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**Philosophy of the article**: framed around answering two questions.

(i) “What path through state space is a cell undergoing differentiation/reprogramming most likely to take?”

(ii) “How much more likely is a cell to occupy one state than another?”

Answer to question (i) given by P\_trans, answer to question (ii) given by P\_ss.

Equivalent to the local landscape vs global landscape dichotomy.

1. Introduction- two questions, and how the landscape idea relates to them. Note that landscapes are not brought up for their own sake, but motivated by the need to answer these fundamental questions. No math.
2. Mathematical models of regulatory networks (CME, SDE), and how central question can be answered mathematically via P\_ss and P\_trans. Discussion of Fokker-Planck and transition path math (including path integrals) goes here. Level of sophistication low enough that non-math expert can follow, but high enough that it is not substance-less for expert.
3. Global vs local landscapes, counterintuitive properties (like increasing noise reduces transition rate, fact that local landscapes can depend strongly on time). At end of section, write down general ‘definition’ and how to think about it.
4. Examples section. Discuss whether a given landscape is global/local, when applicable (i.e. is it only valid in the continuous regime?), what it is good for.
5. Applications. (cancer, development, reprogramming)
6. Challenges for landscape idea. (ex: linking complicated models to data)
7. Conclusion.

**Main points:**

1. landscapes are fundamentally probabilistic entities, and state-dependent noise must be taken into account
   1. state-dependent noise leads to behavior qualitatively different from the deterministic system, and it cannot be averaged away or approximated as unimportant in many cases
2. no landscape can answer both of the above questions; instead, different landscapes are useful for answering different questions
3. landscapes may not be the best tool for predicting transition paths; instead one should consider using the path integral/least action path formalism to get them directly