Summary of Our Previous Results

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SOC control of genome expression

We have investigated the dynamics of collective gene behavior in several biological processes associated with changes in the cell fate from early embryo development in human and mouse (single cell), and terminal cell fates (helper T17 cell (single cell); human leukemia HL-60 cells; human breast cancer MCF-7 cells) at the single-cell and cell-population levels.

Regarding the mechanism of the cell-fate change through the self-organization of whole-genome expression (mRNA: microarray data and RNA: RNA-Seq data), we have demonstrated that, in all of the models analyzed, a self-organized critical transition (SOC) in whole-genome expression [Tsuchiya, M. et al., 2015 and 2016; Giuliani, A. et al., 2017] plays an essential role in the change in the genome state at both the population and single-cell levels:

1) Self-Organization Through Criticality: In the cell-fate change at the terminal phase (determination of differentiation for the cell population), critical dynamics self-organizes whole-genome expression into a few distinct response expression domains (critical states). Two distinguished critical behaviors, sandpile-type transitional behavior and scaling-divergent behavior (genomic avalanche), are observed when overall expressions are grouped according to the fold-change in expression and the temporal variance of expression, *nrmsf* (normalized root mean square fluctuation), respectively (see details in Methods [Tsuchiya, M. et al., 2016]). Sandpile critical behaviors (criticality) are evident in the fold-change in expression for both human and mouse embryo development. A physical explanation for such critical dynamics in the fold-change is that amplification in a critical state stemmed from a stochastic resonance effect in the change in the ensemble of stochastic expression [Tsuchiya, M.

et al., 2015]. Sandpile-type criticality shows diverging behaviors of up- and down-regulation at a critical point (CP), whereas in a genomic avalanche order (scaling) and disorder (divergence) are balanced at the CP (similar to the characteristics at the edge of chaos [Langton, 1990; Waldrop, 1992; de Oliveira, 1992]). Importantly, SOC does not correspond to a phase transition in overall expression from one critical state to another. Instead, it represents self-organization of the coexisting critical states through a critical transition, i.e., SOC consolidates critical states into a genome expression system. In each critical state, coherent (collective/coordinated) behavior emerges in ensembles of stochastic expression by more than 50 elements (coherent-stochastic behavior). The characteristics of the self-organization through SOC become apparent only in the collective behaviors of groups with an average of more than 50 genes (mean-field approach).

2) **Timing of the Genome-State Change**: At both the population and single-cell levels, the cell-fate change in the genome is determined through the erasure of initial-state criticality (as a boundary condition of SOC control):

a) **In terminal cell fates**, the cell-fate change (commitment to cell differentiation) occurs at the end of a dissipative global perturbation in self-organization through the erasure of an initial-state criticality. As a proof of this idea, the EGR-stimulation of MCF-7 cells (cell population), where the cell fates do not change over time (cell proliferation and no differentiation), does not exhibit a transitional change (i.e., no erasure of criticality; see Figure 5 in Tsuchiya, M. et al., 2016) in critical dynamics. The independence of the choice of the initial state at $t = t_0$ for the breakdown of sandpile-type criticality at $t = t_b$ (condition: $t_0 < t_b$) further confirms the timing of the genome-state change. The time point (t_0) of the initial state is earlier or equal to the onset of the pulse-like global perturbation; after the global perturbation, this independence does not hold, which suggests that a pulse-like global perturbation may be related to the first stage of cell-fate determination (process for autonomous terminal differentiation). The result suggests that the terminal cell fate is determined

through two stages: the first stage by means of a pulse-like global perturbation, and the commitment stage through the erasure of initial-state criticality. Quantitative evaluation of global perturbation reveals that dynamic interactions between critical states determine the critical-state coherent regulation. The occurrence of a temporal change in criticality perturbs this between-states interaction, which directly affects the entire genomic system, and thus suggests that the erasure of criticality is associated with a loss of the initial SOC control mechanism for the dynamical change in the entire genomic system (i.e., pruning procedure for the regulation of global gene expression at the initial state).

b) The reprogramming of early human and mouse embryo cells destroys the zygote SOC control to initiate self-organization in the new embryonal genome, which passes through a stochastic overall expression pattern. This timing of reprogramming was further confirmed by the facts that i) the Pearson correlation between overall RNA expression (RNA-Seq data) in the zygote and developed cell states revealed a critical transition between the middle and late 2-cell states; the low correlation showed the loss of zygote embryogenesis after the middle 2-cell state, and ii) the choice of the initial state is independent of the breakdown of sandpile-type criticality; the choice of the initial state before the middle 2-cell state does not change the erasure event of criticality. The breakdown of early SOC zygote control in overall expression indicates that significant global perturbation occurs to destroy SOC zygote control in early embryo development.

The results suggest the existence of specific molecular-physical routes for the erasure of critical dynamics for the cell-fate decision.

3) **SOC-Control Landscape**: The development of SOC control in early mouse embryo development exhibits a transition from a sandpile-type criticality to another one through a stochastic pattern, i.e., an SOC-control landscape: a valley (SOC control: the

zygote single-cell stage to the early 2-cell state) - ridge (non-SOC control: the middle to the late 2-cell state) - valley (SOC control: the 8-cell state to the morula state). This should provide a qualitative image of the epigenetic landscape framed in broad terms of the global activation-deactivation dynamics of the genome that is generally consistent with the DNA de-methylation-methylation landscape [Guo, H. *et al*., 2014].

4) **Existence of a Critical Transition of Collective Expression Dynamics in the Ensemble of Cells**: The onset of the genome-state change (at the breakdown of initial-state SOC control) exhibits a clear difference between single cells and a cell population: cell populations do not exhibit a stochastic pattern, in contrast to single cells in early human and mouse embryonic development. The stochastic pattern is confirmed by a low Pearson correlation between the zygote and early embryo single-cell states at the onset, whereas in cell populations, the Pearson correlation for overall expression at different time points is close to unity. This suggests that there is a transition from single-cell stochastic to highly correlated cell-population behavior at the genome-state change in overall expression as the emergent layer of a relevant collective regulation behaviors starting from a given threshold number of cells. The near-stochastic pattern of helper Tell 17 cell differentiation at the onset (single cell) supports such a transition.

5) **Long-term global mRNA oscillation underlies SOC control**: The sub-critical state (ensemble of low-variance gene expressions) sustains critical dynamics in SOC control of terminal cell fates, where a sub-critical state forms a robust cyclic state-flux with a super-critical state (ensemble of high-variance gene expressions) through the cell nuclear environment. The results show that there is no fine-tuning of an external driving parameter to maintain critical dynamics in SOC control and therefore, the oscillatory expression dynamics of sub-critical states generates a long-term global mRNA oscillation [Tsuchiya, M. et al., 2007] to sustain the self-control of SOC.

References:

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