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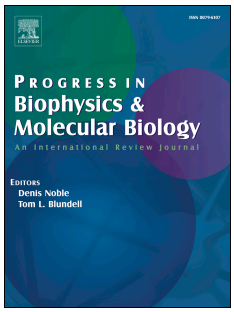

Branching and oscillations in the epigenetic landscape of cell-fate determination

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Branching and oscillations in the epigenetic landscape of cell-fate determination

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Abstract. The well-known Waddington's epigenetic landscape of cell-fate determination is not static but varies because of the dynamic gene regulation during development. However, existing mathematical models with few state variables and fixed parameters are inadequate in characterizing the temporal transformation of the landscape. Here we simulate a decision-switch model of gene regulation with more than two state variables and with time-varying repression among regulatory factors. We are able to demonstrate multi-lineage differentiation at different timescales that portrays the branching canals in Waddington's illustration. We also present a repressilator-type system that activates suppressed genes via sustained oscillations in a flattened landscape, hence providing an alternative scheme for cellular reprogramming. The time-dependent parameters governed by gradient-based dynamics regulate cell differentiation, dedifferentiation and transdifferentiation. Our prediction integrates the theories of branching and structural oscillations in cell-fate determination, which reveals key temporal patterns of cell differentiation and associated diseases, such as cancer.

Keywords. gene regulatory network, stem cells, pluripotency, synthetic biology, multistability, attractor