Automated Design of Pluripotent Stem Cell Self-Organization.

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Authors: Ashley R G Libby, Demarcus Briers, Iman Haghighi, David A Joy, Bruce R Conklin, Calin Belta, Todd C McDevitt

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Public Summary:
Human pluripotent stem cells (PSCs) have the intrinsic ability to self-organize into complex multicellular organoids that recapitulate many aspects of tissue development. However, robustly directing morphogenesis of hPSC-derived organoids requires novel approaches to accurately control self-directed pattern formation. Here, we created an in silico computational model of PSC dynamic movement and organization in a tissue culture dish in vitro using an extended Cellular Potts model. This then enabled a machine learning optimization approach to predict experimental conditions that yield targeted multicellular patterns. Furthermore, in vitro the predicted experimental parameters quantitatively recapitulated the in silico patterns. These results demonstrate that morphogenic dynamics can be accurately predicted through model-driven exploration of hPSC behaviors via machine learning, thereby enabling spatial control of multicellular patterning to engineer human organoids and tissues.

Scientific Abstract:
Human pluripotent stem cells (hPSCs) have the intrinsic ability to self-organize into complex multicellular organoids that recapitulate many aspects of tissue development. However, robustly directing morphogenesis of hPSC-derived organoids requires novel approaches to accurately control self-directed pattern formation. Here, we combined genetic engineering with computational modeling, machine learning, and mathematical pattern optimization to create a data-driven approach to control hPSC self-organization by knock down of genes previously shown to affect stem cell colony organization, CDH1 and ROCK1. Computational replication of the in vitro system in silico using an extended cellular Potts model enabled machine learning-driven optimization of parameters that yielded emergence of desired patterns. Furthermore, in vitro the predicted experimental parameters quantitatively recapitulated the in silico patterns. These results demonstrate that morphogenic dynamics can be accurately predicted through model-driven exploration of hPSC behaviors via machine learning, thereby enabling spatial control of multicellular patterning to engineer human organoids and tissues. A record of this paper's Transparent Peer Review process is included in the Supplemental Information.