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Stochastic Cell Fate Progression in Embryonic Stem Cells[1] LING-NAN ZOU, ADELE DOYLE, SUMIN JANG, SHARAD RAMANATHAN, FAS Center for Systems Biology, Harvard University — Studies on the directed differentiation of embryonic stem (ES) cells suggest that some early developmental decisions may be stochastic in nature. To identify the sources of this stochasticity, we analyzed the heterogeneous expression of key transcription factors in single ES cells as they adopt distinct germ layer fates. We find that under sufficiently stringent signaling conditions, the choice of lineage is unambiguous. ES cells flow into differentiated fates via diverging paths, defined by sequences of transitional states that exhibit characteristic co-expression of multiple transcription factors. These transitional states have distinct responses to morphogenic stimuli; by sequential exposure to multiple signaling conditions, ES cells are steered towards specific fates. However, the rate at which cells travel down a developmental path is stochastic: cells exposed to the same signaling condition for the same amount of time can populate different states along the same path. The heterogeneity of cell states seen in our experiments therefore does not reflect the stochastic selection of germ layer fates, but the stochastic rate of progression along a chosen developmental path.

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Ling-Nan Zou
FAS Center for Systems Biology, Harvard University

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