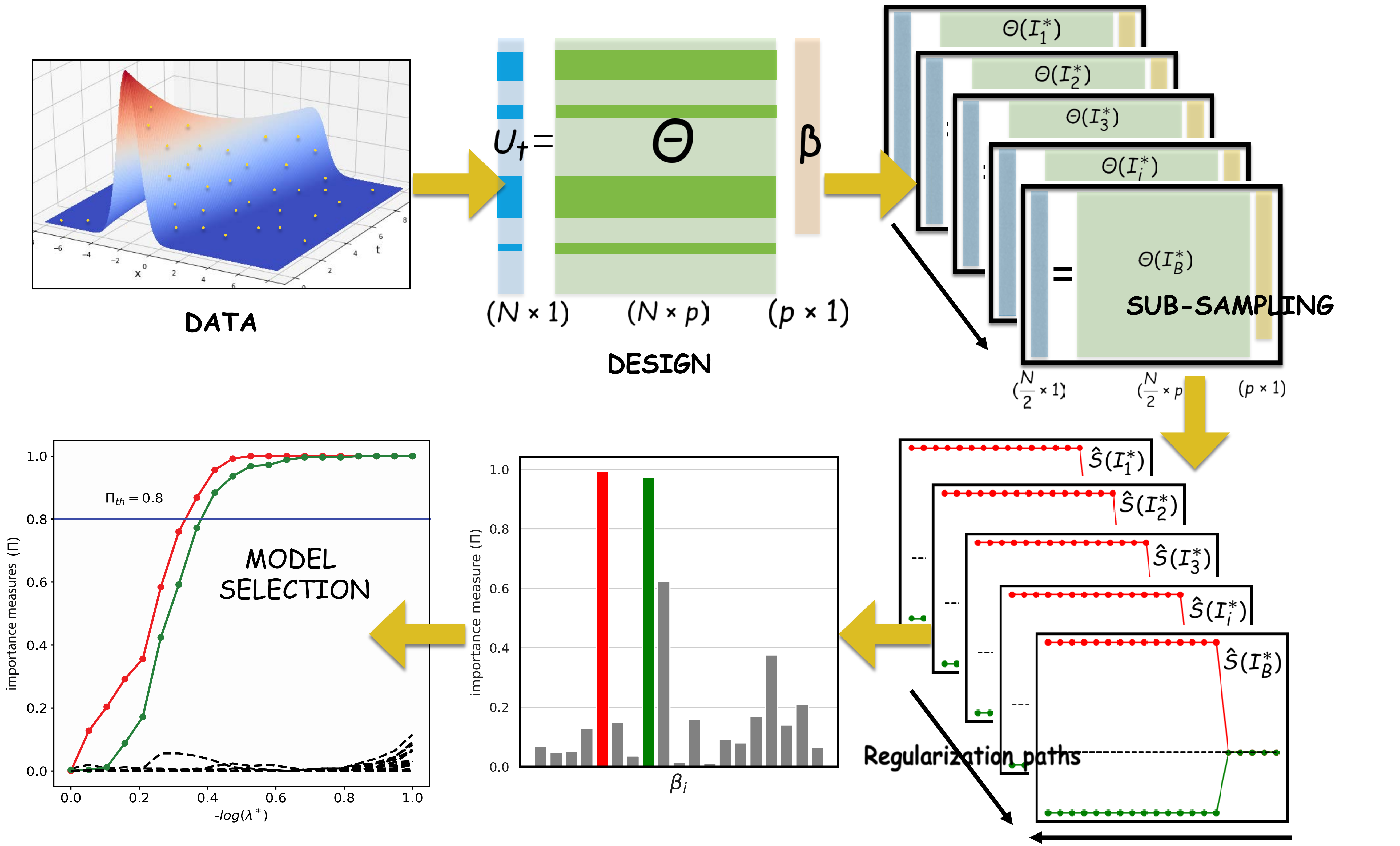
FLATIRON INSTITUTE Center for Computational Mathematics

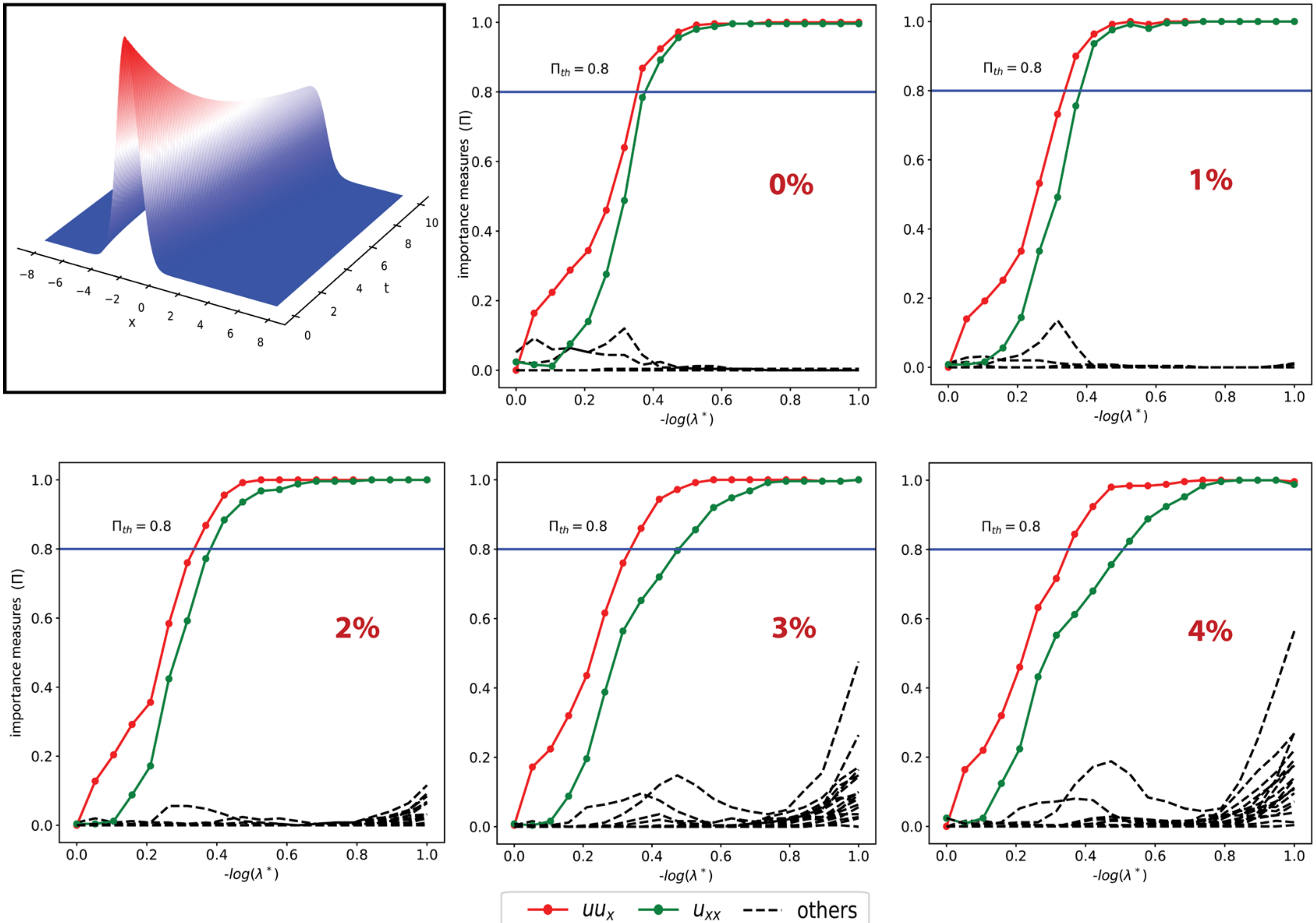
CBG Max Planck Institute of Molecular Cell Biology and Genetics parameter dependence

Stability-based model selection for 1D BURGERS EQUATION



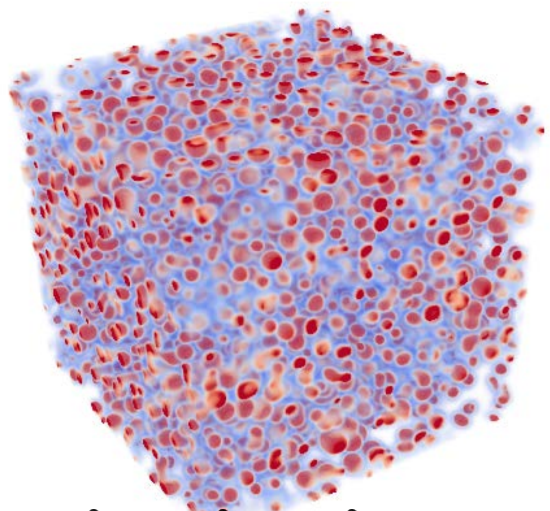
Robustness/ Consistency

Stability-based model selection for 1D BURGERS EQUATION



Design N=200, p=20

Stability-based model selection for 3D Gray-Scott reaction diffusion system

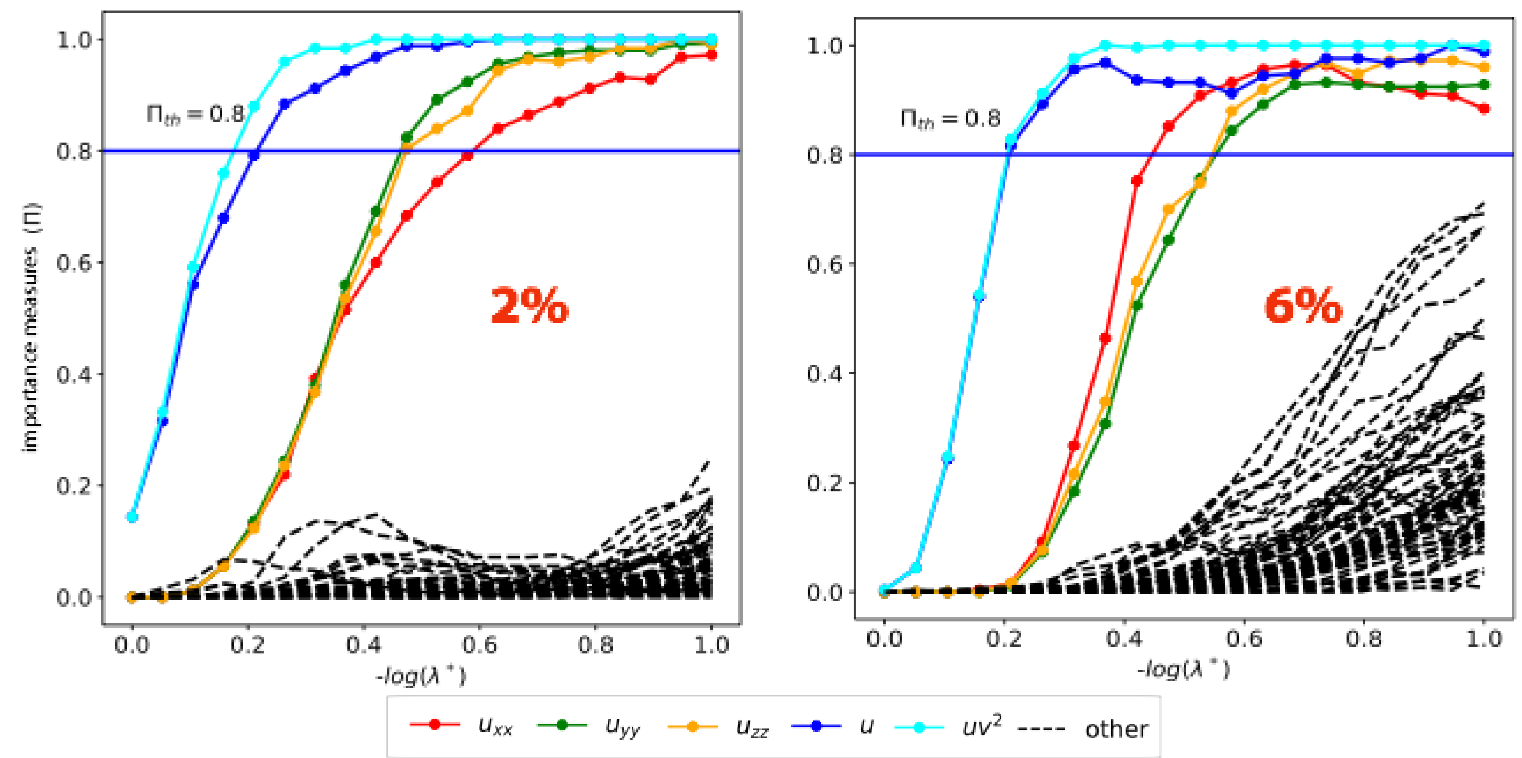


$$u_t = D_u \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) - uv^2 + f(1-u),$$

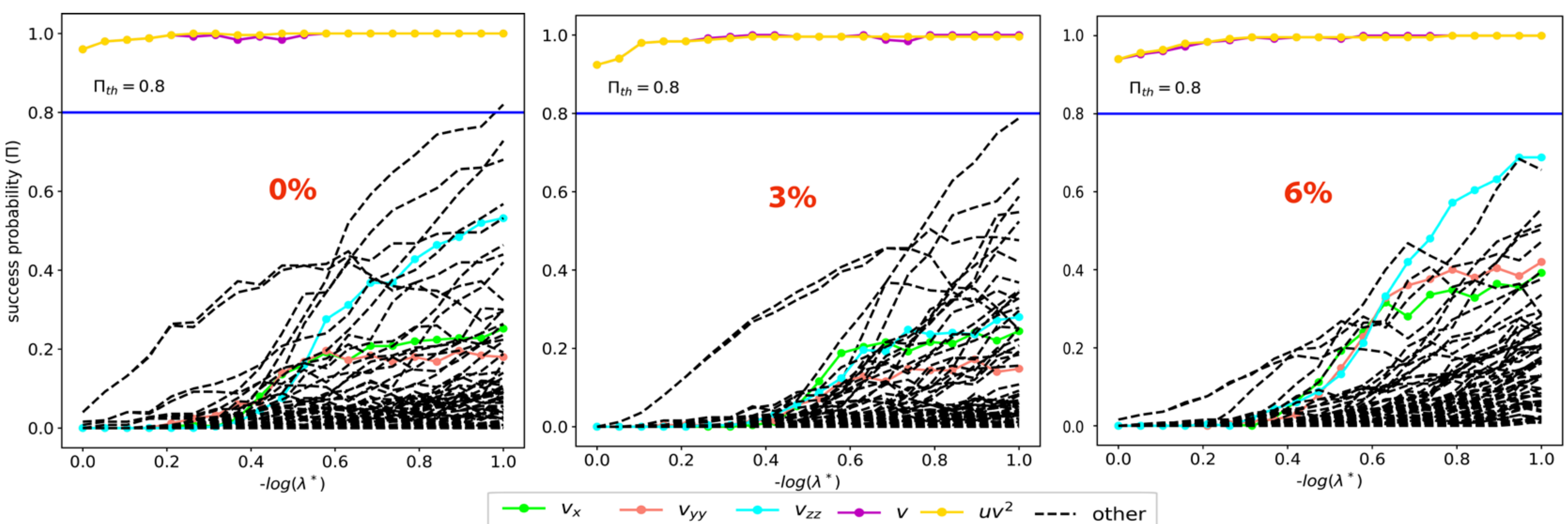
$$v_t = D_v \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + uv^2 - (f+k)v.$$

$$k = 0.053,\ f = 0.014,\ D_u = 2e^{-5},\ D_v = 1e^{-5}$$

periodic boundary conditions

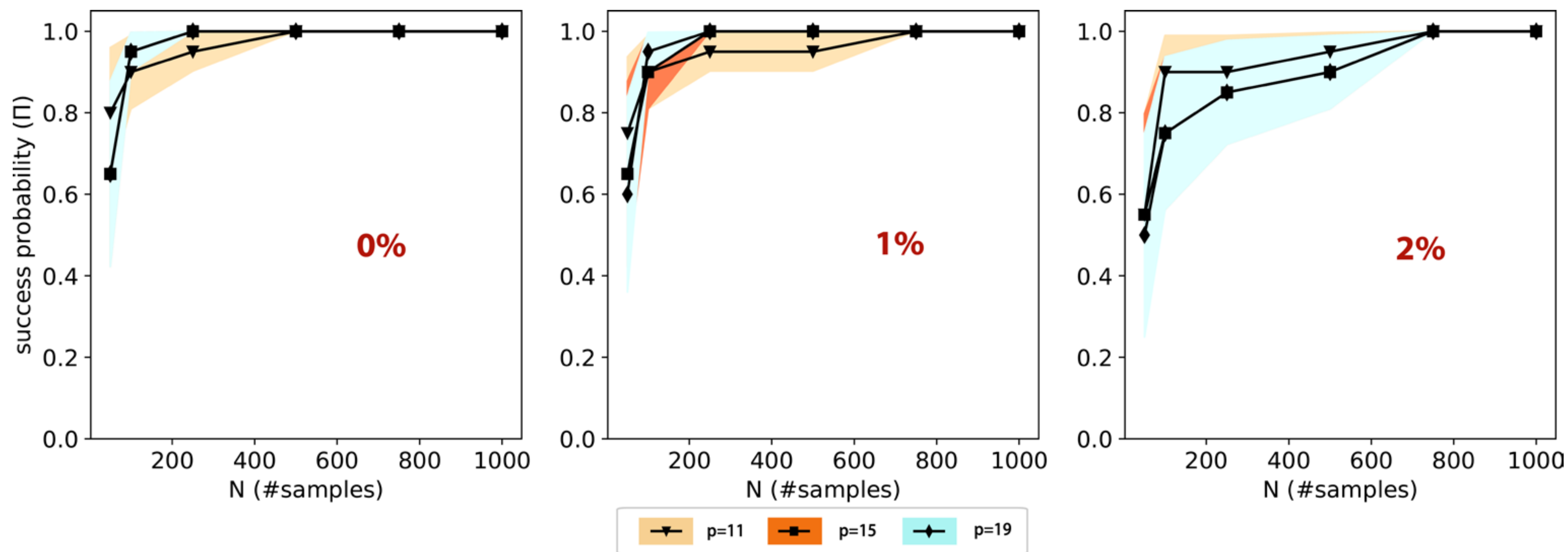


Design N=400, p=69

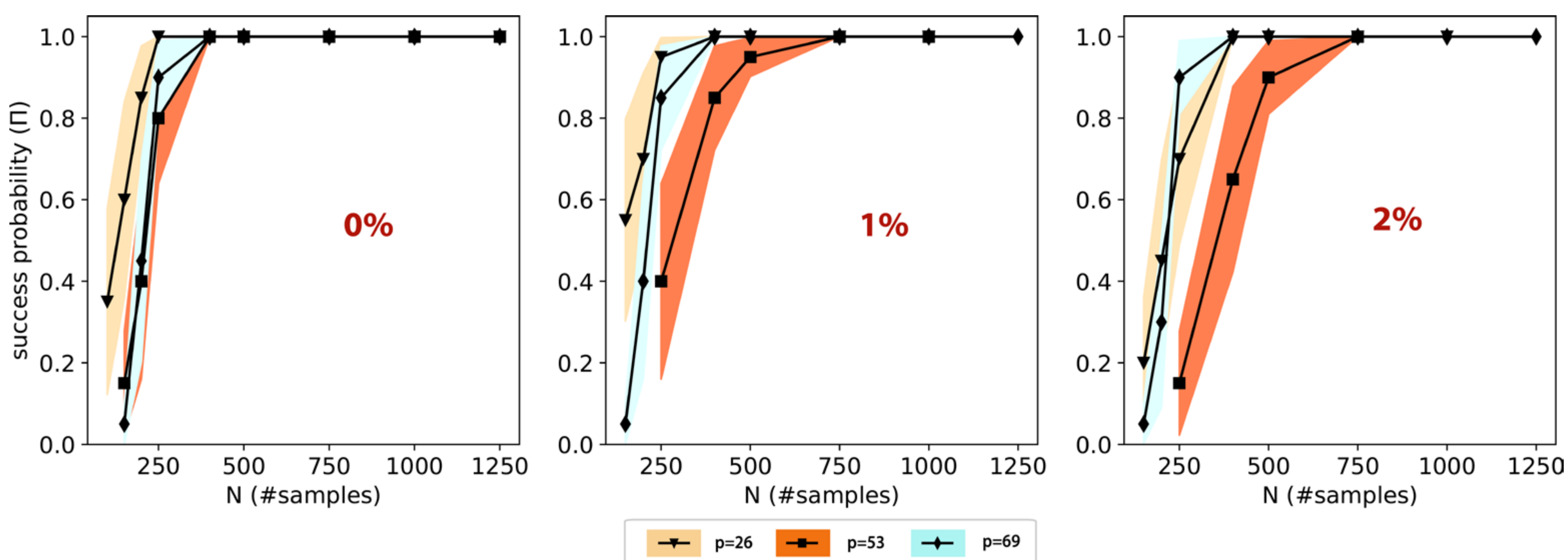


Achievability results

1D Burgers equation

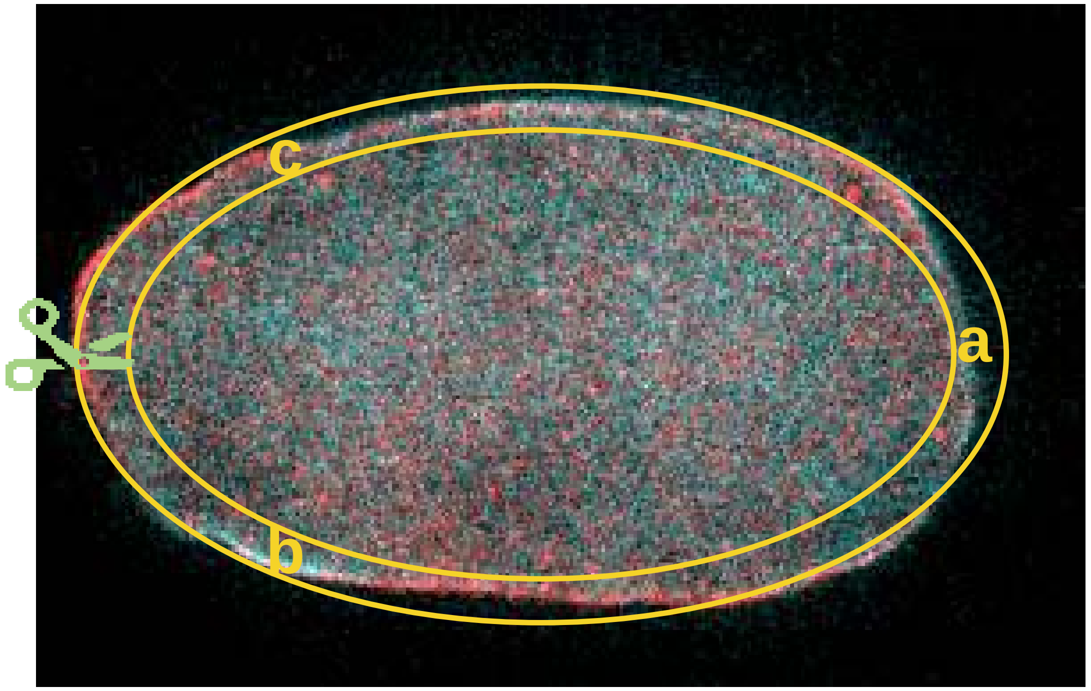


3D Gray-scott equation

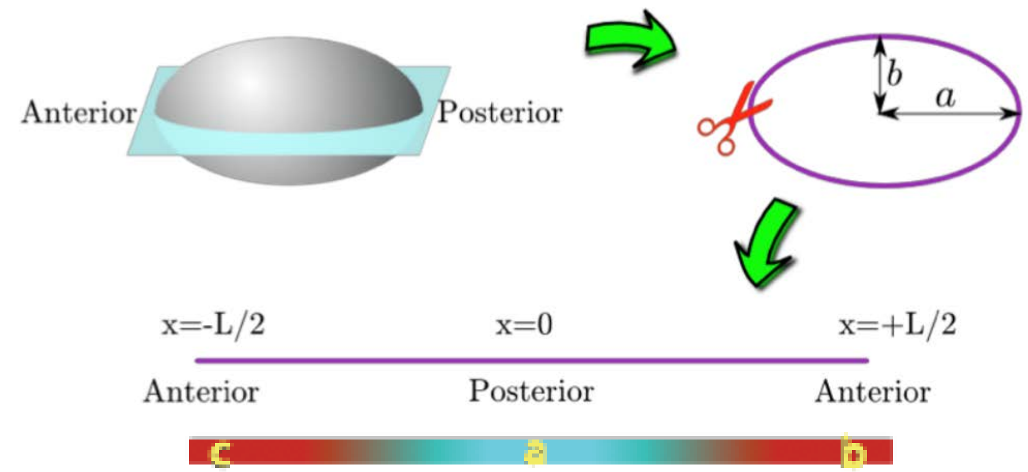


Experimental data

PAR Proteins patterning in the *Caenorhabditis elegans* zygote



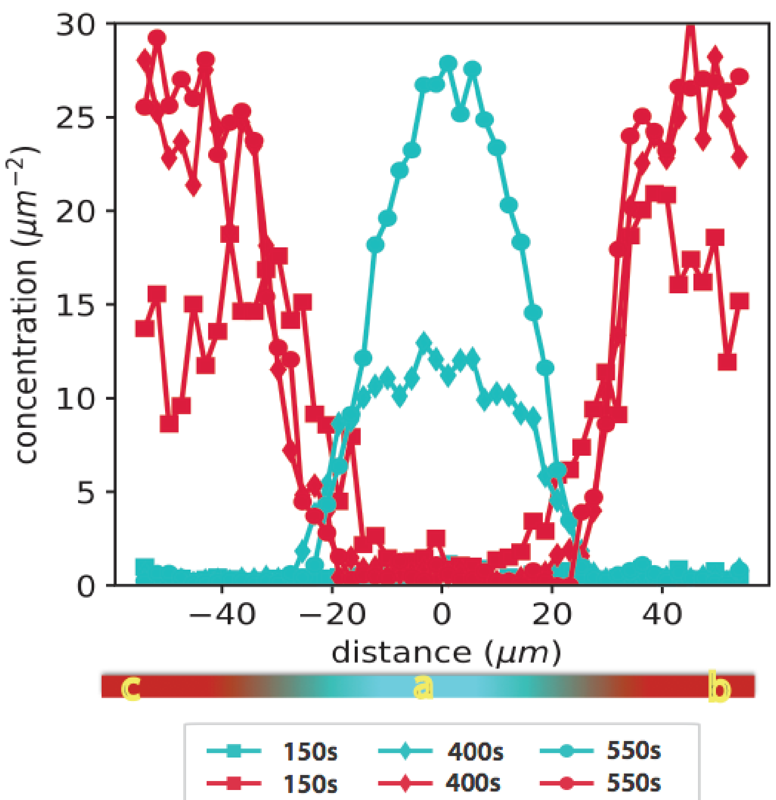
Grill lab, MPI-CBG

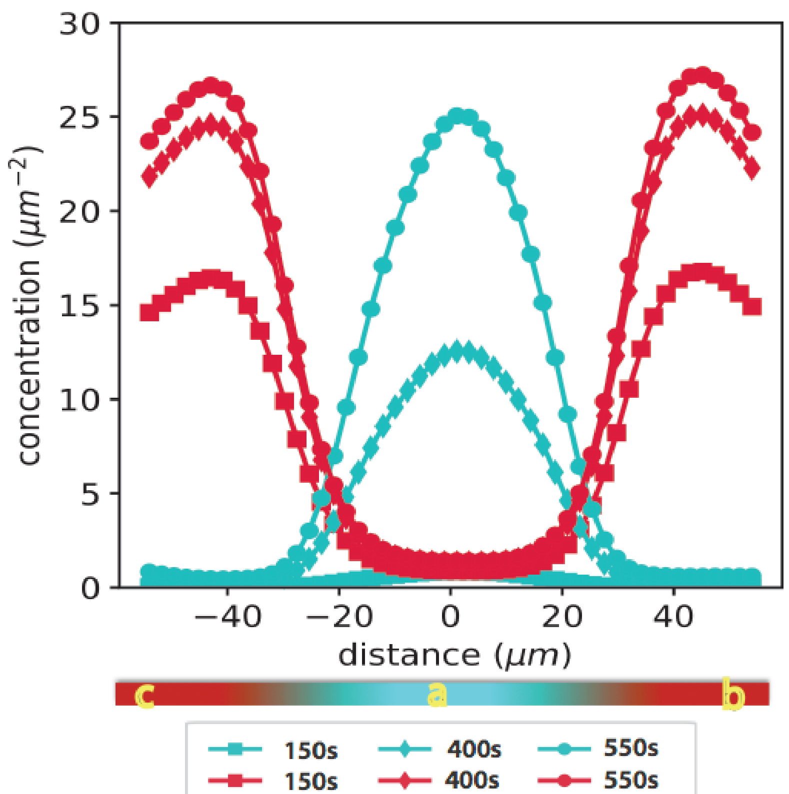


$$\partial_t A = D_A \partial_x^2 A - \partial_x(vA) + R_A \qquad R_A = k_{on,A} A_{cyto} - k_{off,A} A - k_{AP} P^{\alpha} A$$

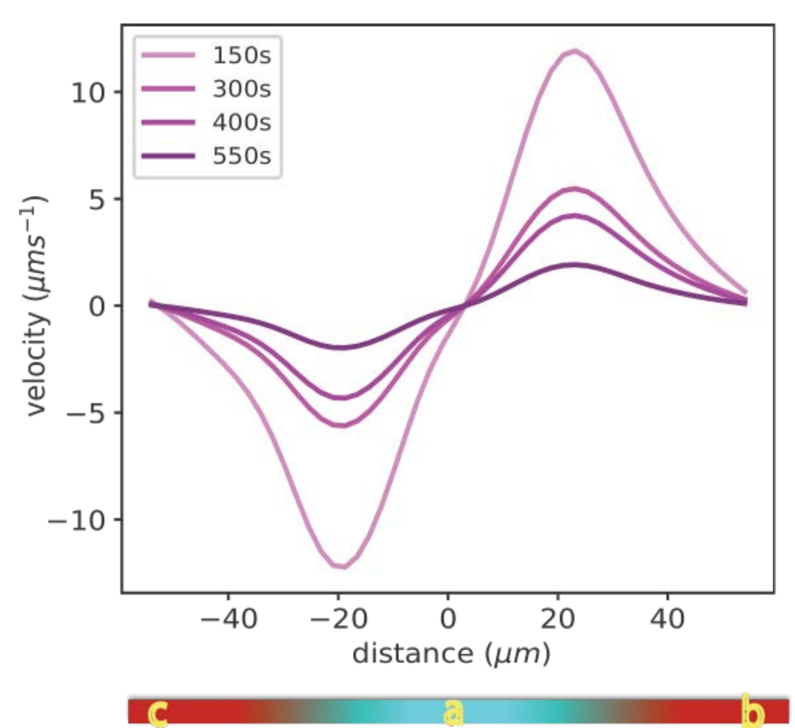
$$\partial_t P = D_P \partial_x^2 P - \partial_x(vP) + R_P \qquad R_P = k_{on,P} P_{cyto} - k_{off,P} P - k_{PA} A^{\beta} P$$

Protein Concentration



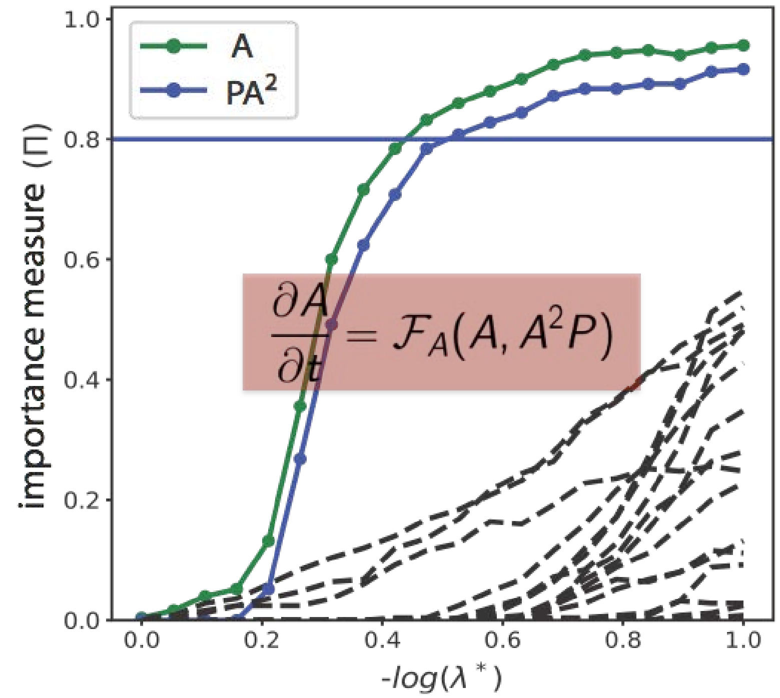


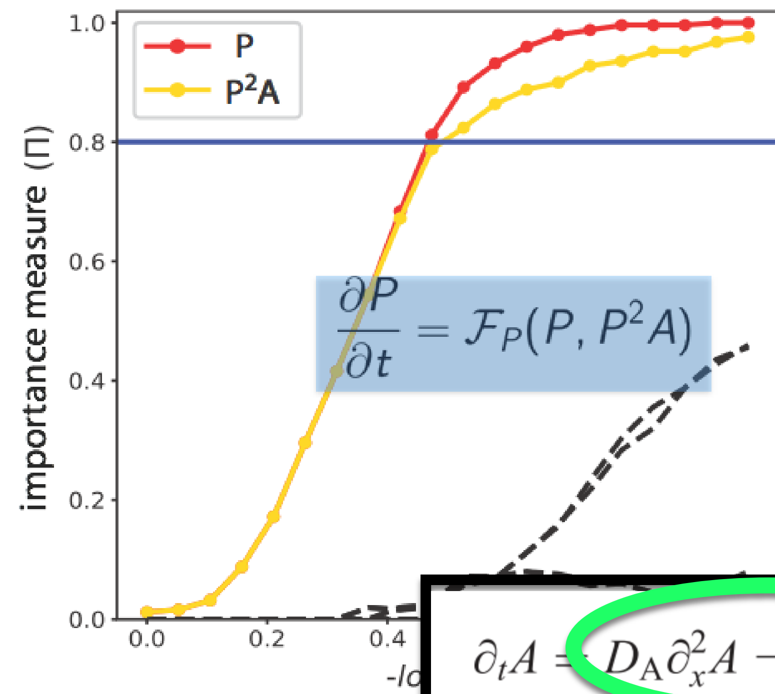
cortical flow field

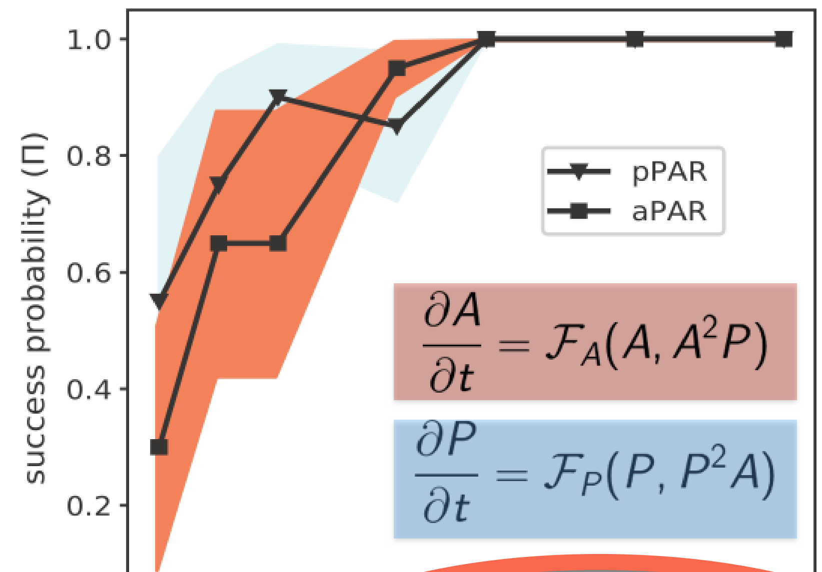


Goehring et al, Science (2011)

Stability-based PDE inference for PAR system experimental data



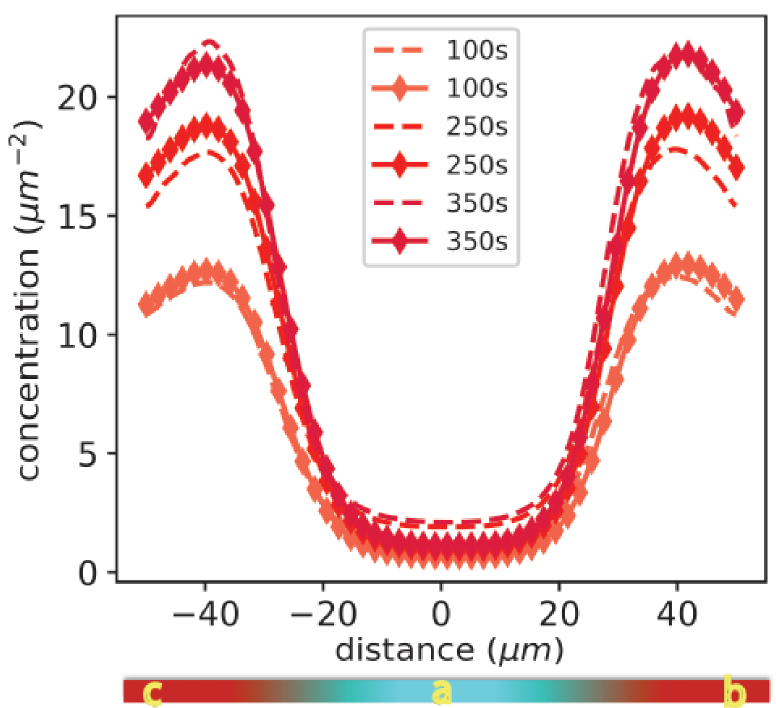


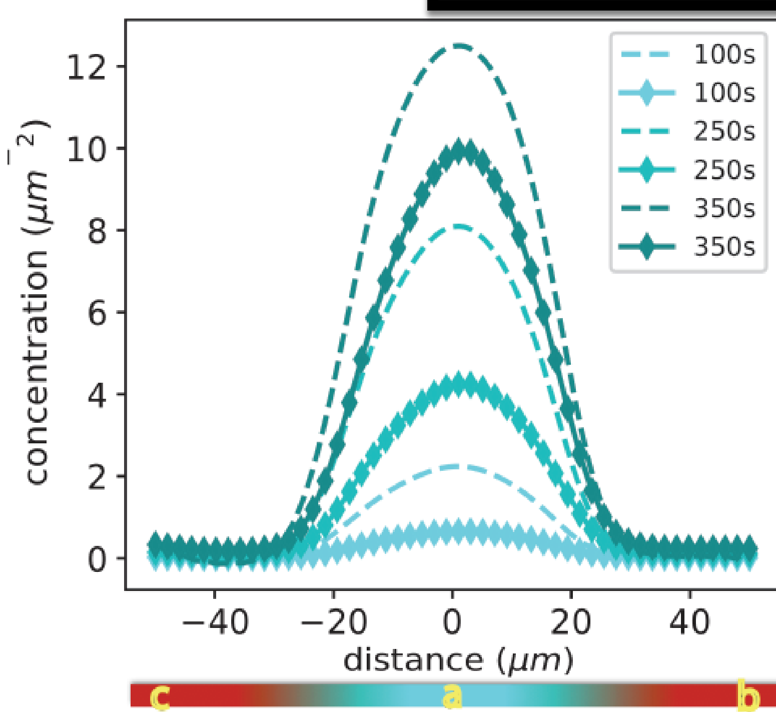


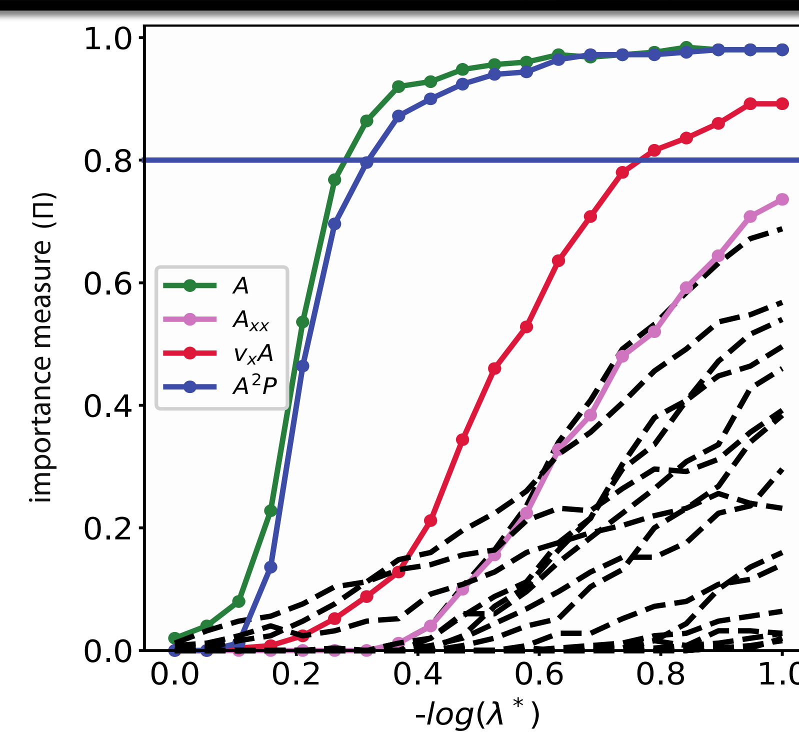
$$\partial_t A = D_A \partial_x^2 A - \partial_x(vA) + R_A \qquad R_A = k_{on,A} A_{cyto} - k_{off,A} A - k_{AP} P^{\alpha} A$$

$$\partial_t P = D_P \partial_x^2 P - \partial_x(vP) + R_P \qquad R_P = k_{on,P} P_{cyto} - k_{off,P} P - k_{PA} A^{\beta} P$$

Design N=500, p=20







Next steps

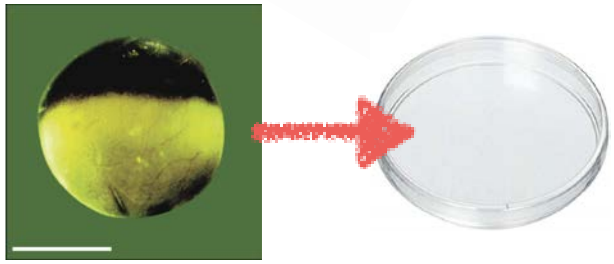
What kind of problems can be addressed with such methods ?

red flour beetle
(Tribolium castaneum)

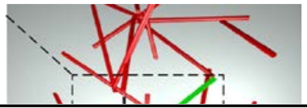
Tissue flows in Tribolium embryo
(Tomancak lab, MPI-CBG)

Can active gel mechanical models be Inferred from the intensity and flow data ?

Xenopus laevis



J Foster, eLife(2015)

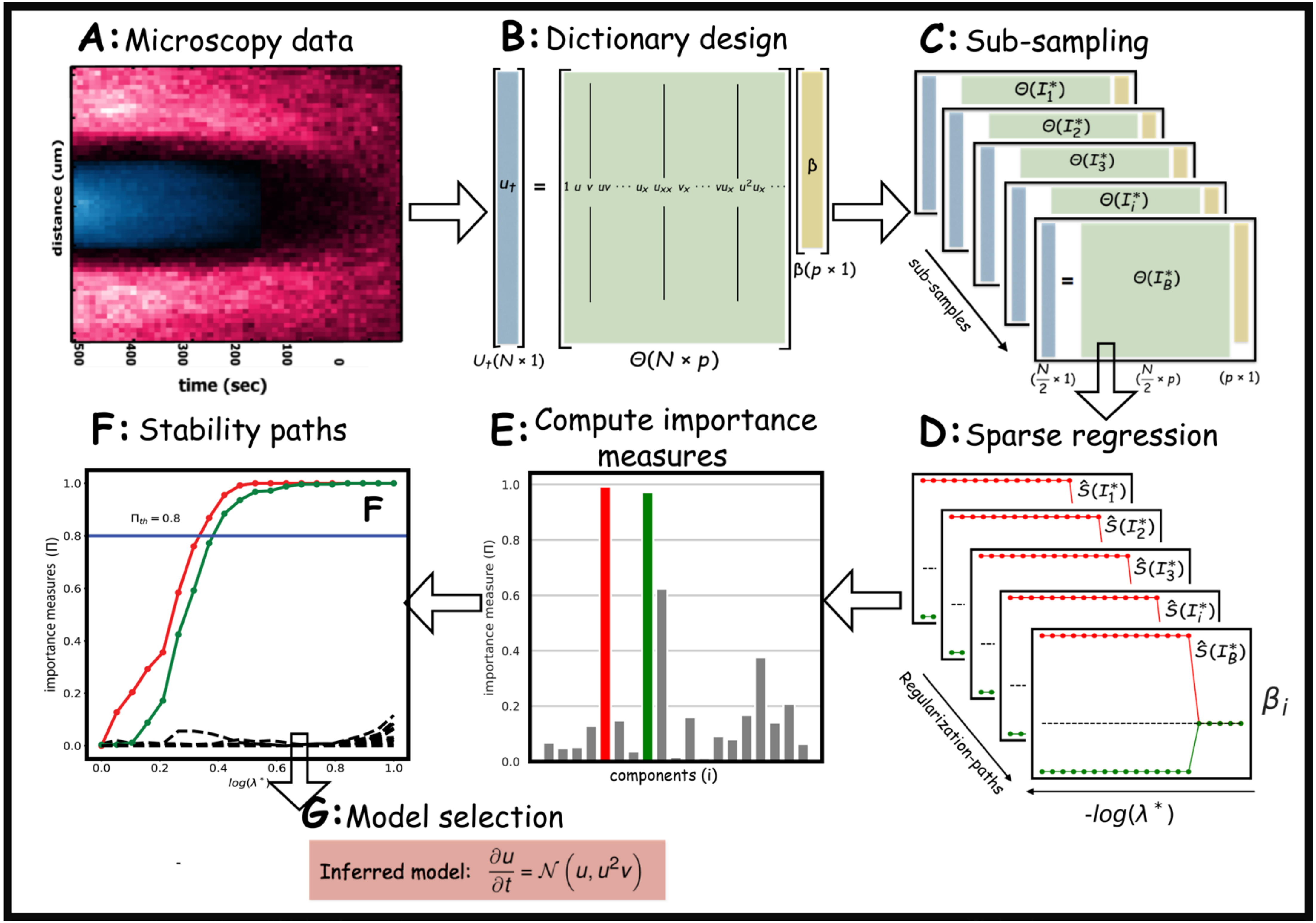


Sebastian Fürthauer (Flatiron Institute,NY)

Can we bridge the gap using data-driven coarse-grained modeling ?

center for systems biology dresden | TECHNISCHE UNIVERSITÄT DRESDEN | FLATIRON INSTITUTE Center for Computational Mathematics | CBG Max Planck Institute of Molecular Cell Biology and Genetics

Stability-based PDE inference from limited noisy spatial-temporal data
data



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THANK YOU