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Stochastic Model of Stem Cell Differentiation

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Abstract

Human embryonic stem cells (hESCs) are pluripotent cells which can differentiate to many cell types such as heart muscle cells and insulin-secreting cells. As such, hESCs have great potential for future therapies. An important issue in the field of hESC research is the lack of a quantitative framework capturing the process of stem cell differentiation. We developed a mathematical model to simulate the gene expression interaction between Nanog and Sox17, i.e. two critical genes in specifying hESCs to endoderm cells and further into insulin-secreting cells. Mathematically we employed the Runge-Kutta (RK4) method to solve stochastic differential equations with the expression levels of Nanog and Sox17 as equation variables. The model results show that as the expression of Nanog is suppressed in hESC differentiation, its inhibition effect on Sox17 is reduced, resulting in more hESCs differentiated into endoderm cells. The model results are in good agreement with experimental data and can quantitatively illustrate the effect of growth factors on the hESC differentiation process.

Methods

We constructed a gene expression network describing the interactions among Nanog, Oct4 and Sox17 (NOS) in hESCs (Figure 1). To better match the model with the observed gene expression, we consider gene expression noise in Nanog expression as suggested previously [2].

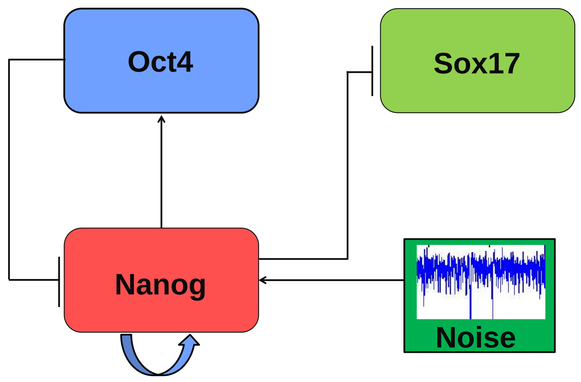

Figure 1: Schematic of relationship between different transcription factors. Nanog activates Oct4 promoting self-renewal (indicated by blue arrow). Oct4 also demonstrates negative feedback for Nanog inhibition. Nanog also inhibits Sox17.

The model consisted of three stochastic/ordinary differential equations with parameters acquired or estimated [2]. Noise was introduced to account for stochastic processes in the regulatory network. The equations were solved by the RK4 method.

Results

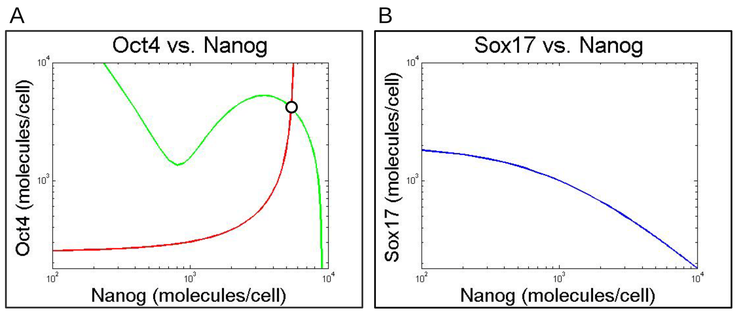

Figure 2: The dynamic behavior of the NOS gene regulatory network. (A) The interaction between Oct4 and Nanog is shown here. The white circle is steady state for both Nanog and Oct4. If small perturbation applied, the system will return to its steady state. (B) The steady-state expression level of Sox17 at different level of Nanog is shown. Suppression of Nanog would increase the expression level of Sox17.

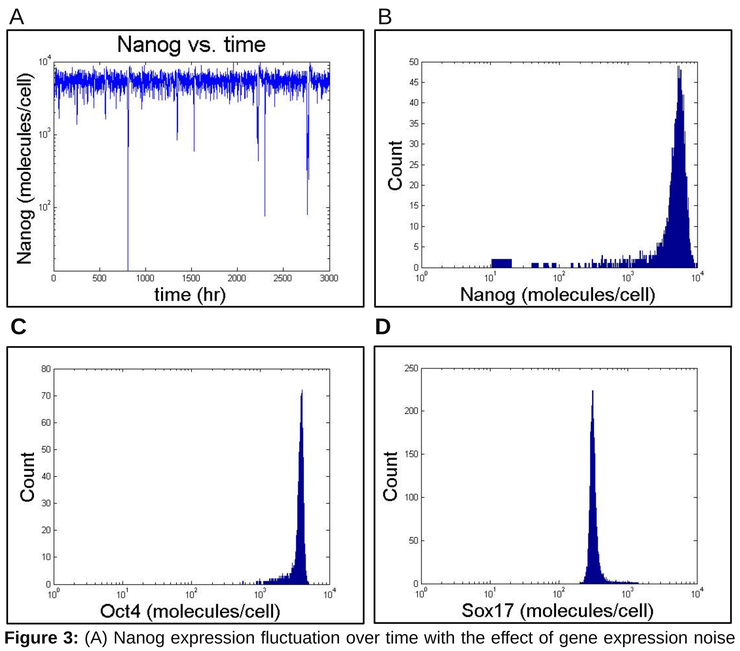

Figure 3: (A) Nanog expression fluctuation over time with the effect of gene expression noise considered. Cells with temporal low-Nanog level eventually restore the population with high-Nanog expression. (B-D) Model results of distribution of the three genes (N=10,000 cells). Gene expression noise leads to the dispersion of the distribution.

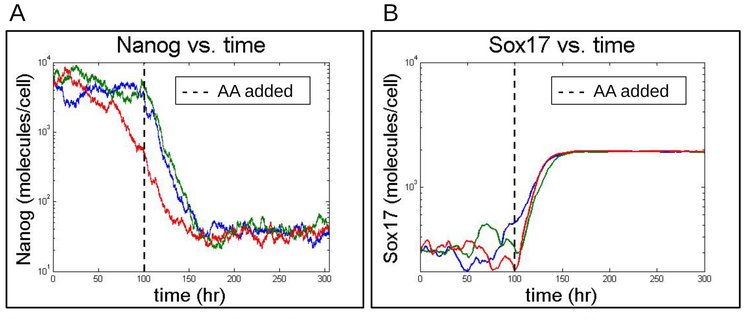

Figure 4: Model simulation of the differentiation process. Assuming at t=100 hour, Activin A is added to the medium inducing stem cells to differentiate. (A) Nanog and (B) Sox17 expression dynamics over time from three randomly selected cells. The expression level of Nanog and Sox17 reached steady-state at t=160 hrs.

Results

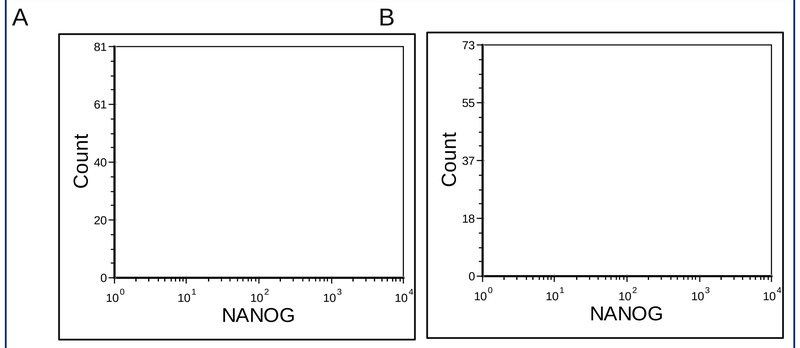

Figure 5: Experimental data of Nanog expression distribution (A) before differentiation and (B) after 4-day differentiation induced by 100 ng/ml Activin A. Data was acquired *via* flow cytometry and 10,000 cells were analyzed for each sample. Nanog expression level is shown as relative fluorescence intensity.

Conclusion

- A mathematical model has been constructed to study NANOG, OCT4 and SOX17 (NOS) gene expression interaction in hESCs.
- The incorporation of gene expression noise can better illustrate the cell-to-cell variation observed in stem cell populations.
- Model results capture the differentiation dynamics of hESCs toward endoderm.

Future Work

- The model can be extended to incorporate larger networks of gene expression.
- Expressions are developed to capture the action of growth factors utilized for the differentiation of hESCs.

References

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2. T. Kalmar *et al.*, Regulated fluctuations in nanog expression mediate cell fate decisions in embryonic stem cells. *PLoS biology* **7**, e1000149 (Jul, 2009).
3. N. Jeremy Kasdin. Runge-Kutta algorithm for the numerical integration of stochastic differential equations. *Journal of Guidance, Control, and Dynamics*, **18**(1):114–120 (Jan, 1995).

Acknowledgements

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