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The tale of the mouse and the fly: Biophysical modeling, optimization and inference for elucidating distinct developmental strategies

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For different organisms, early development unfolds under very different 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. In this talk, 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 way. I will then present our results on elucidating early development of two distinct organisms while making use of both strategies of parametrization: (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 preimplantation phase mouse embryo via SBI (simulation-based inference), a powerful recent AI-based inference toolkit. These results exemplify how optimization of normative models and inference or fitting strategies can be combined for sucessfully determining complex spatial-stochastic models, and at the same time highlight that significantly different developmental strategies emerged under the vastly different circumstances faced by the fly and mouse embryos.

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