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Sloppiness is universal in systems biology: making predictions nonetheless RYAN GUTENKUNST, Physics, Cornell, FERGAL CASEY, Applied Math, Cornell, JOSHUA WATERFALL, Physics, Cornell, KEVIN BROWN, Molecular and Cellular Biology, Harvard, CHRISTOPHER MYERS, Theory Center, Cornell, JAMES SETHNA, Physics, Cornell — Quantitative models of complex biological systems often possess dozens of unknown parameters. We argue that such systems are universally “sloppy”; their behaviors are orders of magnitude more sensitive to moves in some directions in parameter space than others. To establish this, we survey models from the literature and show that their “complete and perfect data” Fisher Information Matrices possess eigenvalues typically spanning a range of more than 10^6 . Sloppiness implies that collectively fitting model parameters to even the best experimental data will tightly constrain only a few parameter combinations, perhaps suggesting the necessity of a difficult experimental program to measure each individual parameter. An example demonstrates, however, that a collective fit to a modest amount of real data may tightly constrain model behavior even though it only poorly constrains many parameter combinations. Low uncertainty predictions can thus be made without knowledge of precise values for individual parameters.

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