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AI-powered simulation-based inference of a genuinely spatial-stochastic model of early mouse embryogenesis

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Understanding how multicellular organisms reliably orchestrate cell-fate decisions is a central challenge in developmental biology. This is particularly intriguing in early mammalian development, where early cell-lineage differentiation arises from processes that initially appear cell-autonomous but later materialize reliably at the tissue level. In this study, we develop a multi-scale, spatial-stochastic simulator of mouse embryogenesis, focusing on inner-cell mass (ICM) differentiation in the blastocyst stage. Our model features biophysically realistic regulatory interactions and accounts for the innate stochasticity of the biological processes driving cell-fate decisions at the cellular scale. We advance event-driven simulation techniques to incorporate relevant tissue-scale phenomena and integrate them with Simulation-Based Inference (SBI), building on a recent AI-based parameter learning method: the Sequential Neural Posterior Estimation (SNPE) algorithm. Using this framework, we carry out a large-scale Bayesian inferential analysis and determine parameter sets that reproduce the experimentally observed system behavior. We elucidate how autocrine and paracrine feedbacks via the signaling protein FGF4 orchestrate the inherently stochastic expression of fate-specifying genes at the cellular level into reproducible ICM patterning at the tissue scale. This mechanism is remarkably independent of the system size. FGF4 not only ensures correct cell lineage ratios in the ICM, but also enhances its resilience to perturbations. Intriguingly, we find that high variability in intracellular initial conditions does not compromise, but rather can enhance the accuracy and precision of tissue-level dynamics. Our work provides a genuinely spatial-stochastic description of the biochemical processes driving ICM differentiation and the necessary conditions under which it can proceed robustly.

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