HelmholtzZentrum münchen
German Research Center for Environmental Health

COMBINE16, Newcastle

AMICI: An ODE simulation framework for sensitivity analysis of large-scale models

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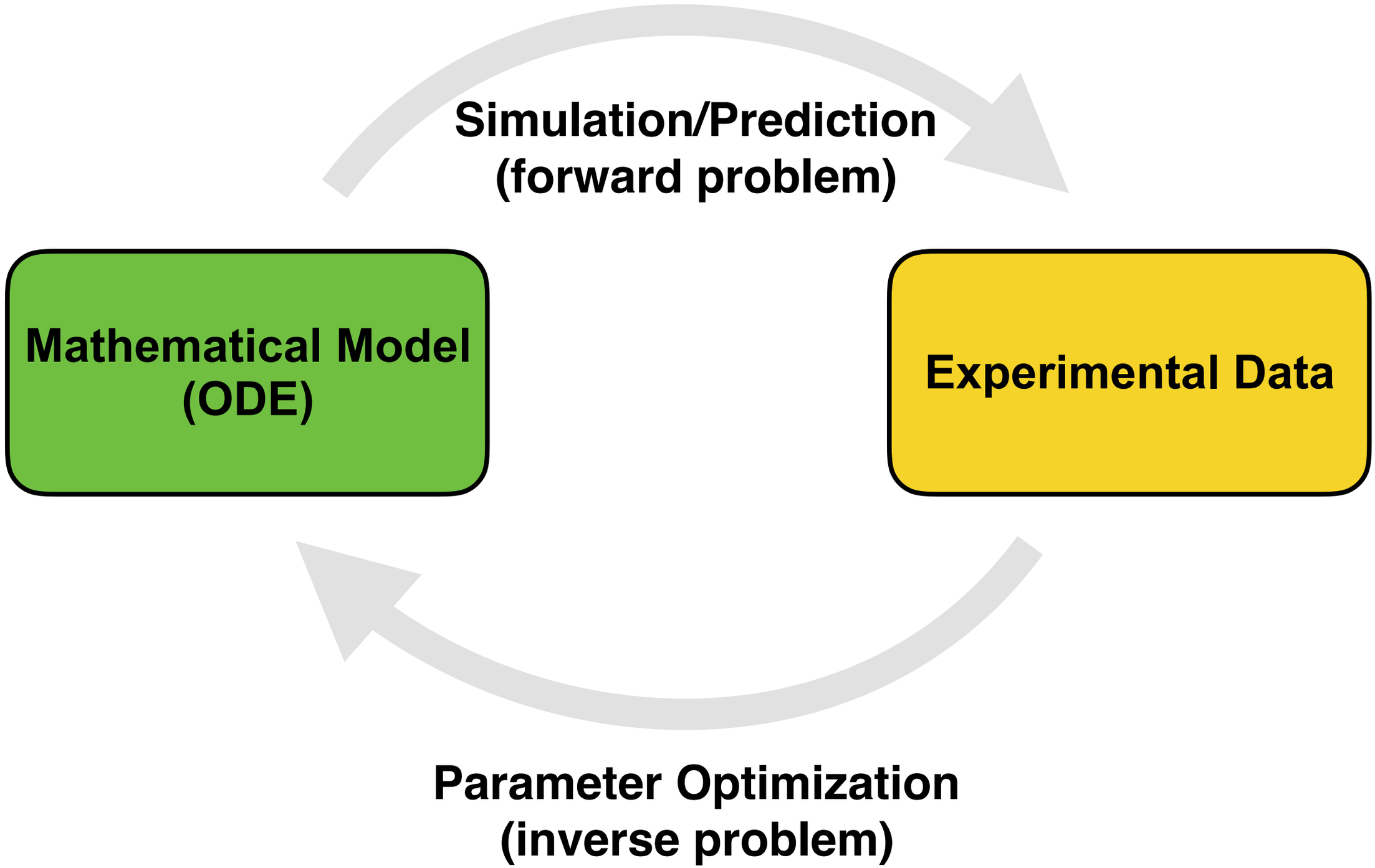
Forward/Inverse Problem



Optimization Algorithms

Global Optimization

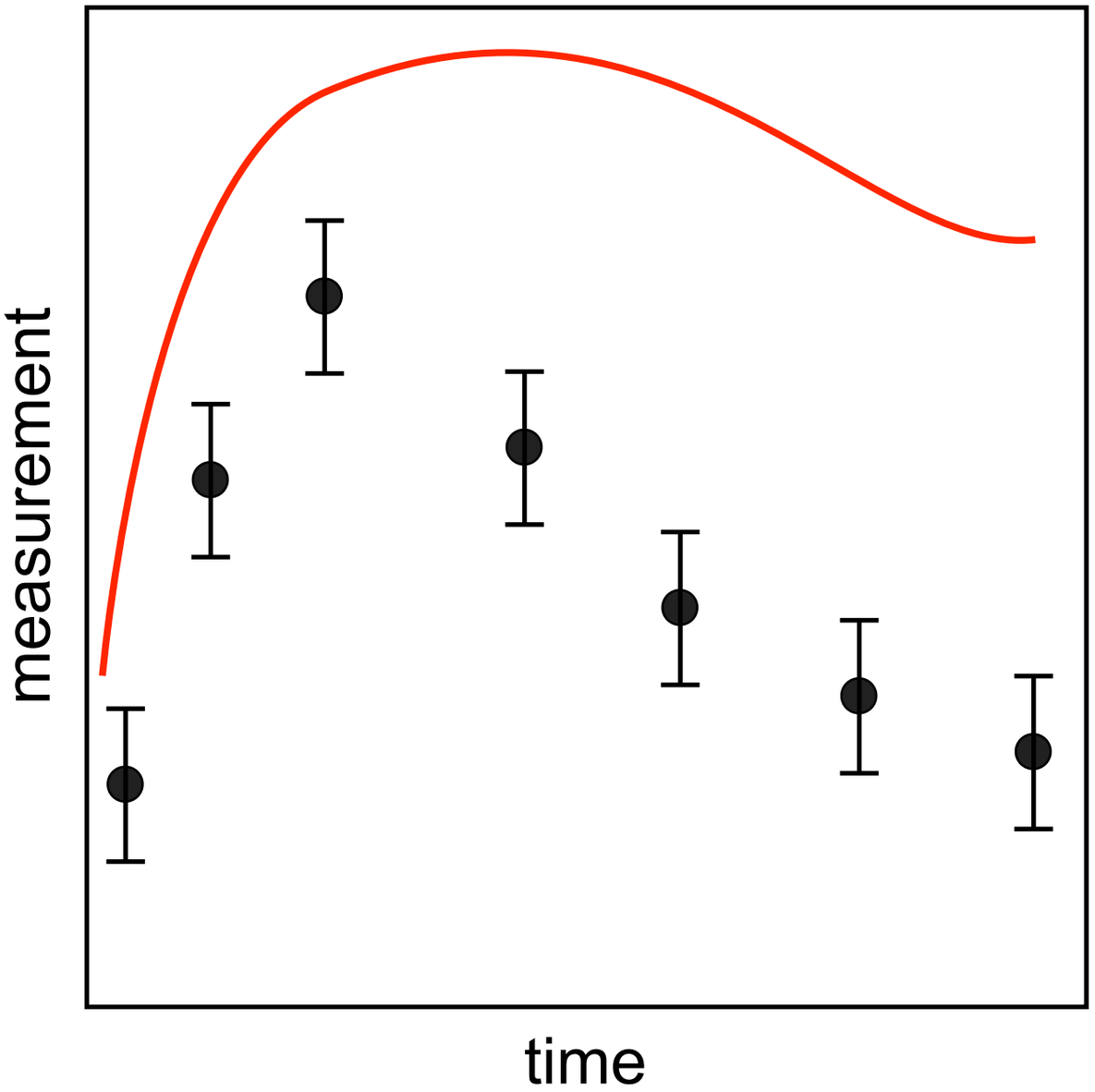
Heuristics

Local Optimization

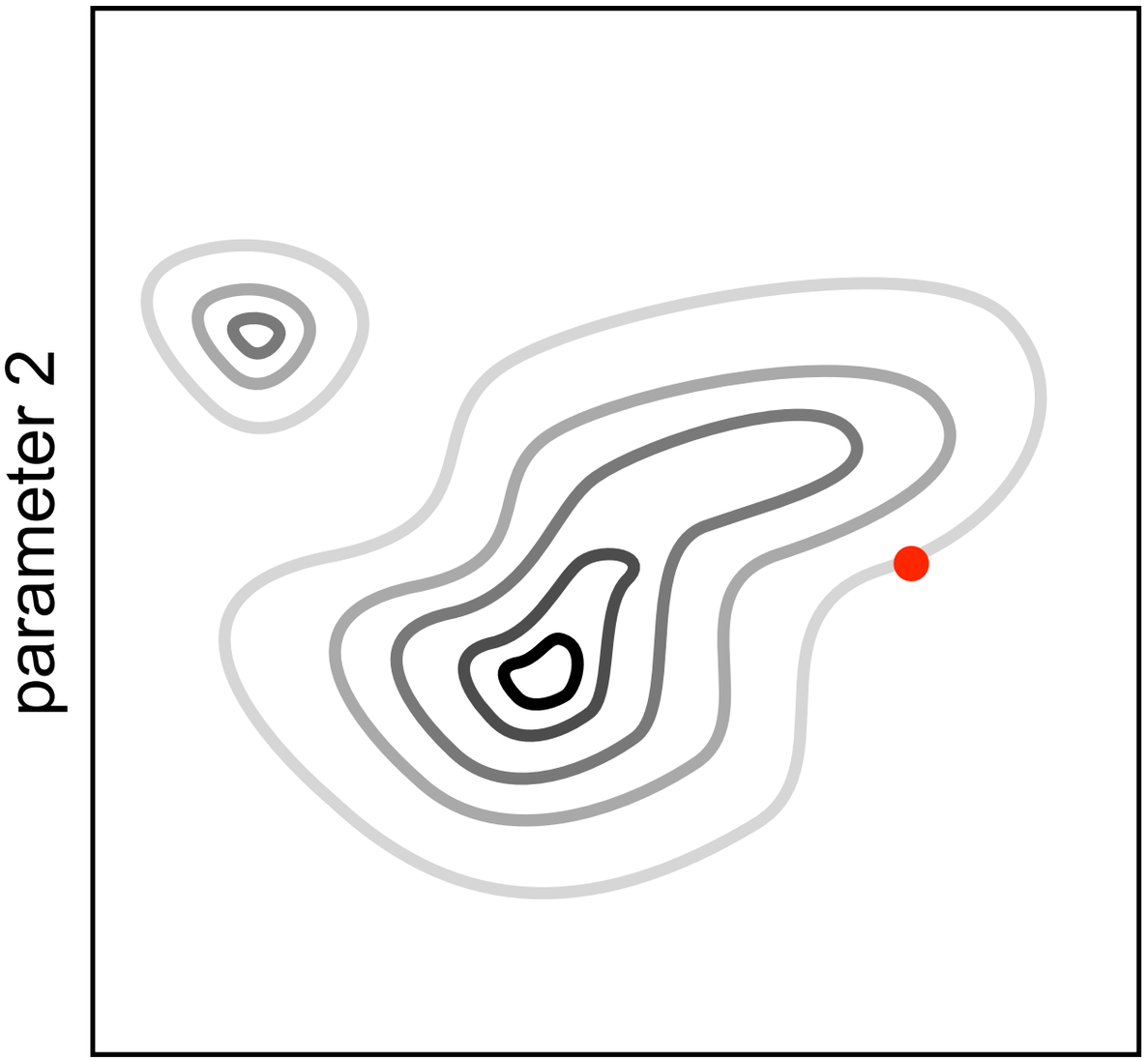
in our group: multi-start local gradient based optimization

Parameter Estimation

Model-data comparison



Objective function landscape



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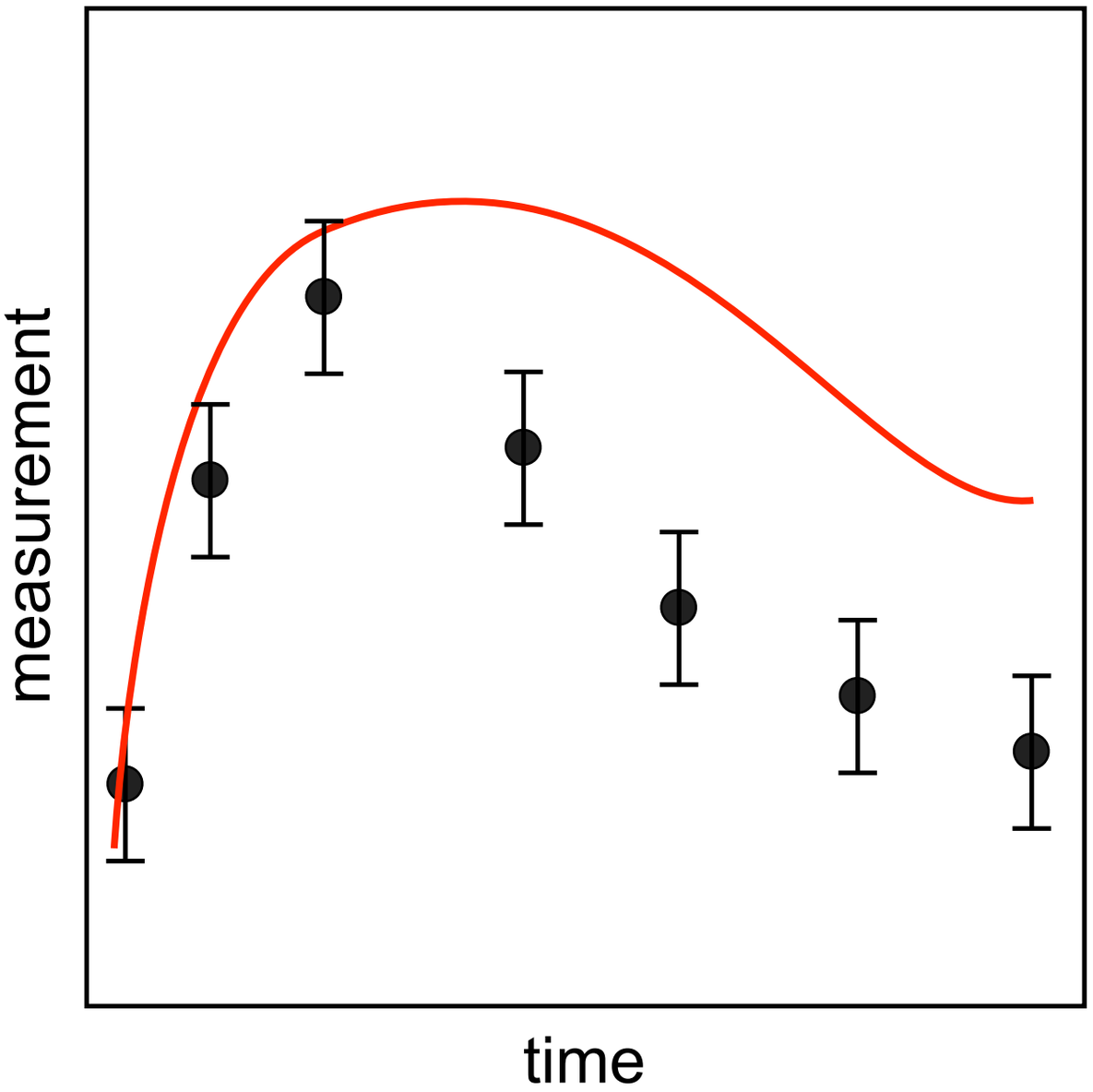

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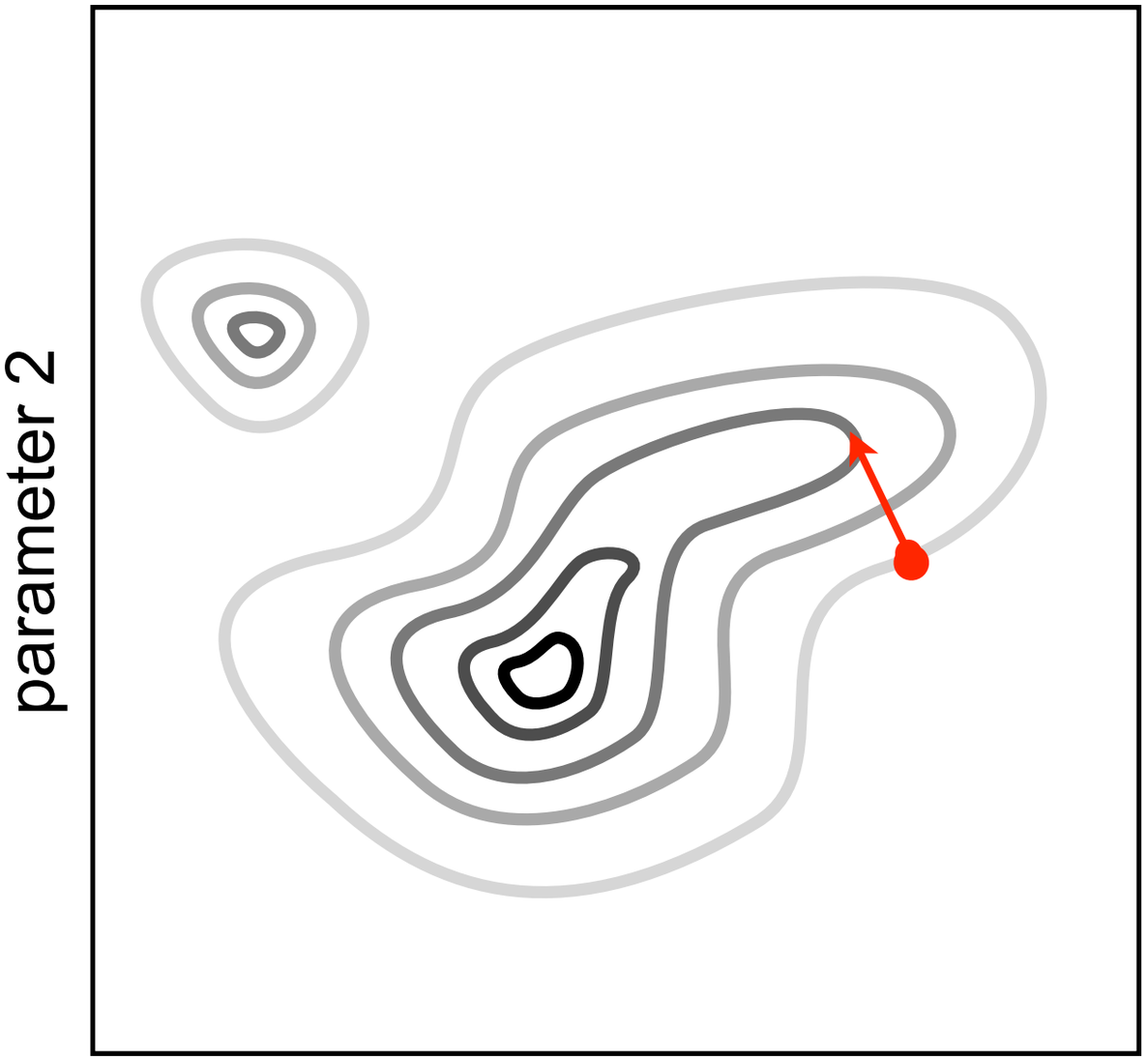

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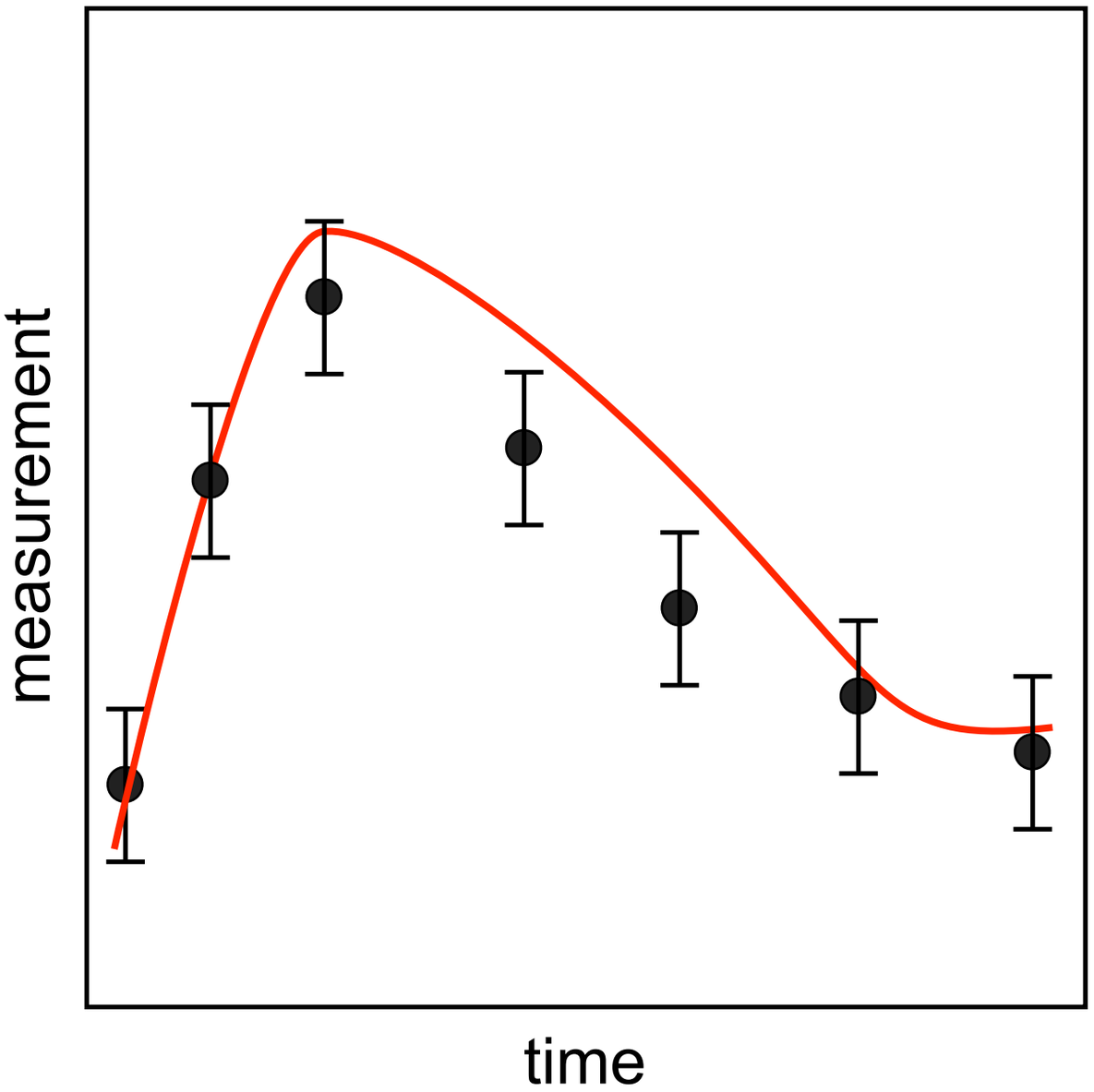

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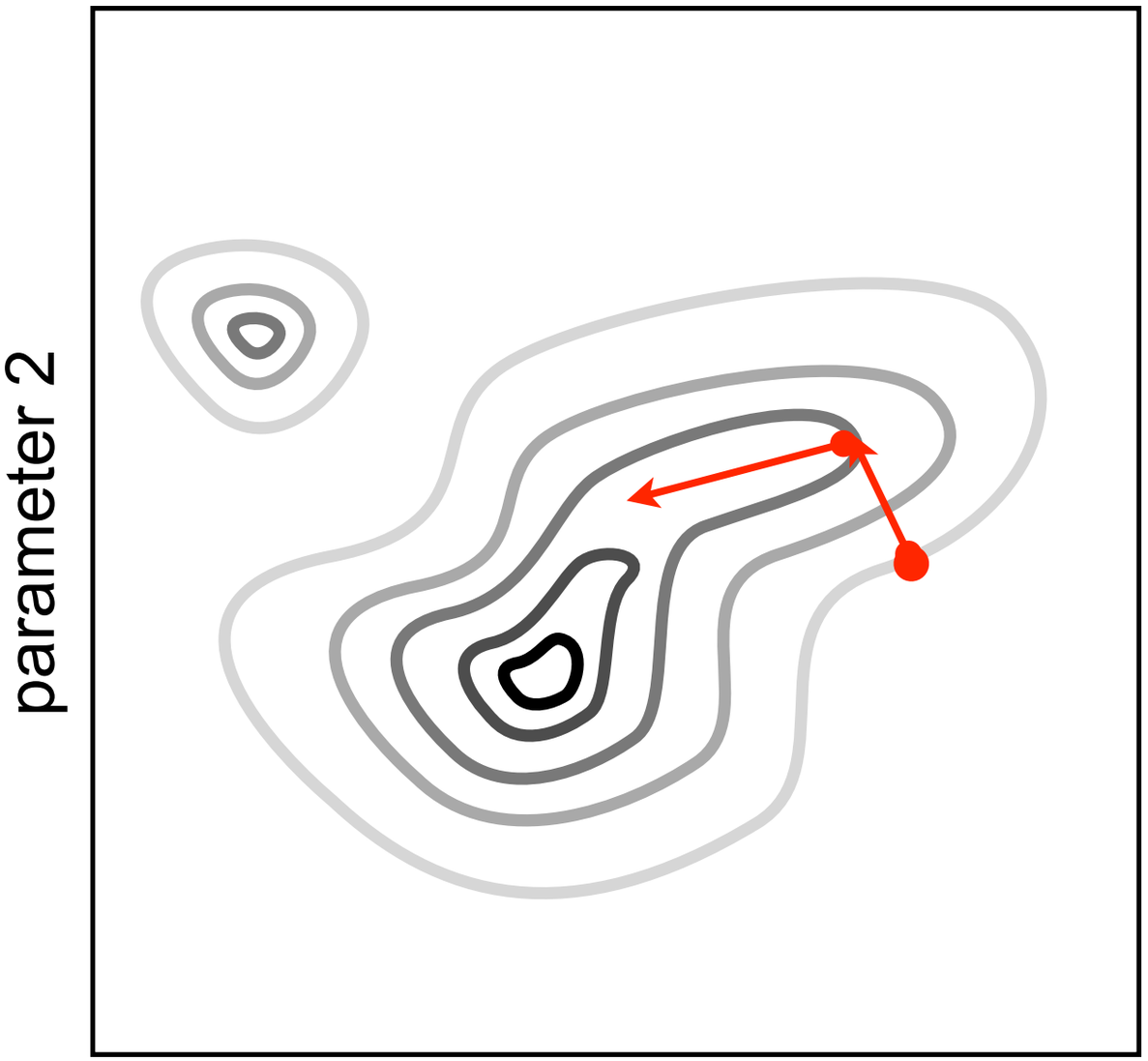

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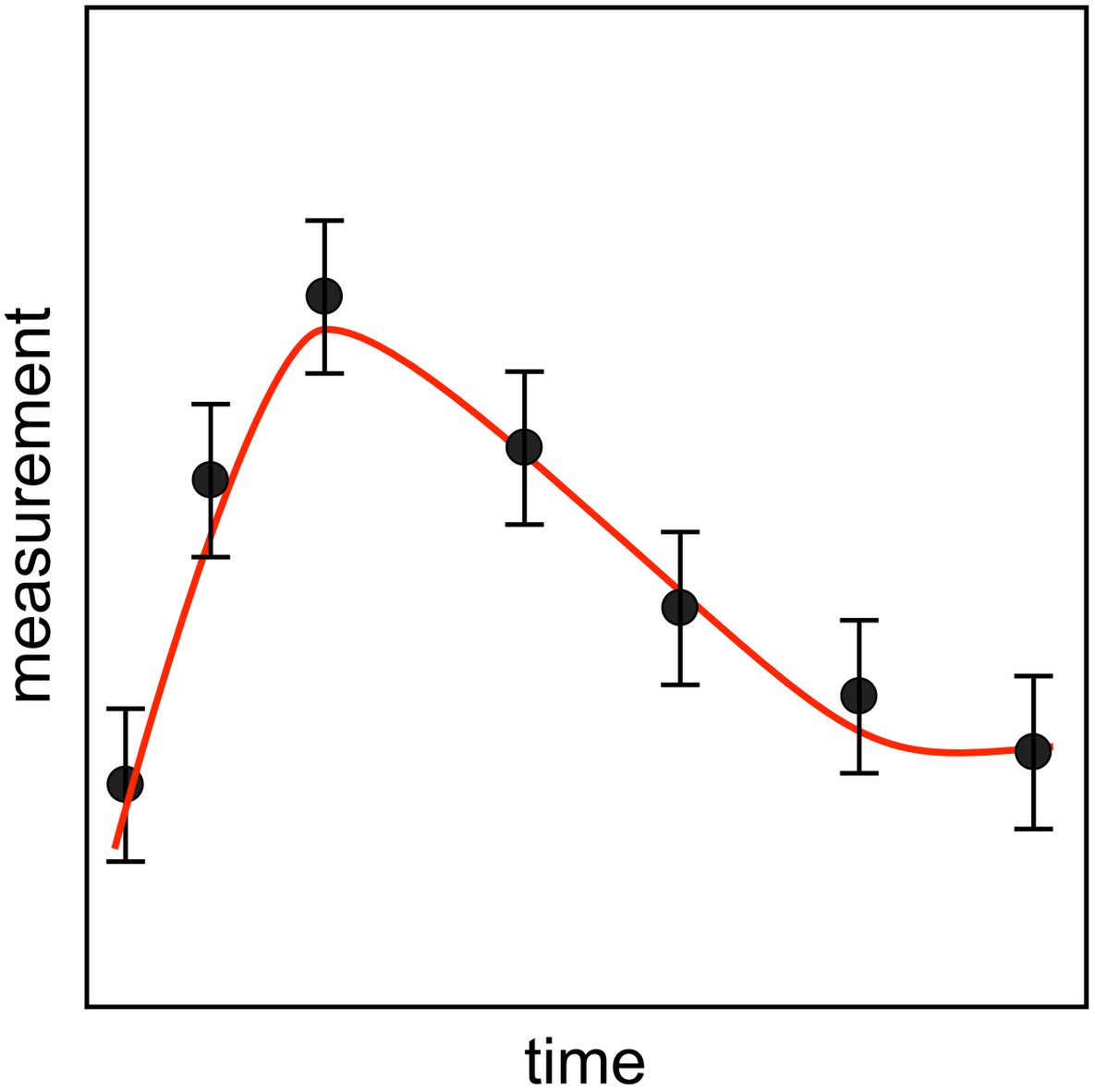
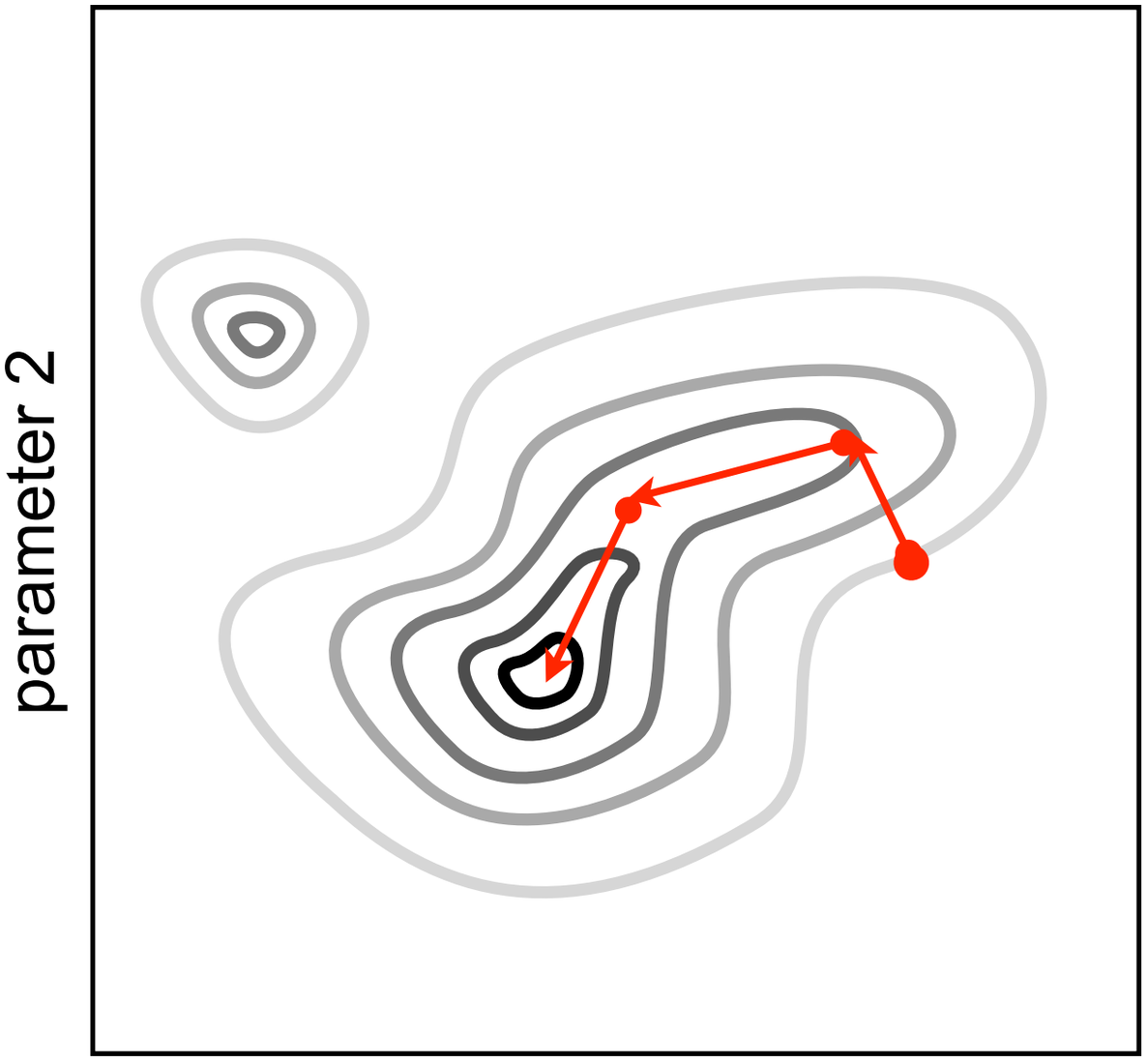
Model-data comparison

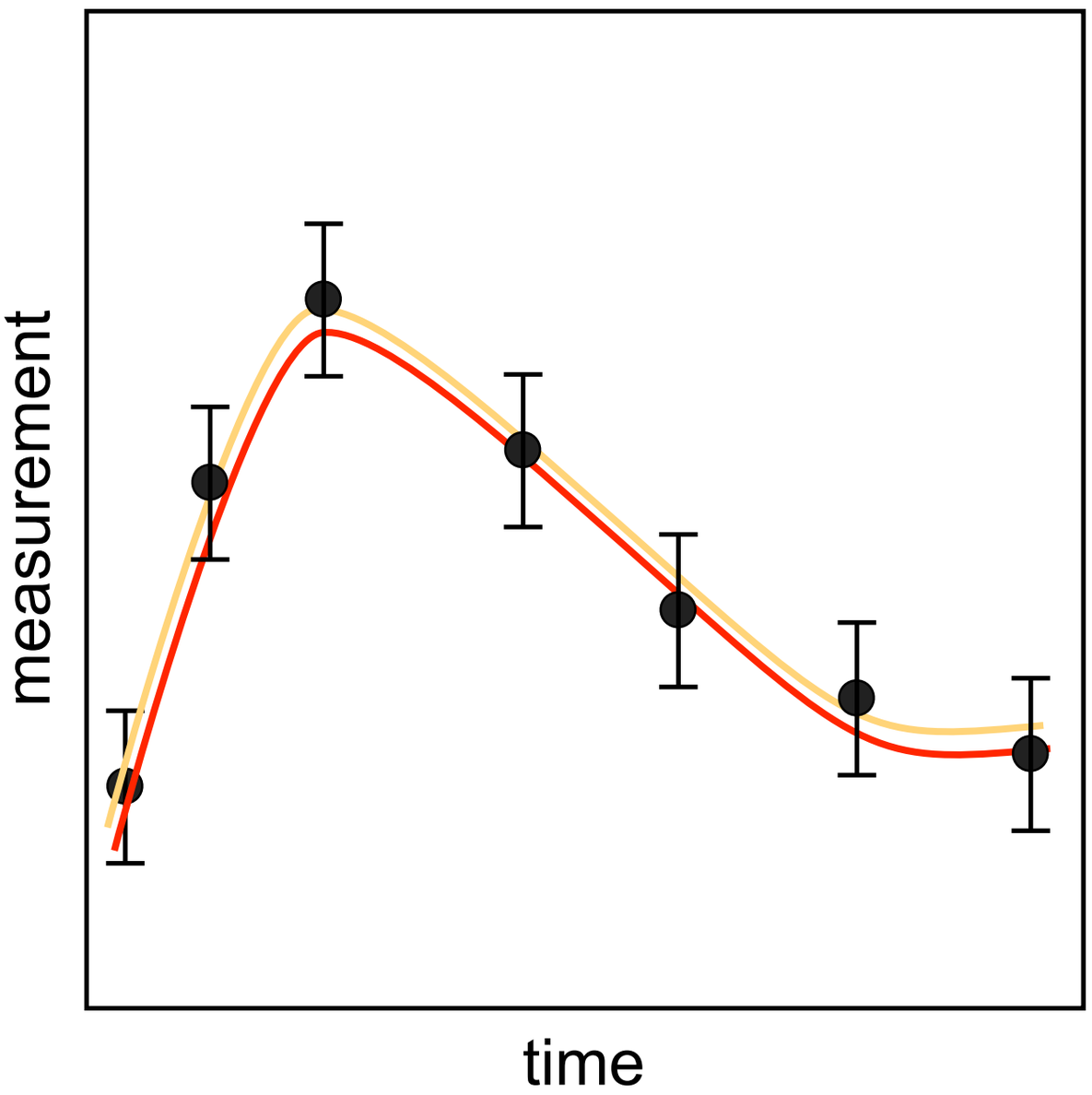


Objective function landscape



Parameter Estimation

Model-data comparison



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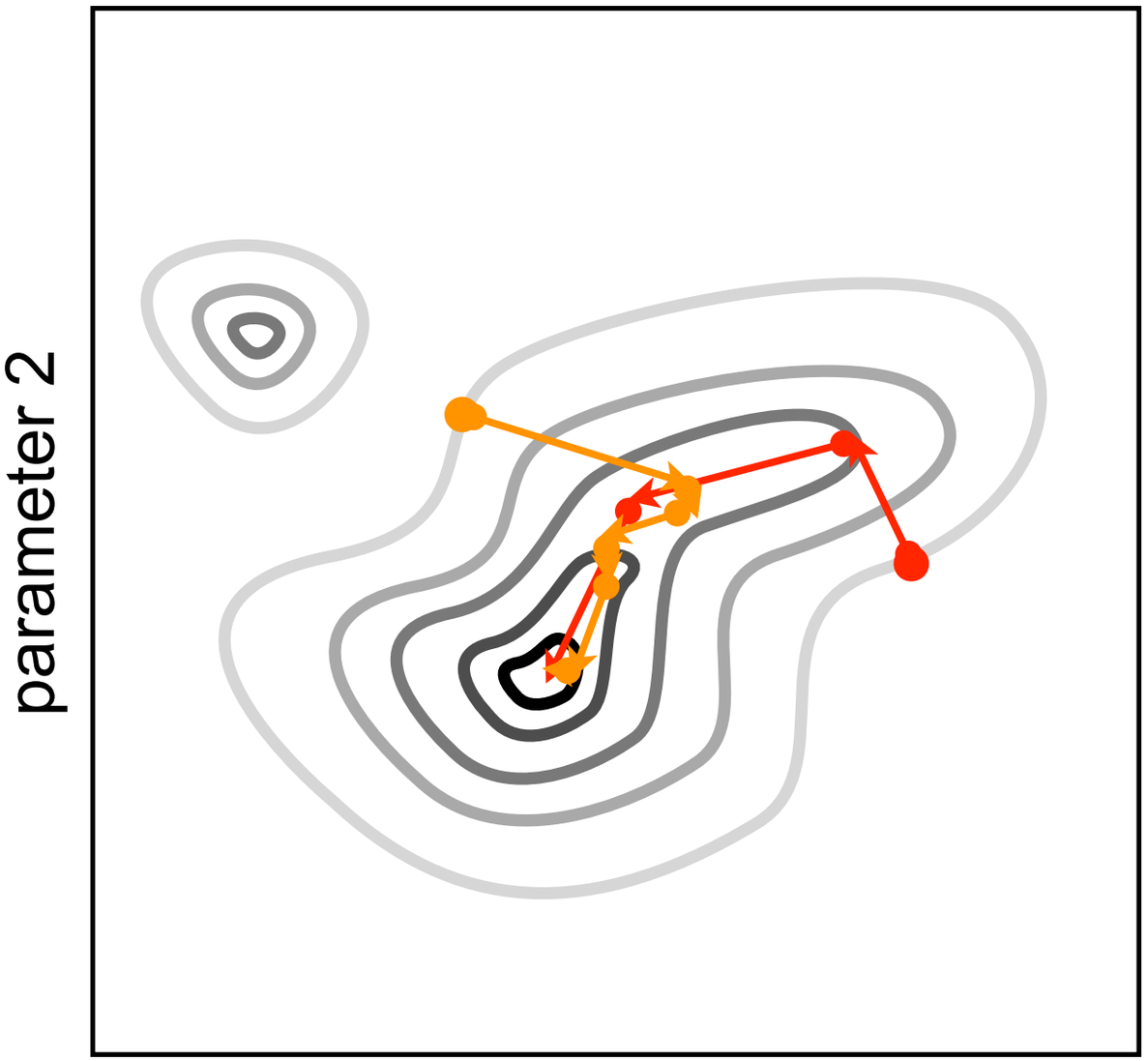
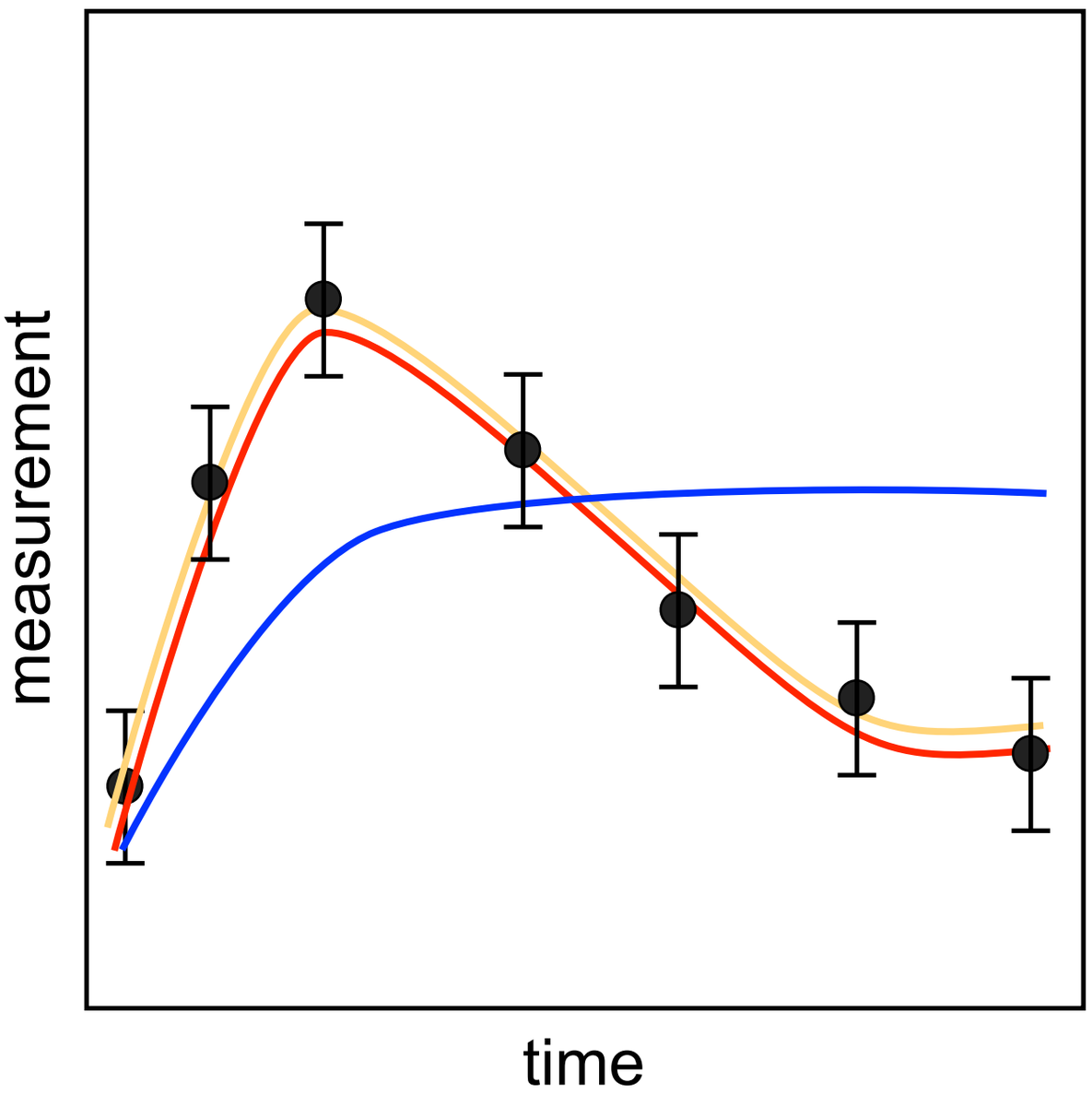
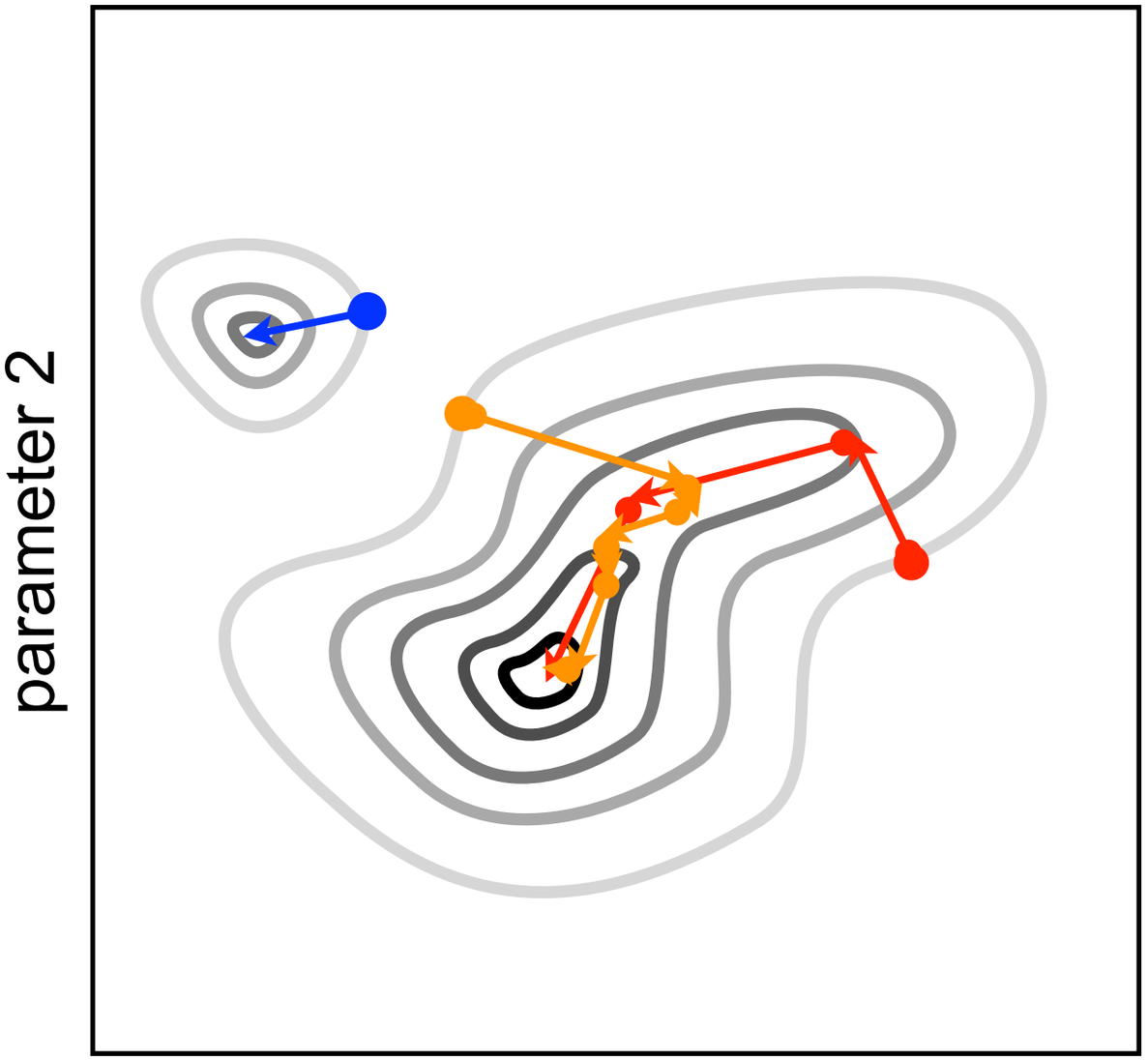


Parameter Estimation

Model-data comparison

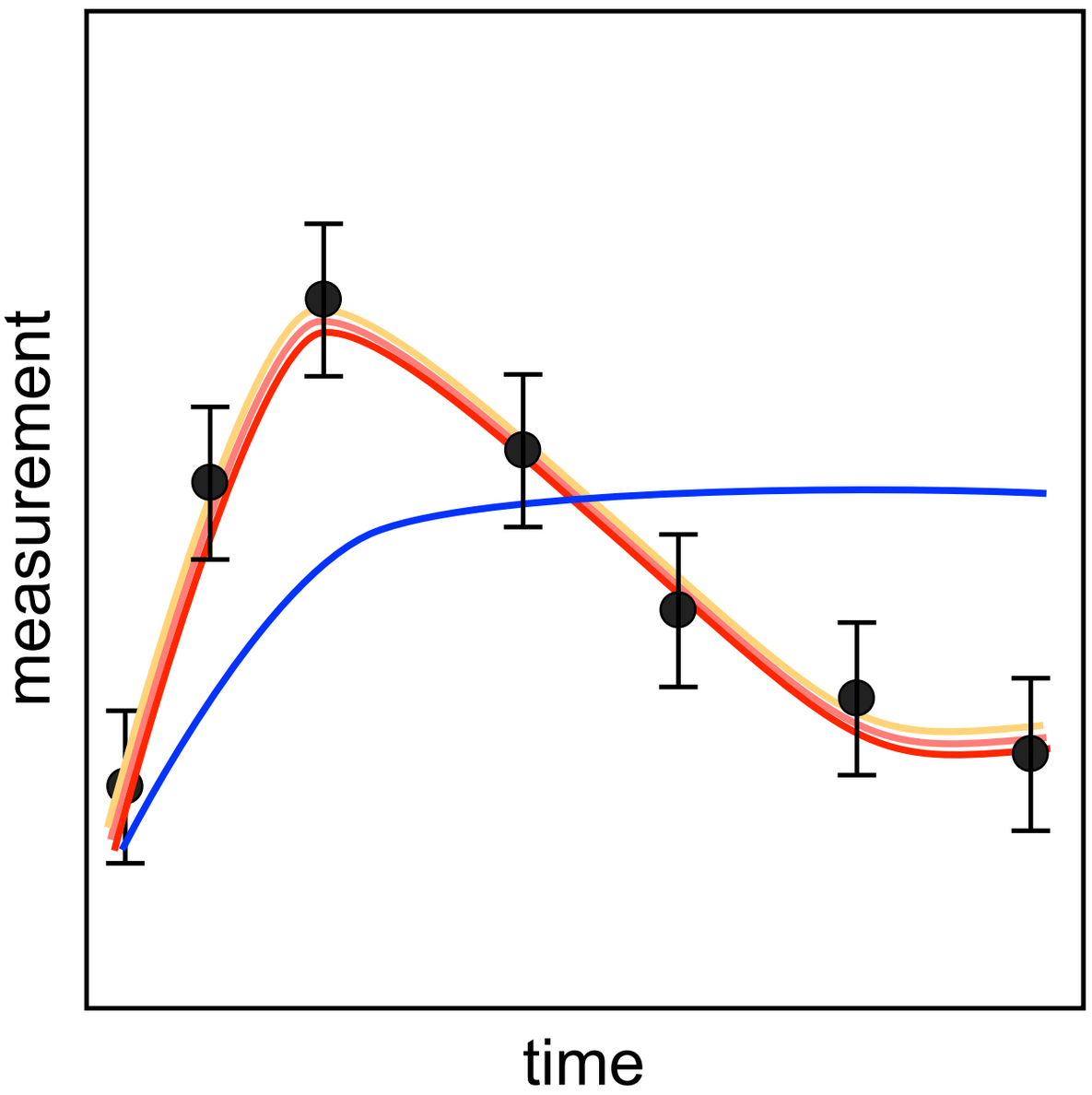


Objective function landscape



Parameter Estimation

Model-data comparison



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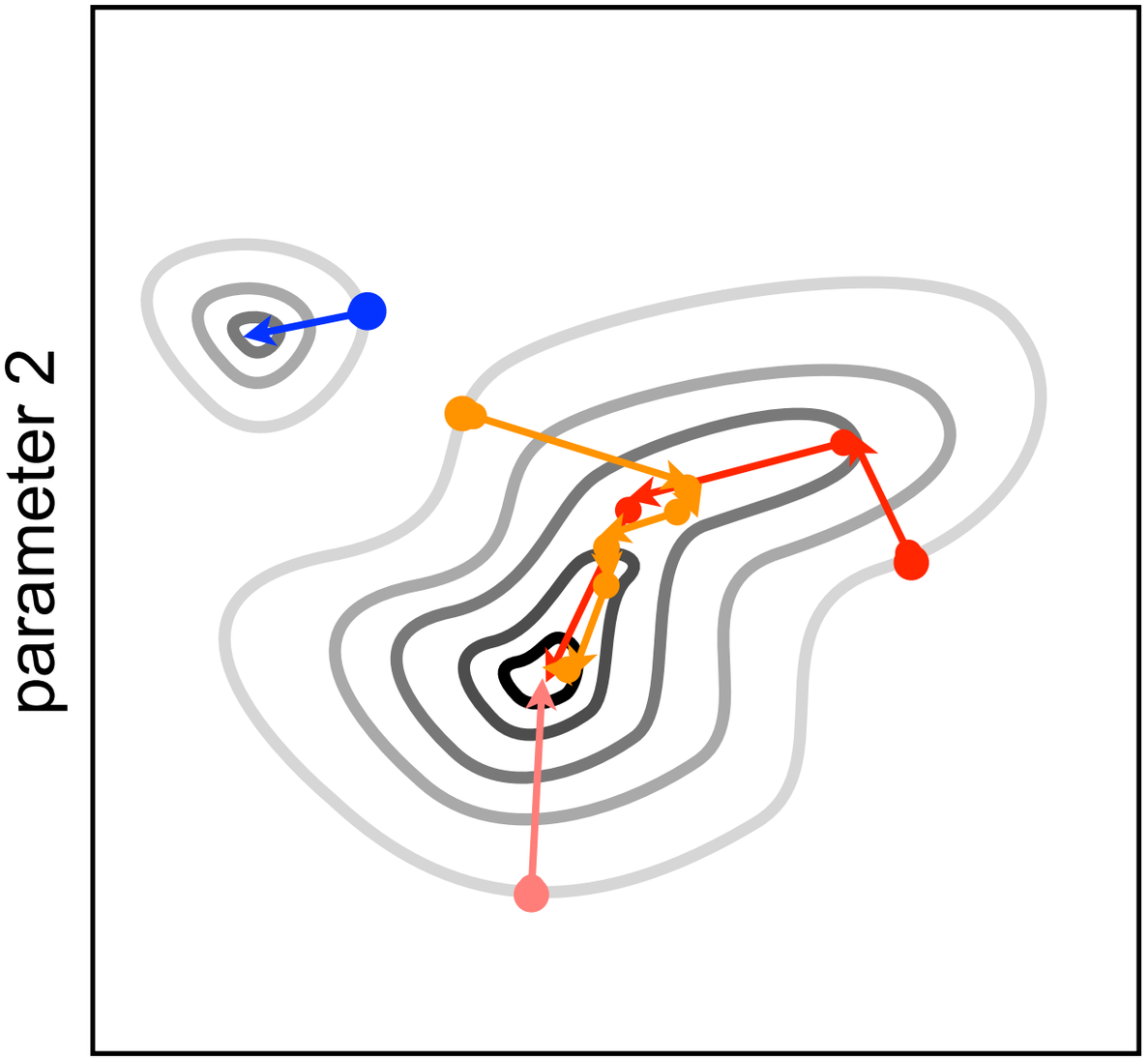
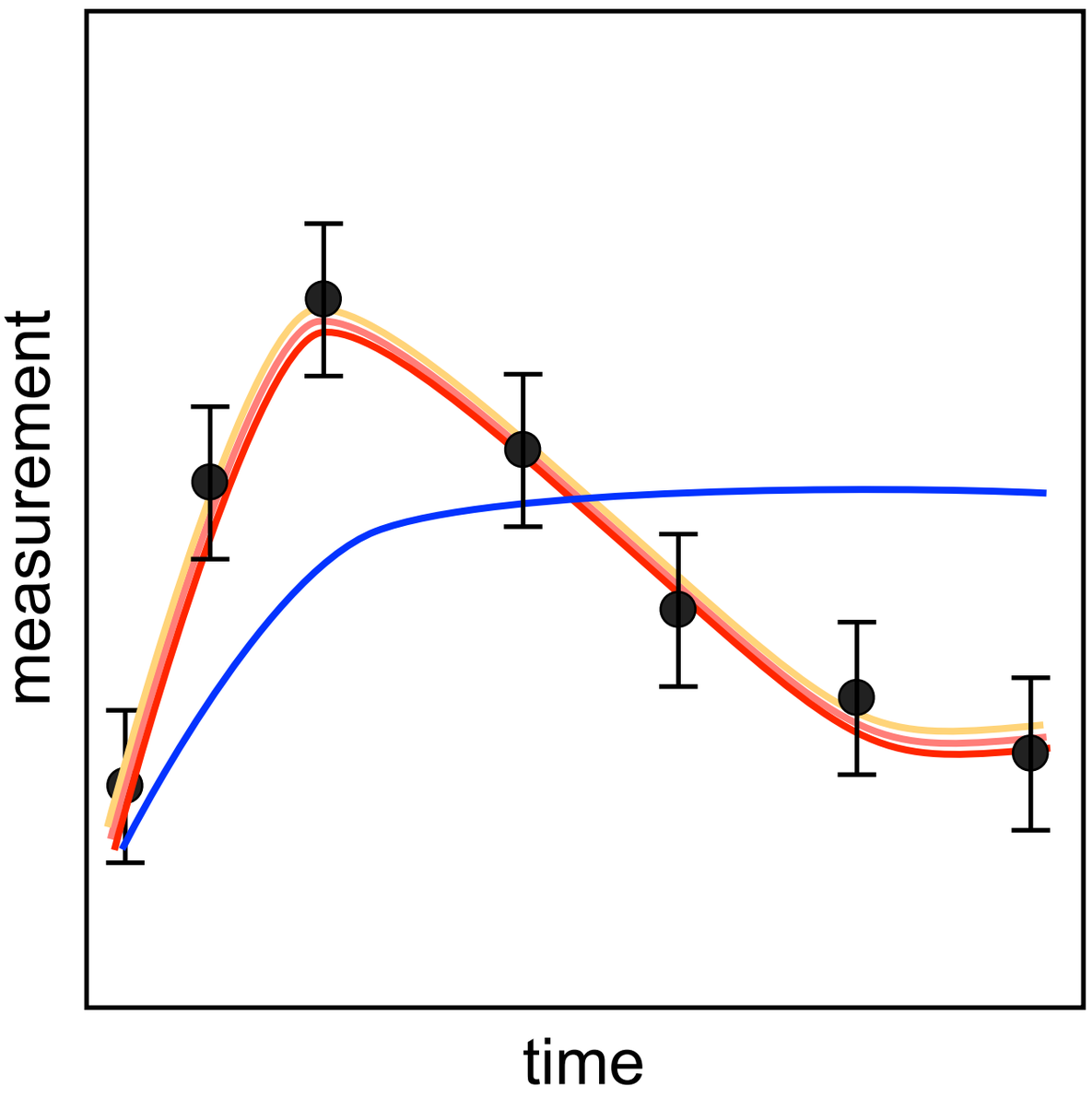
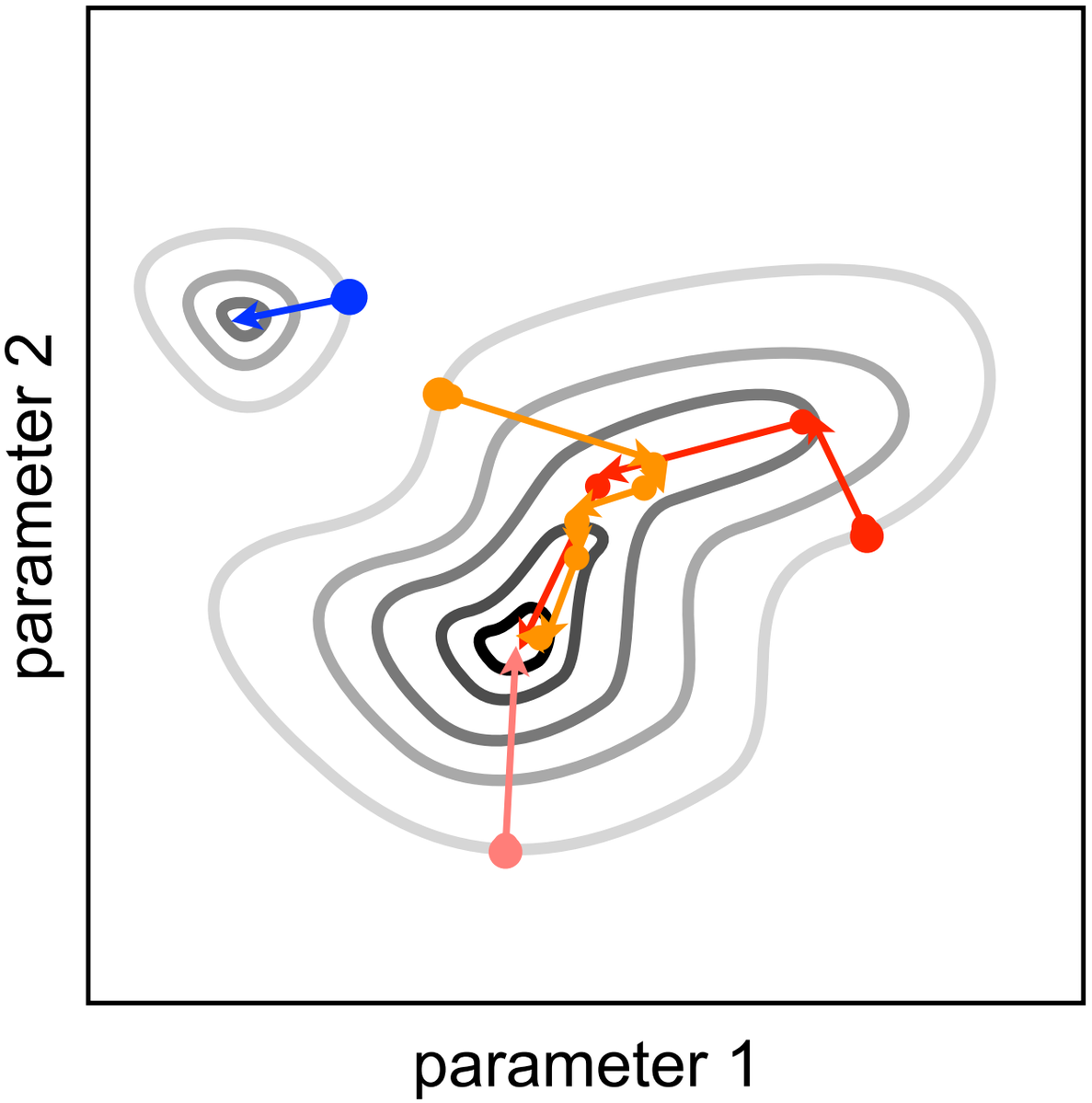


Parameter Estimation

Model-data comparison



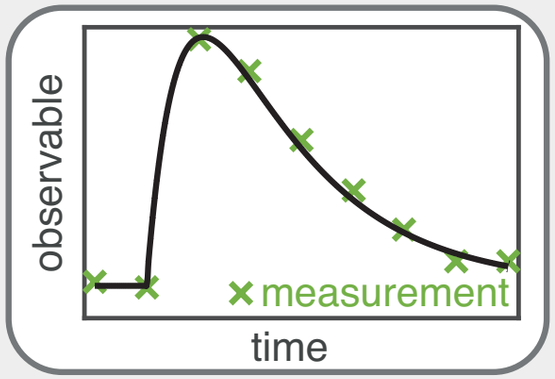
Objective function landscape



Bottleneck: gradient computation

Gradient Computation Schemes

Finite Differences



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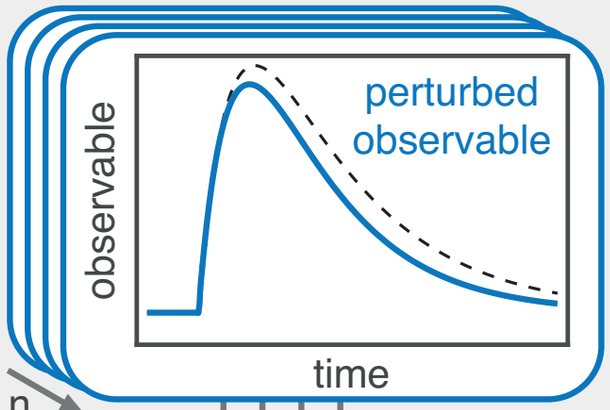
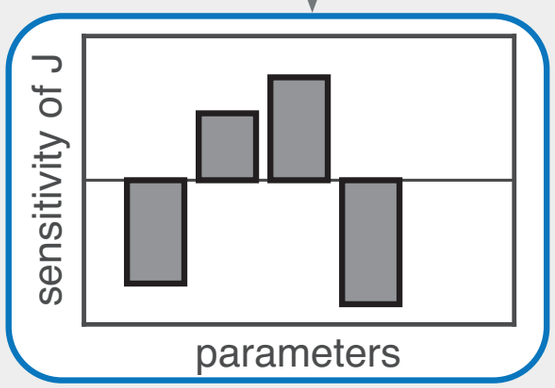
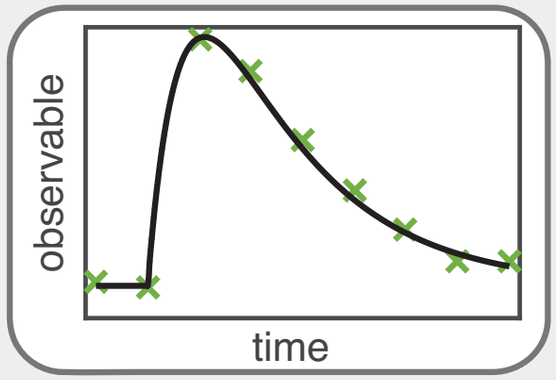




Forward Sensitivities



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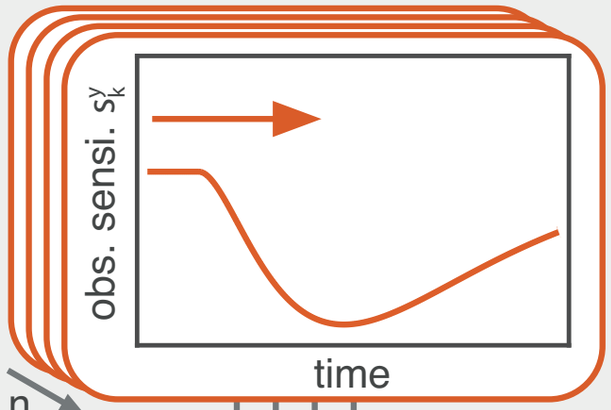
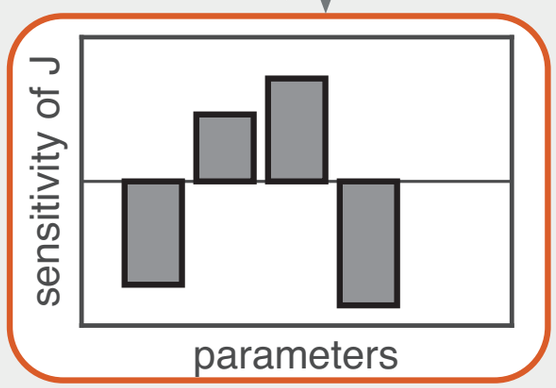
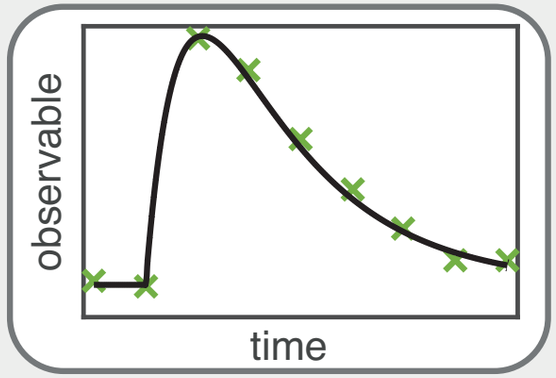




Adjoint sensitivities



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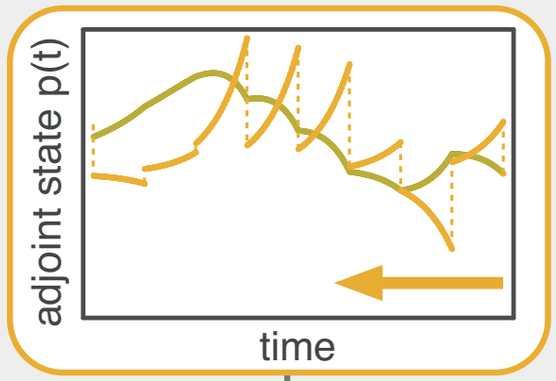
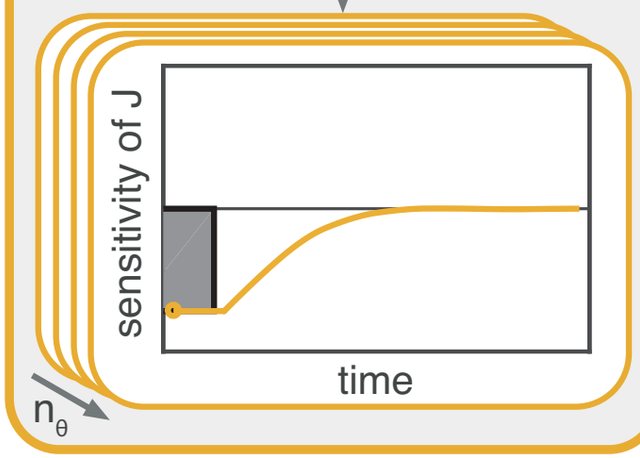




Step 1

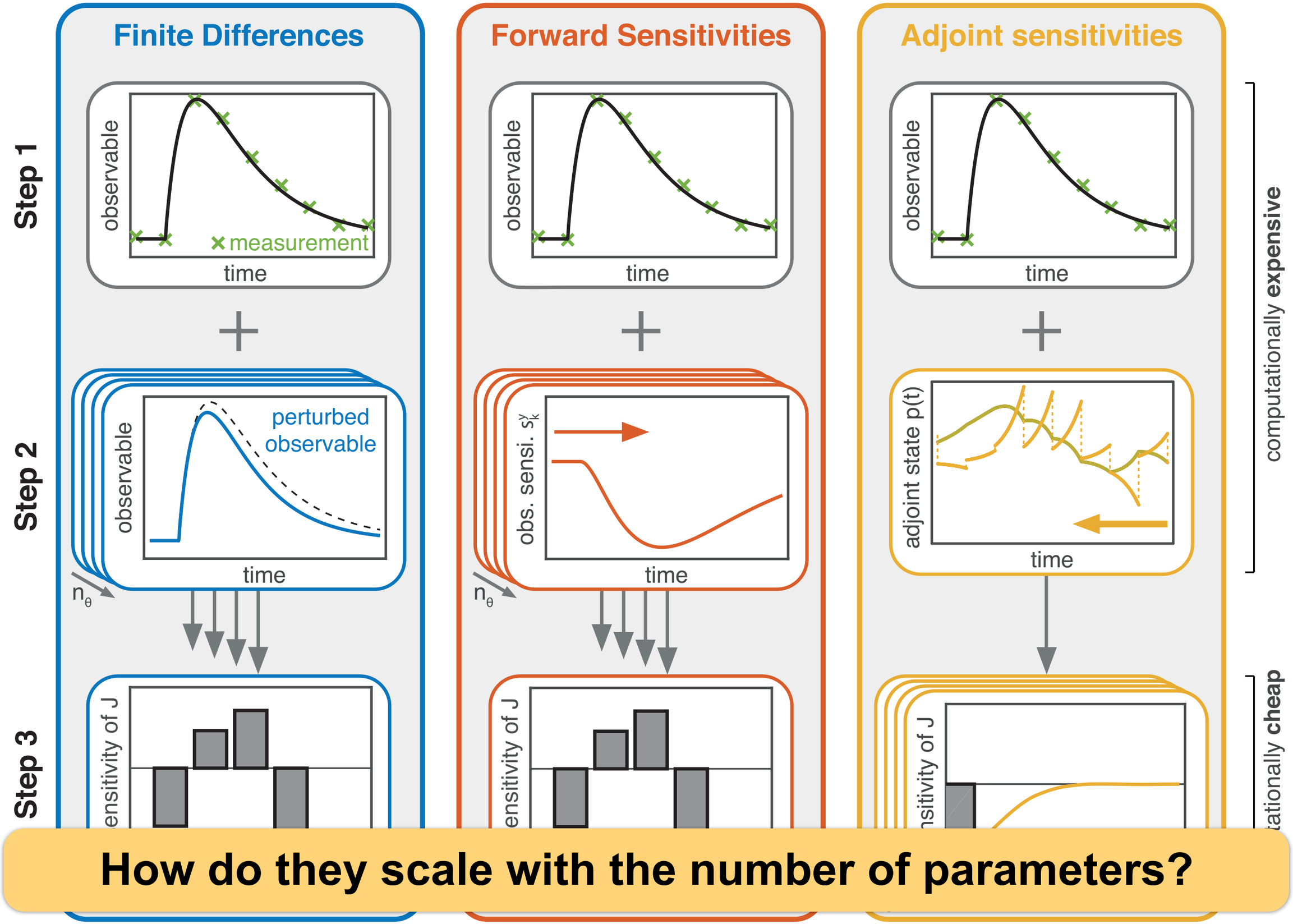
Step 2

Step 3

computationally **expensive**

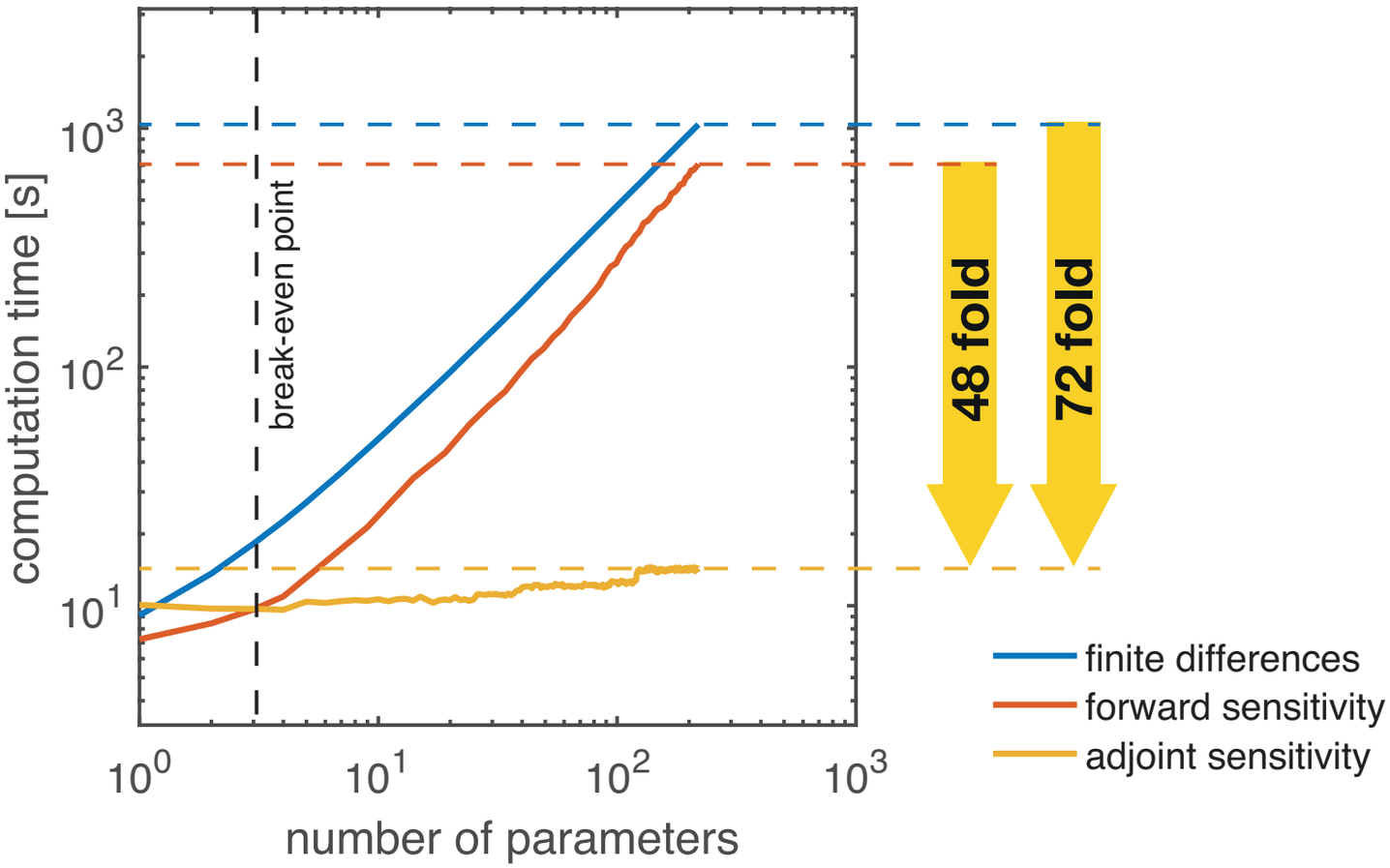
computationally **cheap**

Gradient Computation Schemes



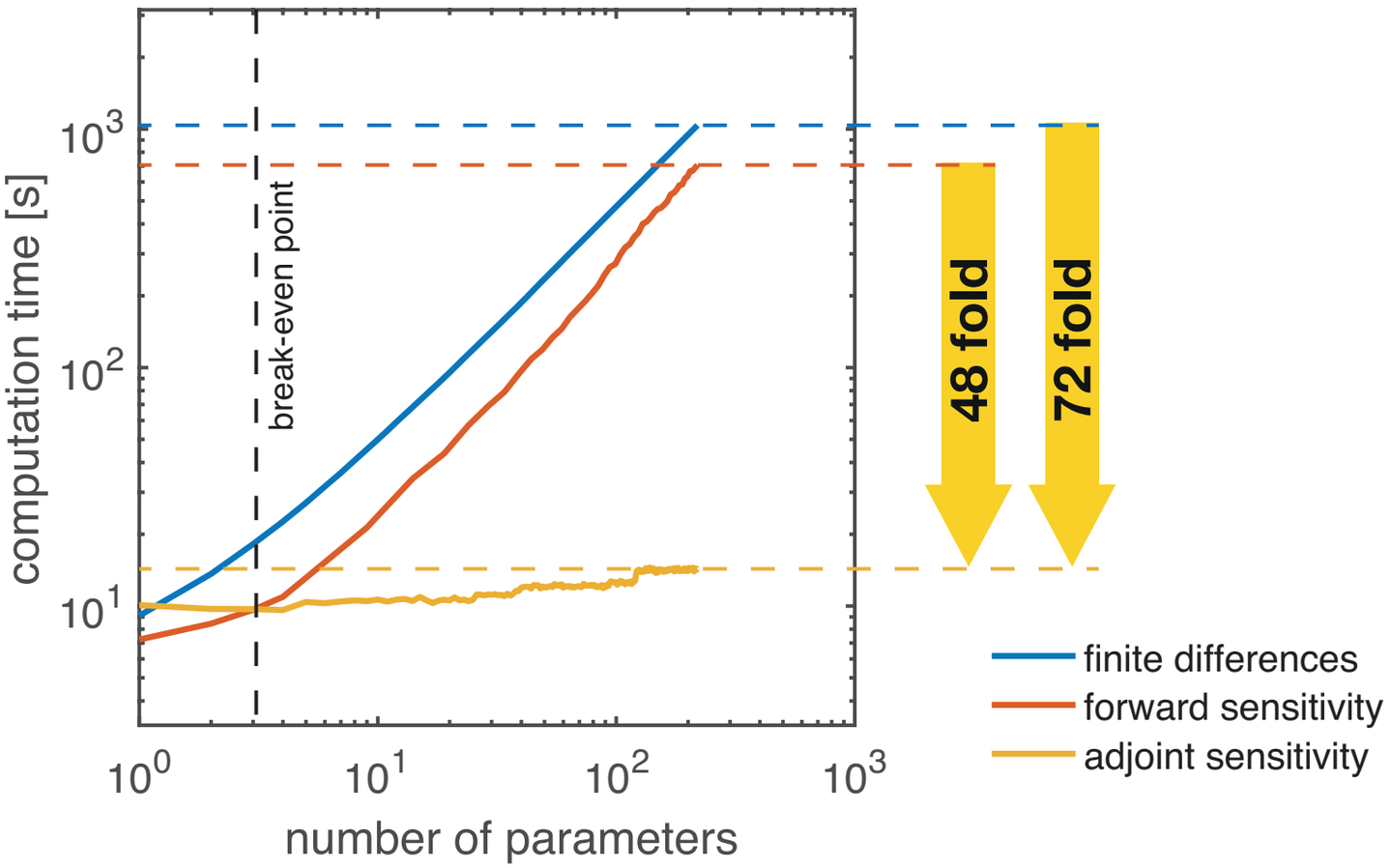
How do they scale with the number of parameters?

Speedup of Gradient Computation



Model:
BIOMD0000000255
Chen2009 ErbB Signaling
219 parameters
500 state variables

Speedup of Gradient Computation



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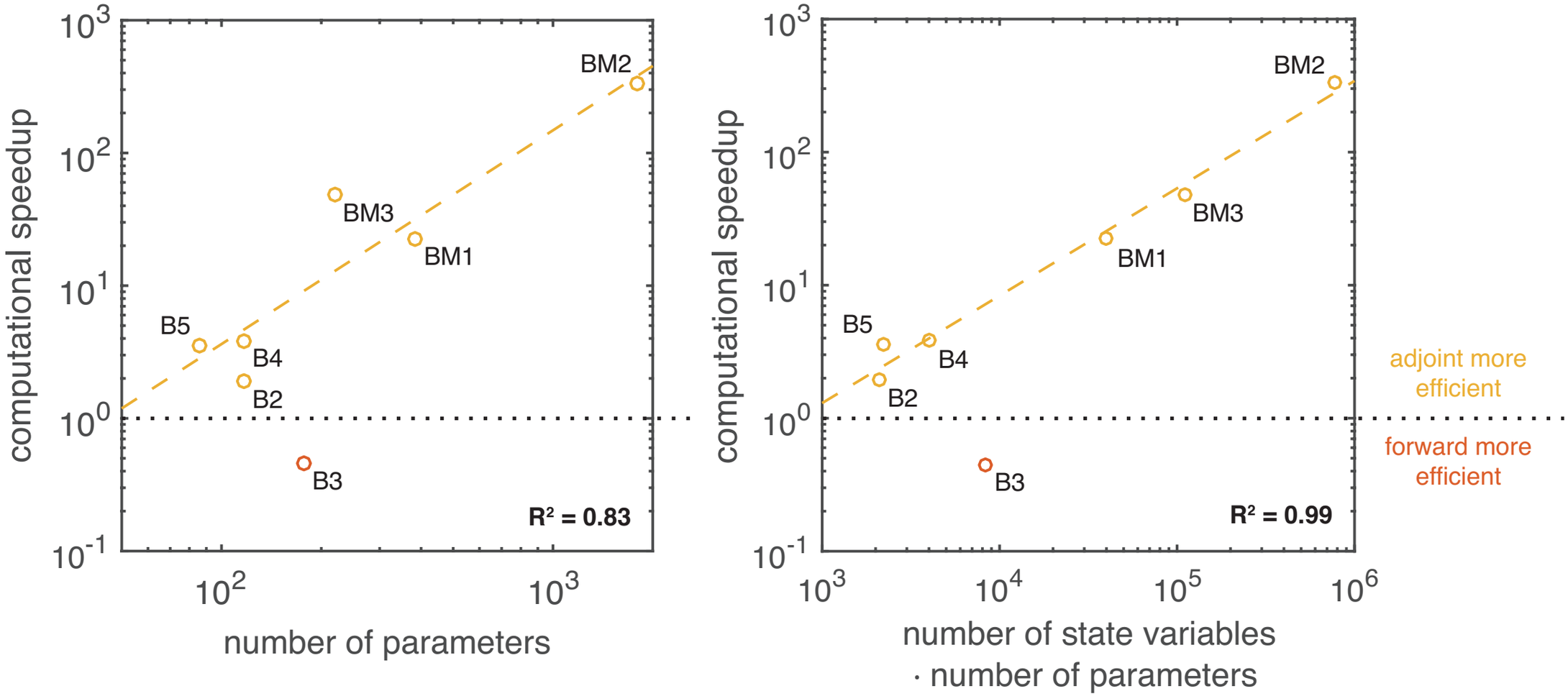
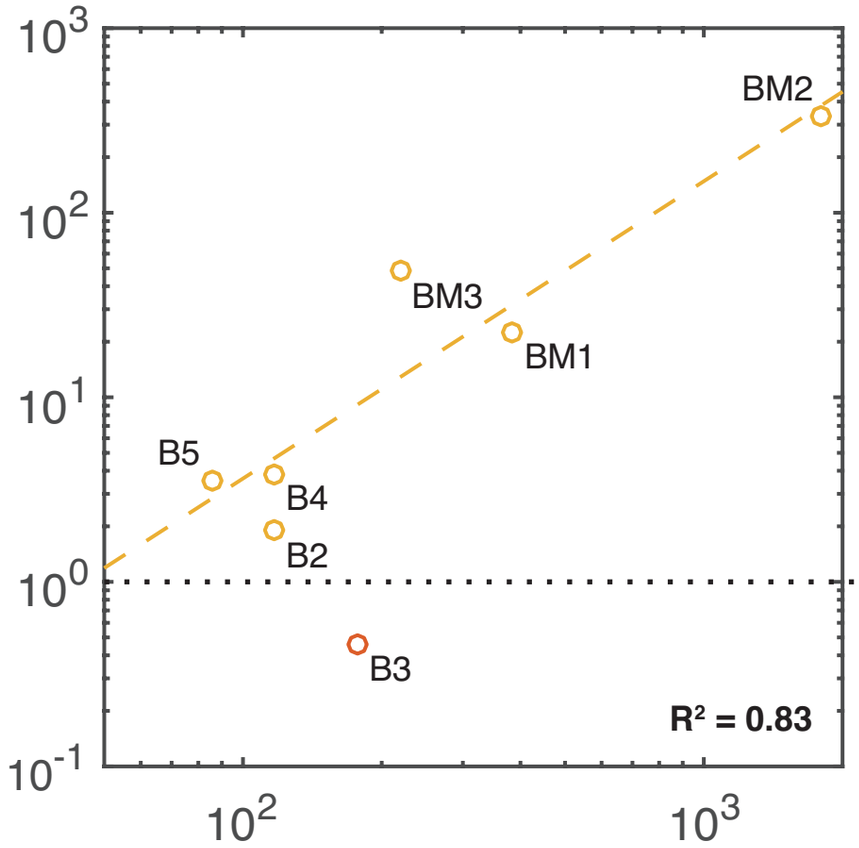
Does this translate to other models?

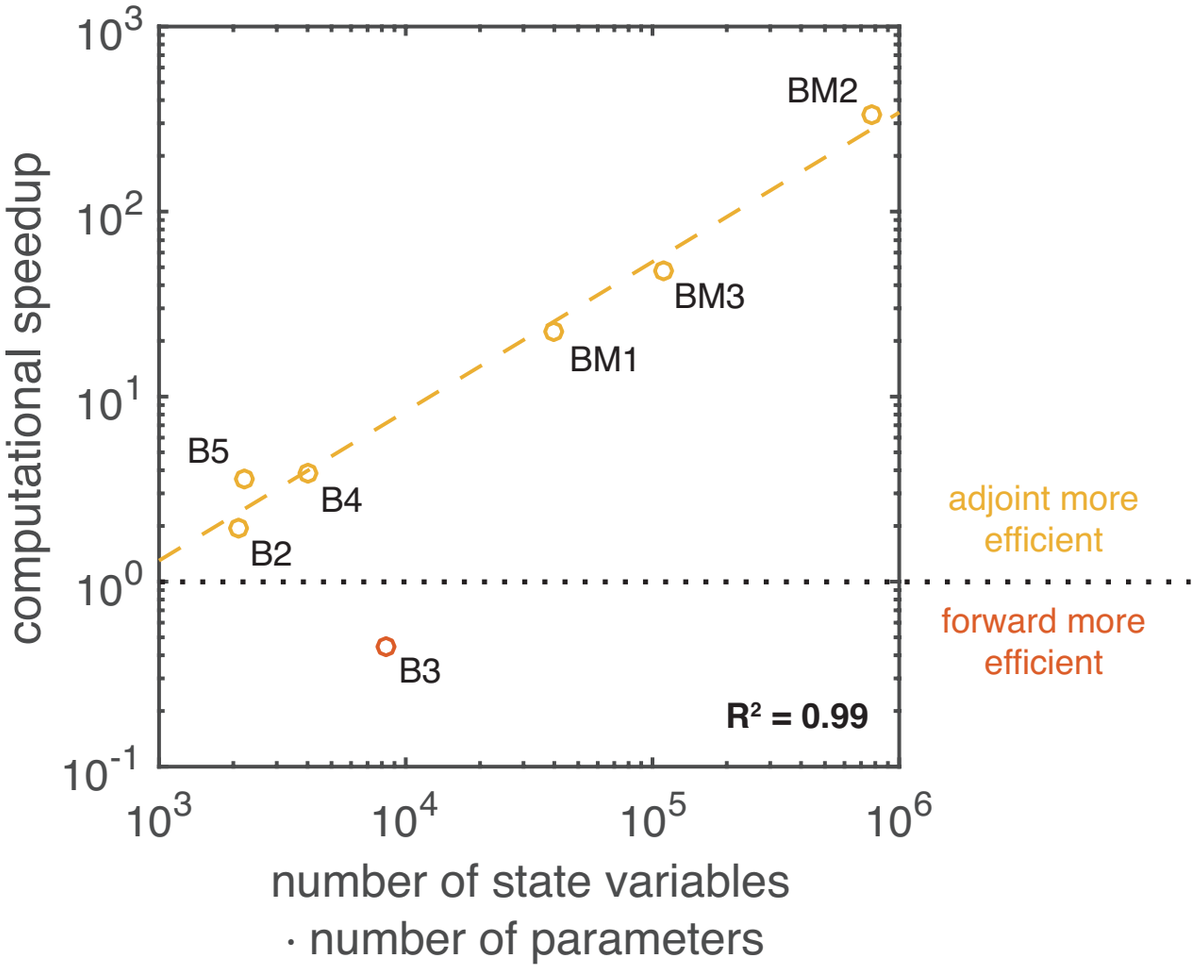
Speedup of Gradient Computation



	B2	B3	B4	B5	BM1	BM2	BM3
#states	18	47	34	26	104	431	500
#parameters	116	178	117	86	383	1801	219
BIOM ID					474	235	255
	BioPreDynBench, Villaverde et. al 2015						

Speedup of Gradient Computation





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#states	18	47	34	26	104	431	500
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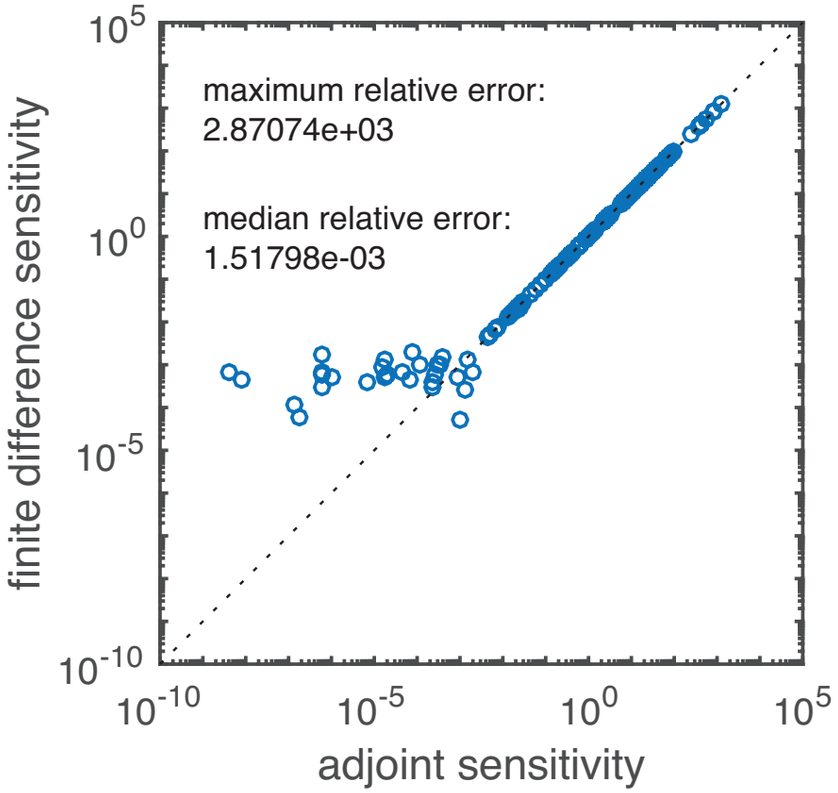
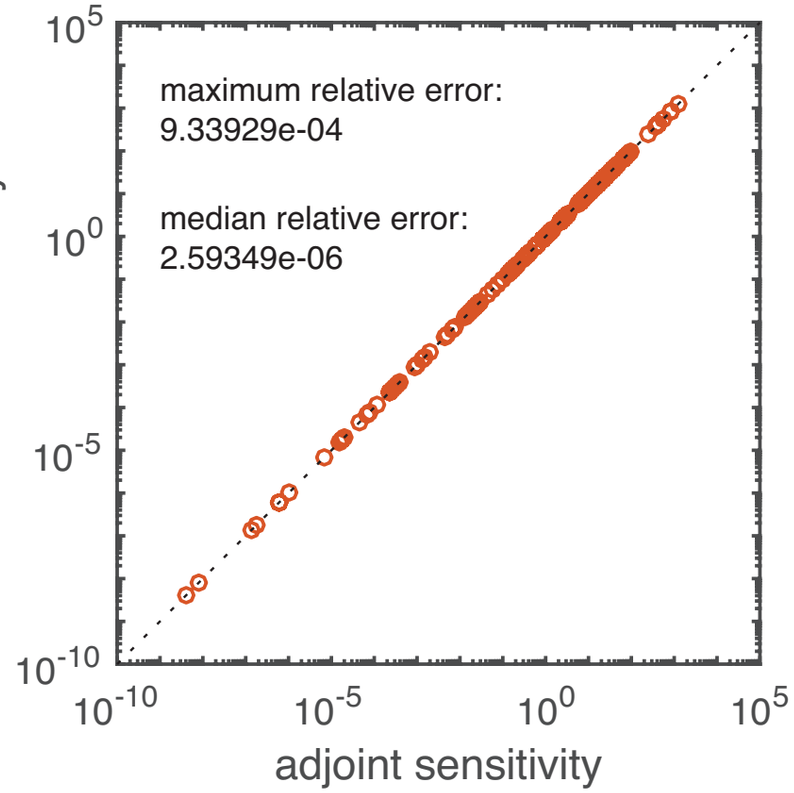
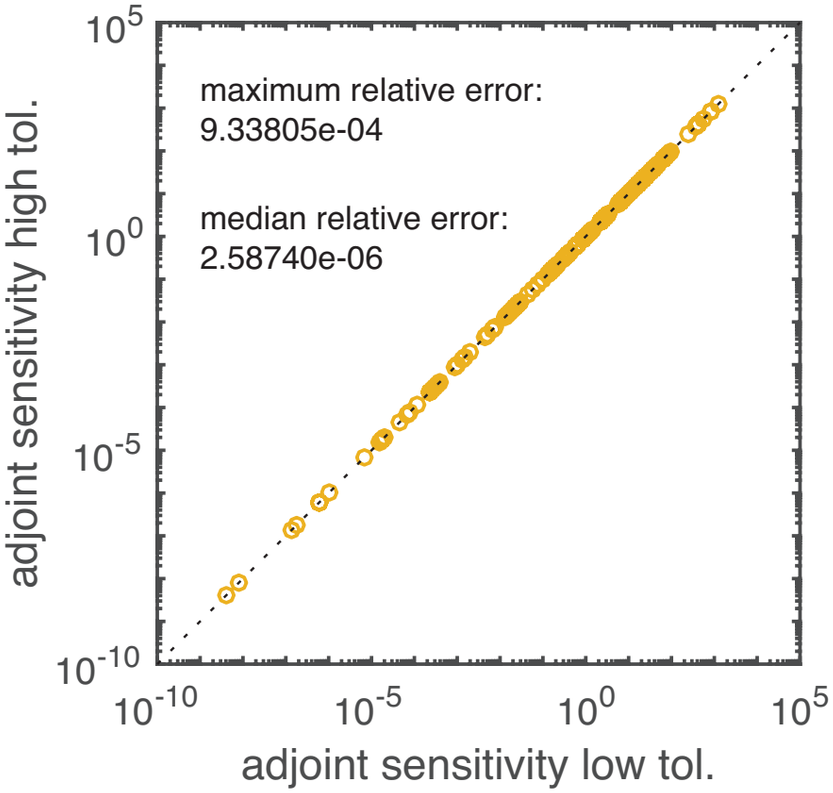
Speedup is almost universal.

Accuracy of Gradient Computation







absolute tolerance: 10^{-16}
relative tolerance: 10^{-8}

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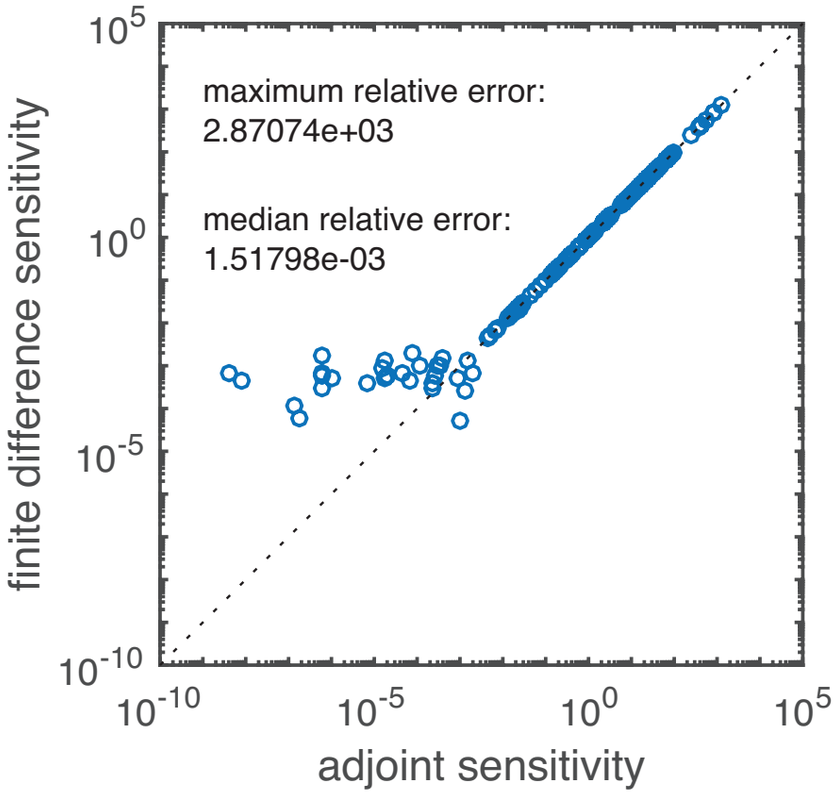
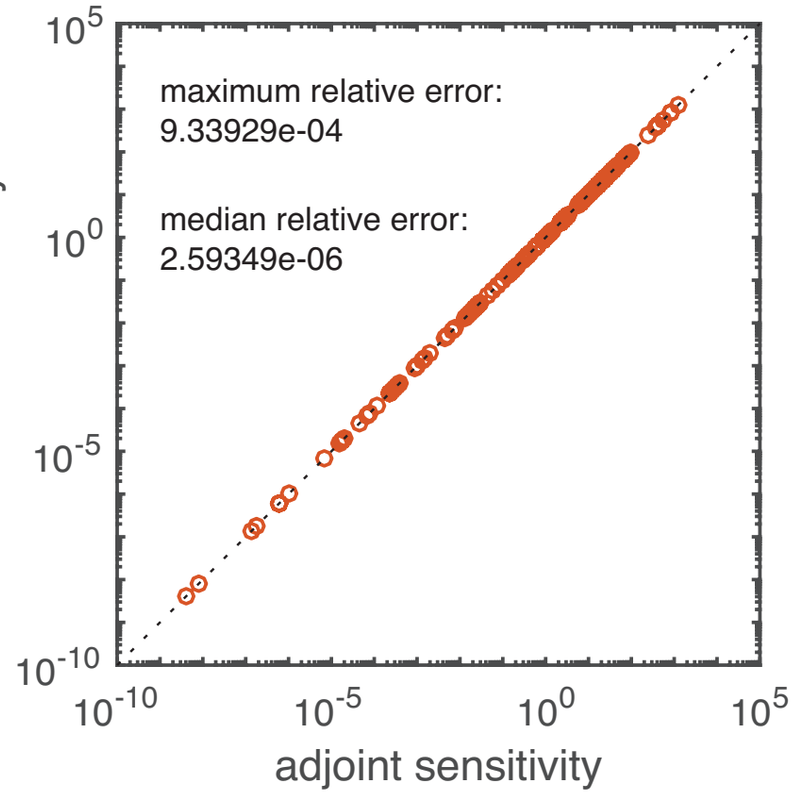
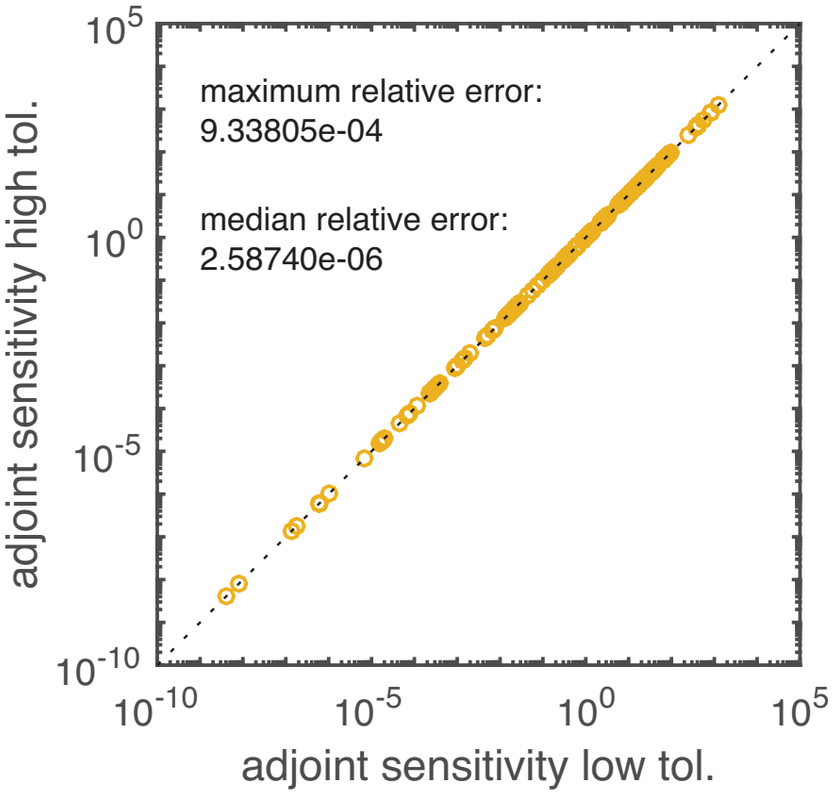
Accuracy of Gradient Computation







absolute tolerance: 10^{-16}
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Model:
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Chen2009 ErbB Signaling
219 parameters
500 state variables

Forward and adjoint sensitivities have similar accuracy.

Application: Cancer Signalling

ALACRiS Theranostics GmbH

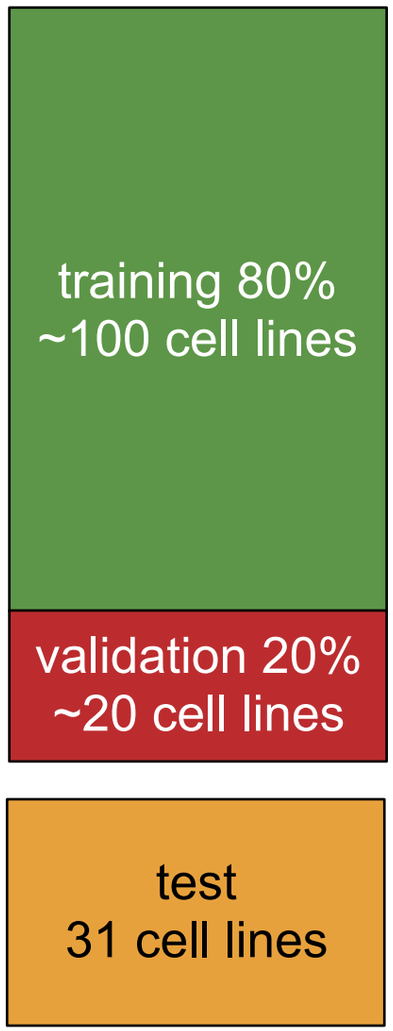
Model properties

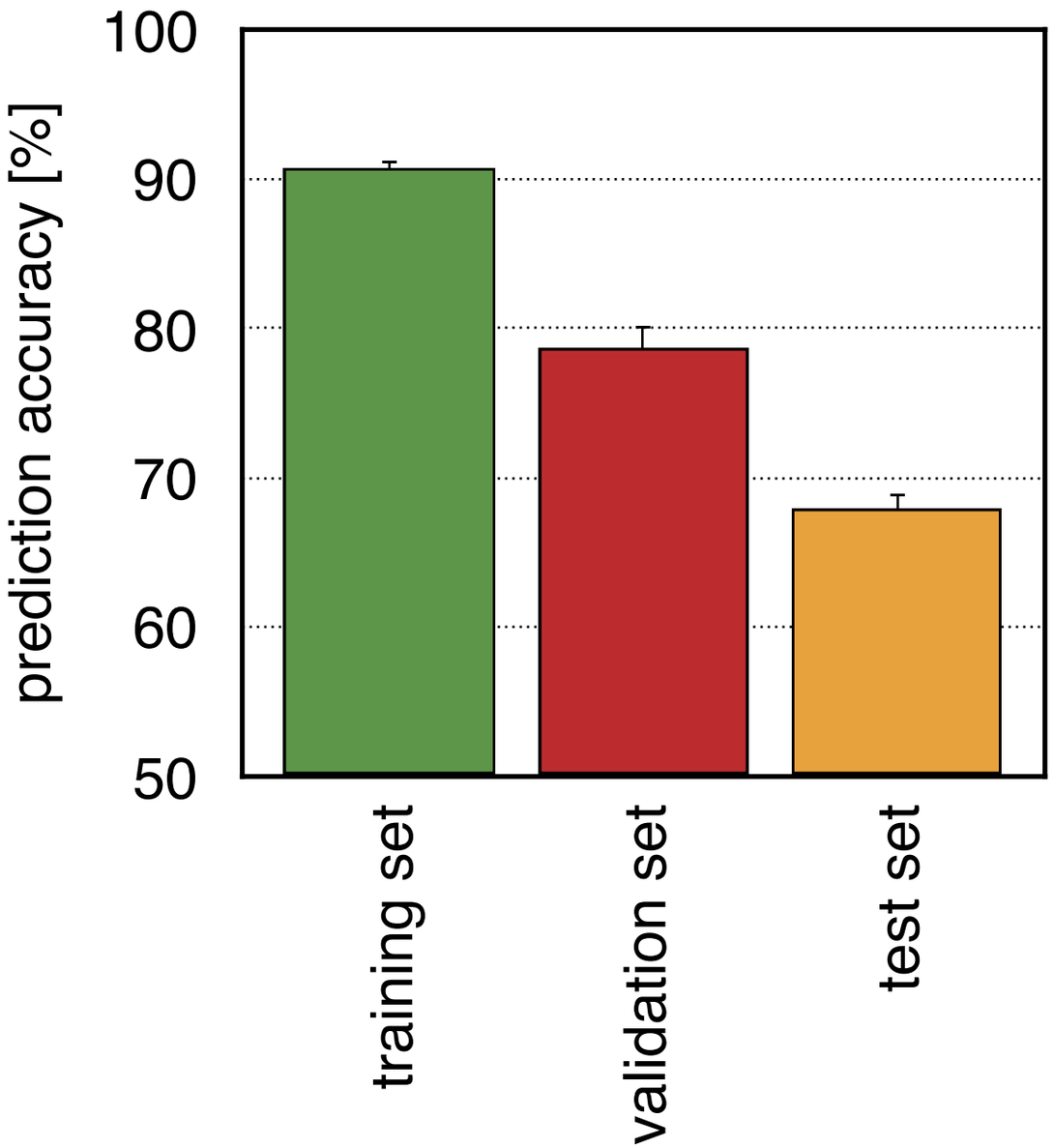
State variables: 1230
Parameters: 4256
Experimental Conditions: 5500

CCLE

Classification

Responder/Non-Responder to 7 different drugs





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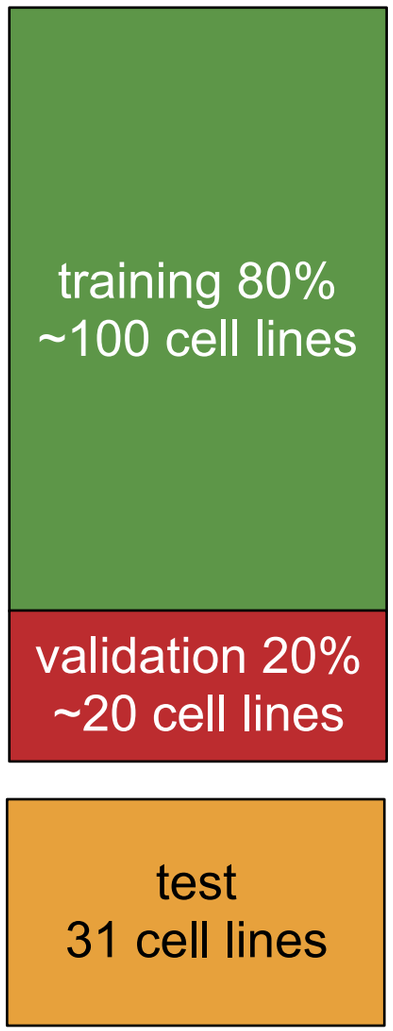
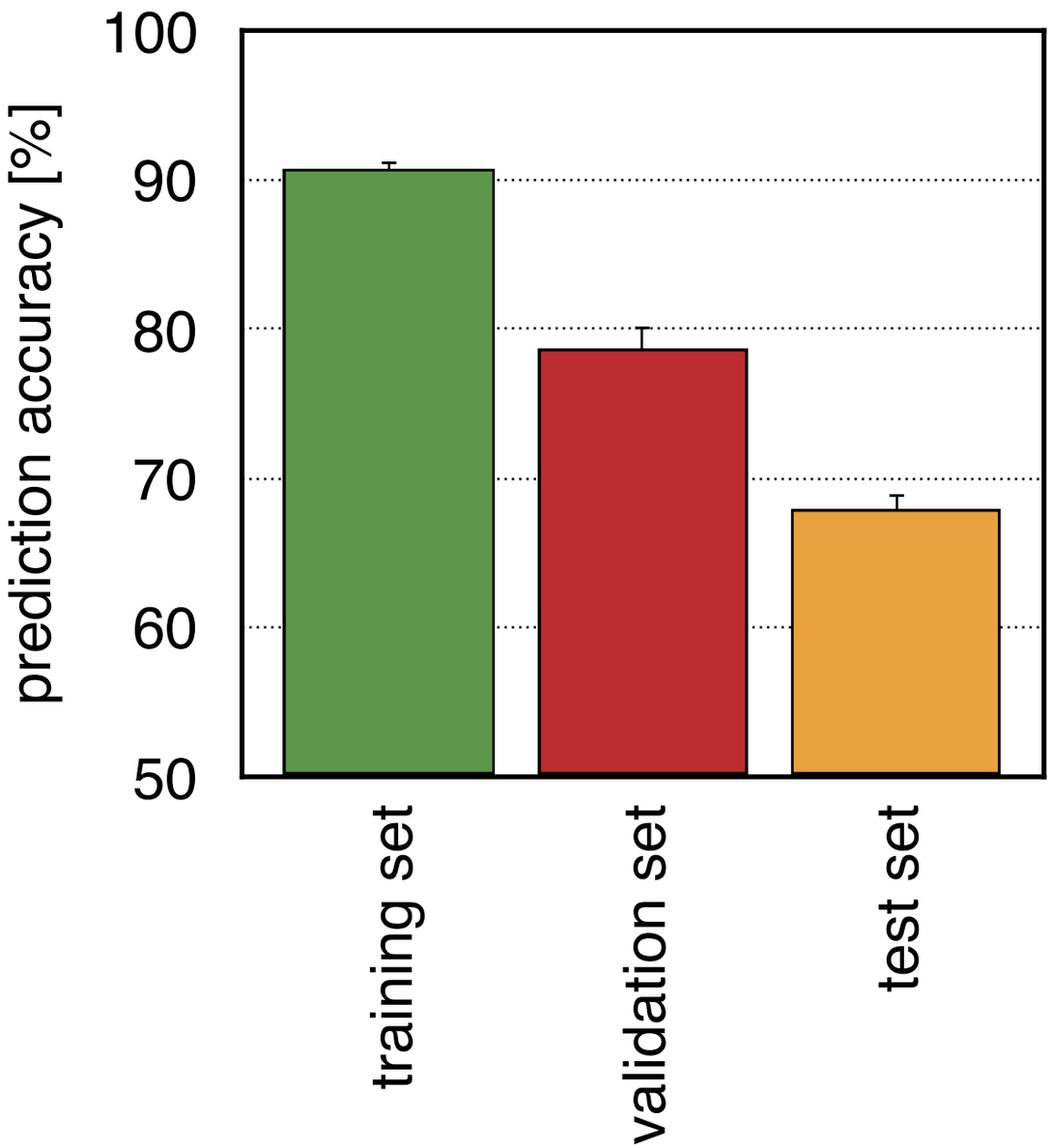
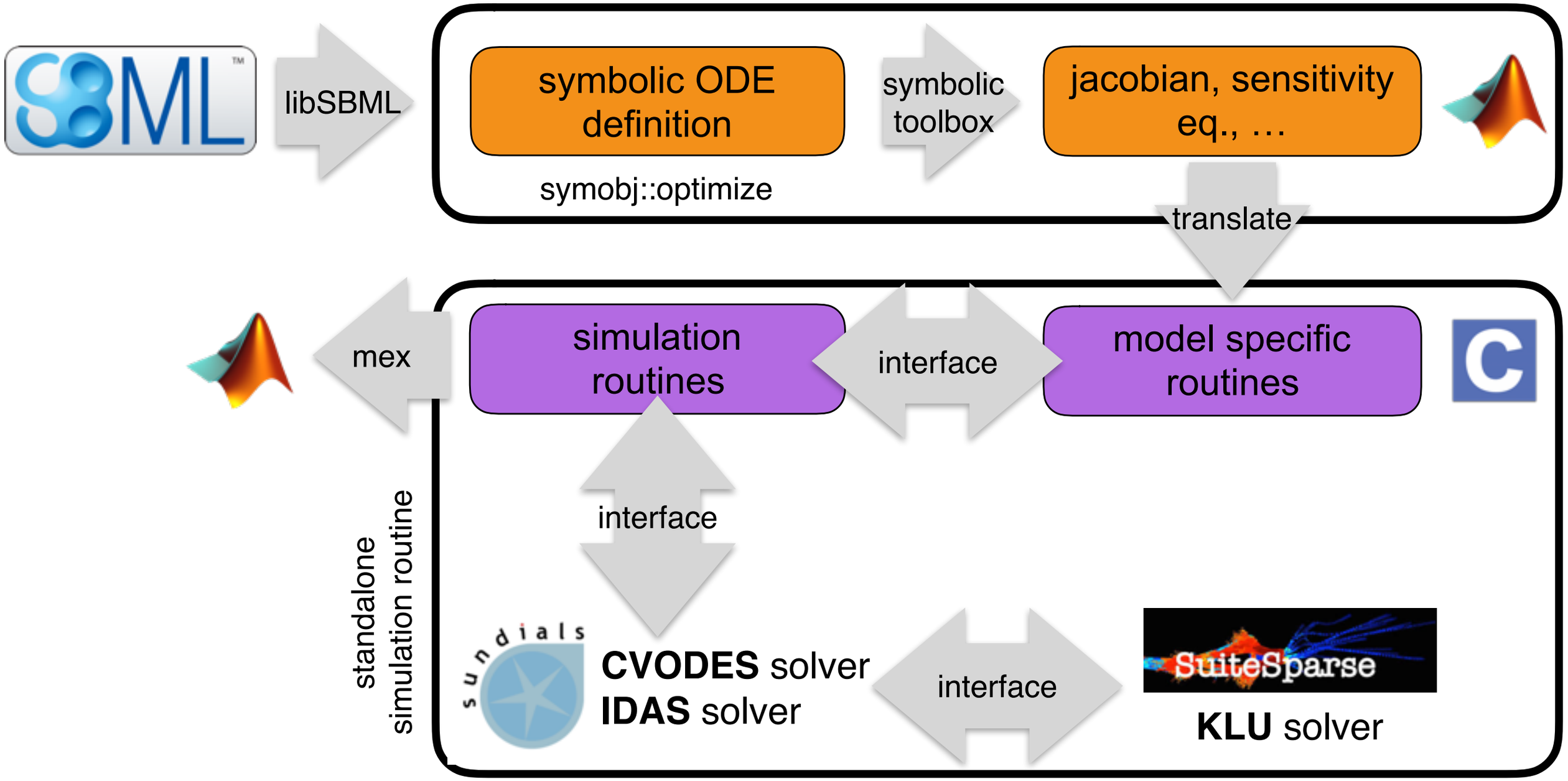




Adjoint approach makes large-scale parametrization possible

Implementation: AMICI



AMICI: Key Features

- Forward and Adjoint sensitivity analysis
- Second order sensitivities analysis
- Directional second order sensitivities
- Stead state sensitivities
- Support for models with events
- Supports models with thousands of states and parameters

AMICI

https://github.com/ICB-DCM/AMICI

Summary

- Adjoint sensitivity analysis is more efficient and as accurate as forward sensitivity analysis for large scale models
- Modular Implementation in AMICI which generates simulation routines as native C code

Outlook

- HPC support
- Support for SED-ML
- Support for different ODE solvers?
- Rewrite of symbolic processing in C/python?
- Standard for model-data metric?

Acknowledgment

ICB, Helmholtz Zentrum München

Jan Hasenauer

Paul Stapor
Daniel Weindl
Fabian Theis

University of Klagenfurt

Barbara Kaltenbacher

Thank you for your attention!