



# Ab-initio optimization and AI-powered inference for parametrizing complex biological models under low data availability

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For different organisms, early development unfolds under very diverse circumstances and time scales, but constantly facing the impacts of inevitable biological noise, resulting from the inherently stochastic nature of the processes driving it. To cope with this, a variety of developmental strategies and mechanisms evolved, and their differences were shaped by the constraints imposed by physical laws and the natural environment of the organism. In spite of decades of research on early development of various paradigmatic organisms, we are still lacking theories and models that explain these processes in a truly mechanistic fashion. The advent of increased computational power has enabled us to construct developmental models with ever increasing complexity. However, since experimental reports on microscopic cell-physical quantities are scarce, the parametrization of such models becomes a key problem itself and posits a new frontier in biophysical modeling. I will contrast two distinct strategies for parametrizing biophysically realistic models in development and beyond:

optimization of normative theories, and Bayesian inference, which in principle can operate even in a model-free regime. I will first demonstrate that both approaches can be unified into a single mathematical framework which allows smooth transition between both strategies in a quantitative fashion. I will then present our results on elucidating early development of two distinct organisms, which employ both parametrization strategies: (1.) optimization of a detailed spatial-stochastic model of the gap gene system in the fruit fly, and (2.) characterization of the spatial regulatory processes driving early cell-fate assignment in the mouse embryo via AI-powered simulation-based inference (SBI). These results exemplify how optimization of normative models and inference or fitting strategies can be combined for successfully determining complex spatial-stochastic models. At the same time they highlight that significantly different developmental strategies emerged under the vastly different circumstances faced by the fly and mouse embryos.

