Report for the Course Modelling in Computational Science, HT23

Project 2: Cell reprogramming

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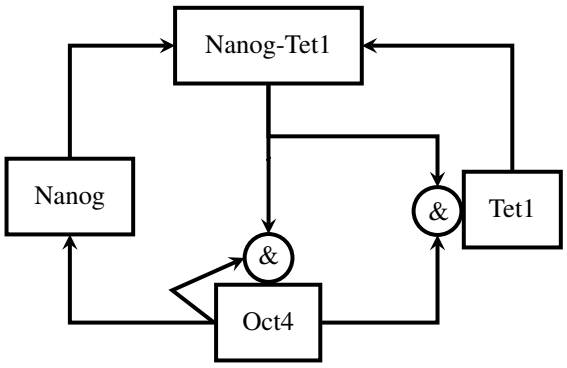

Figure 1: A flowchart showing the dependence of the transcription factors.

Introduction

The following report is part of the second project of the course Modelling in Computational Science, BERN01, taken at Lund university. In this project we model the interplay of three transcription factors which are relevant for mouse embryonic stem cells to reach induced pluripotency. For this we will discuss the setup of the model in the first part of the report and then reproduce the results from [1] in the second part. The code to the project was implemented in `python`. The project report and code can be found online under **repository**.

The setup

According to [1] the transcription factors Nanog and Oct4 are crucial in establishing pluripotency of a cell. In our simplified model the dependence of the transcription factors Nanog, Oct4 and Tet1 is given by figure 1. Here Nanog and Tet1 form a complex Nanog-Tet1 together and the & symbol denotes that two transcription factors are required for activation. Using the Michaelis-Menten model one obtains the ordinary differential equation

$$\begin{bmatrix} \mathrm{N} \\ \mathrm{O} \\ \mathrm{T} \end{bmatrix}' = \begin{bmatrix} N_{\text{over}} + \mathrm{LIF} + p_N \cdot \frac{\mathrm{O}/K_O}{1+\mathrm{O}/K_O} - \mathrm{N} \\ O_{\text{over}} + \mathrm{LIF} + p_O \cdot \frac{\mathrm{O}/K_O}{1+\mathrm{O}/K_O} \cdot \frac{(\mathrm{N\text{-}T}/K_{NT})^n}{1+(\mathrm{N\text{-}T}/K_{NT})^n}, \mathrm{O}) - \mathrm{O} \\ T_{\text{over}} + p_T \cdot \frac{\mathrm{O}/K_O}{1+\mathrm{O}/K_O} \cdot \frac{(\mathrm{N\text{-}T}/K_{NT})^n}{1+(\mathrm{N\text{-}T}/K_{NT})^n} - \mathrm{T} \end{bmatrix}. \tag{1}$$

Here N, O, T and N-T denote the concentration in the cell of Nanog, Oct4, Tet1 and Nanog-Tet1 respectively[1]. The other parameters are given for mouse embryonic fibroplast steady state (MEF) by table 1. We note that parameter LIF models the effect of the leukemia inhibiting factor in promoting the differentiation of the cells. The parameters N_{over}, O_{over} and T_{over} describe how much Nanog, Oct4 and Tet1 are overexpressed in

[1]Here we deviate from the notation in [1] by ommitting the concentration brackets and subscript.

Parameter	value
Over expression N_{over}	0
Over expression O_{over}	0
Over expression T_{over}	0.05
Probability p_N	1
Probability p_O	1
Probability p_T	1
Hill coefficient K_{NT}	0.2
Leukemia inhibiting factor LIF	0
Dissociation constant K_d	0.1
Dissociation constant K_O	0.3
Dissociation constant K_{NT}	0.2

Table 1: Default parameter choices. Taken from [1]

the cell. We also note that the system 1 has two equilibrium configurations. One where N, O and T are all > 0.5 one where all are small. We will inspect this behaviour more closely in our simulation experiments.

The experiments

In the following part of the report we will discuss our reproduction of some figures given in [1]. To solve the system 1 we used the built-in solver from `scipy` with default parameters since this yielded satisfactory results.

Variying Nanog, Oct4 and Tet1 seperately

Our first experiment series was taken from [1]. The results can be seen in figure **fi:NOT˙0.3**. This figure consists of 3 subplots for each of which the x-axis represents time and the y-axis represents the concentration of the corresponding parameter O_{over}, N_{over} and T_{over}. Each simulation in the 3 subplots consists of 3 parts in which the parameters given in table 1 are varied. The parameters which deviate are given on the x-axis. In the first part of each simulation the cell is allowed to reach the MEF steady state. In the second part one of the transcription factors is overexpressed. In the third part the simulation returns to the MEF state or the MEF state with LIF set to 0.06 depending on whether the cell succeeded in reaching a pluripotent state. In the first subplot one sees that setting N_{over} alone to 0.3 is insufficient to reach pluripotency. In the second and third subplots one sees that setting O_{over} and T_{over} respectively to 0.3 is sufficient to reach pluripotency. Thus in these cases LIF is activated. All of this agrees with what we expect from the diagram and laboratory experiments (see [1] for more).

The second experiment is analogous to the first with the difference that we now set N_{over}, O_{over} and T_{over} to 0.2 in the respective experiments. Figure **??** shows the results. Once again we see that for Oct4 and Tet1 the state reaches pluripotency whilst it fails to reach pluripotency for Nanog. If we compare figure **??** with figure **??** we see that

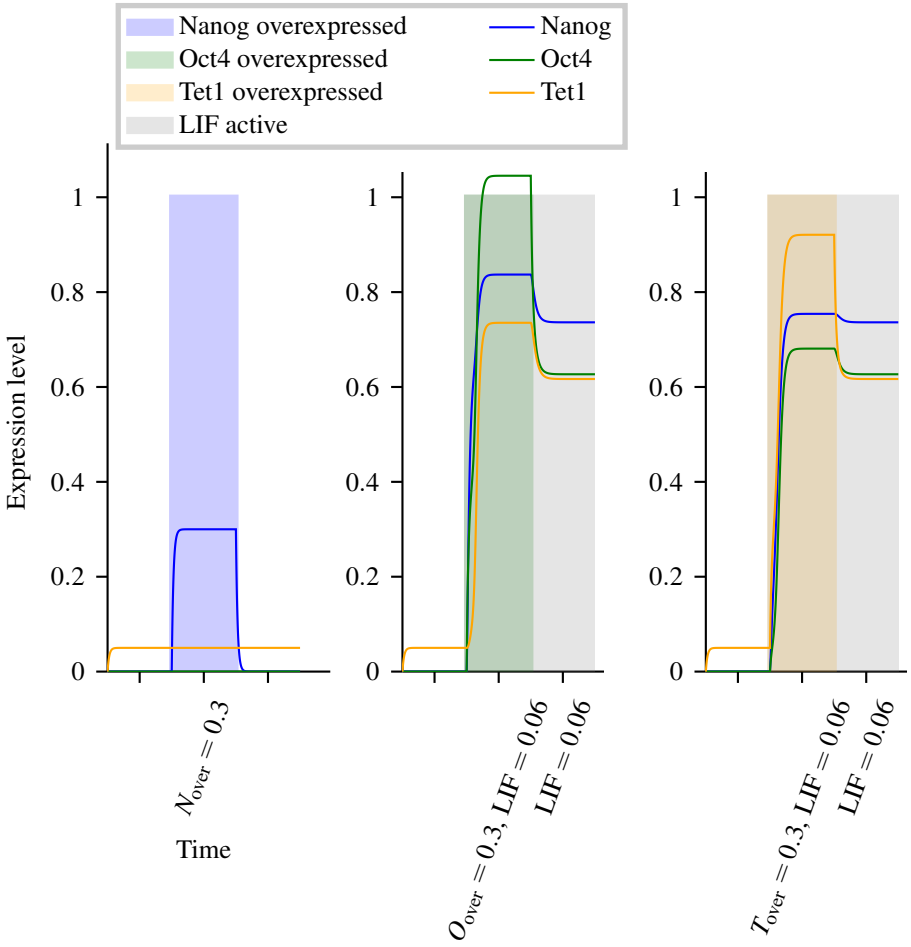

Figure 2: Overexpression of 0.3.

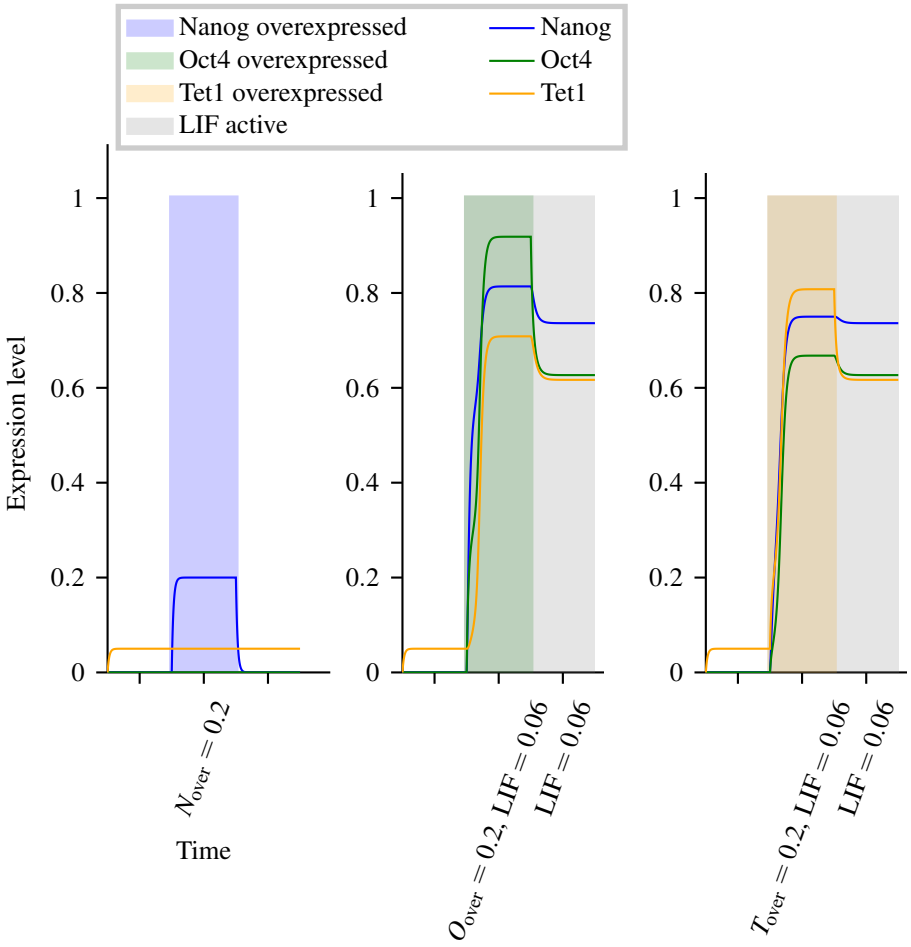

Figure 3: Overexpression of 0.2.

the concentrations during the overexpression phase of the experiment are lower than for the previous experiment. This is to be expected since there are no repressors in this particular model. Also as expected the steady states in the first and third part of each simulation is identical to the previous experiment.

Figure **??** gives the results with an overexpression of 0.13 and yields the same result as the previous experiment. Once again the concentration levels are reduced for the overexpression phase.

In a final experiment of this series the overexpression was set to 0.1. Figure **??** shows the results. We see here that in all cases the cells fail to reach pluripotency as the concentrations of Nanog, Oct4 and Tet1 fail to meet the threshold.

We note that our figures differ a little from [1] in that we let the simulation run for longer to reach the steady state. This explains why our charts are not exactly clones.

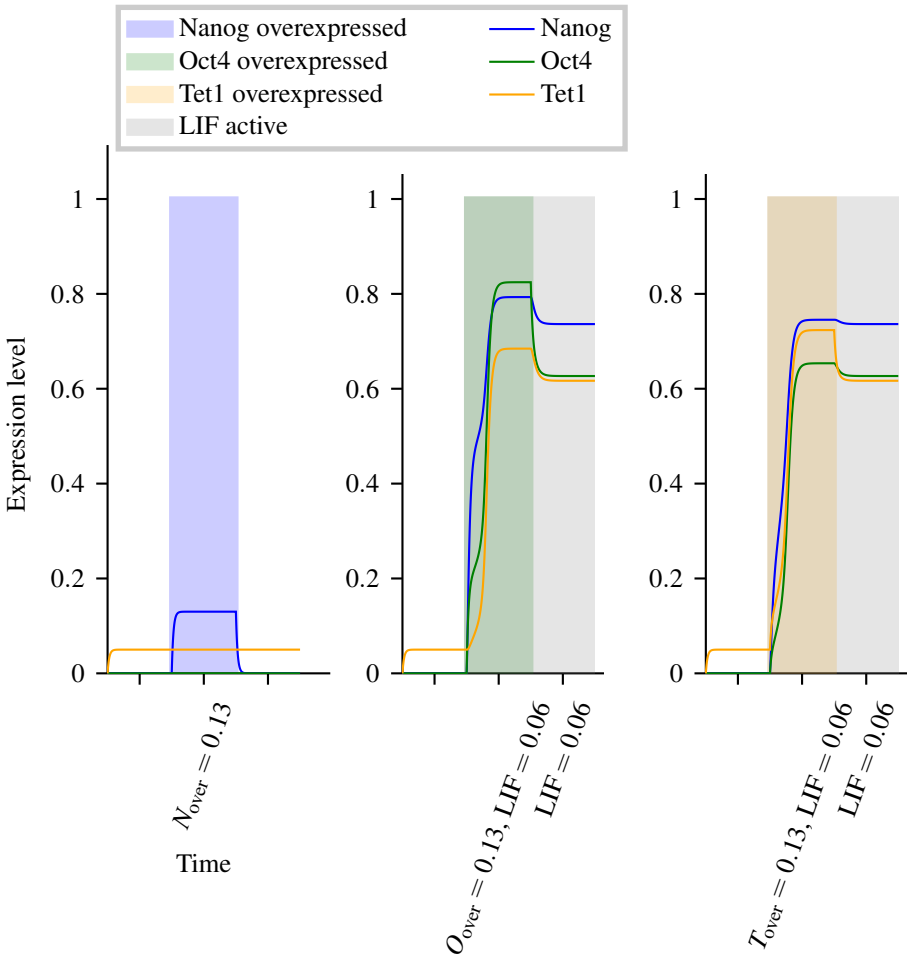

Figure 4: Overexpression of 0.13.

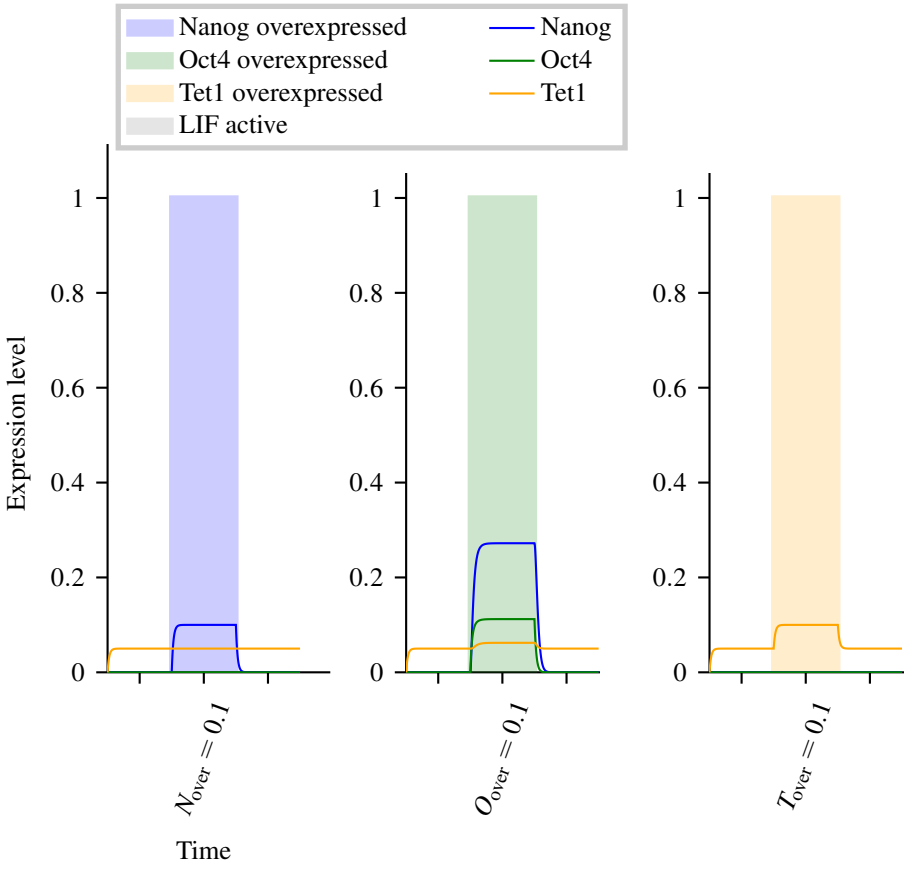

Figure 5: Overexpression of 0.1.

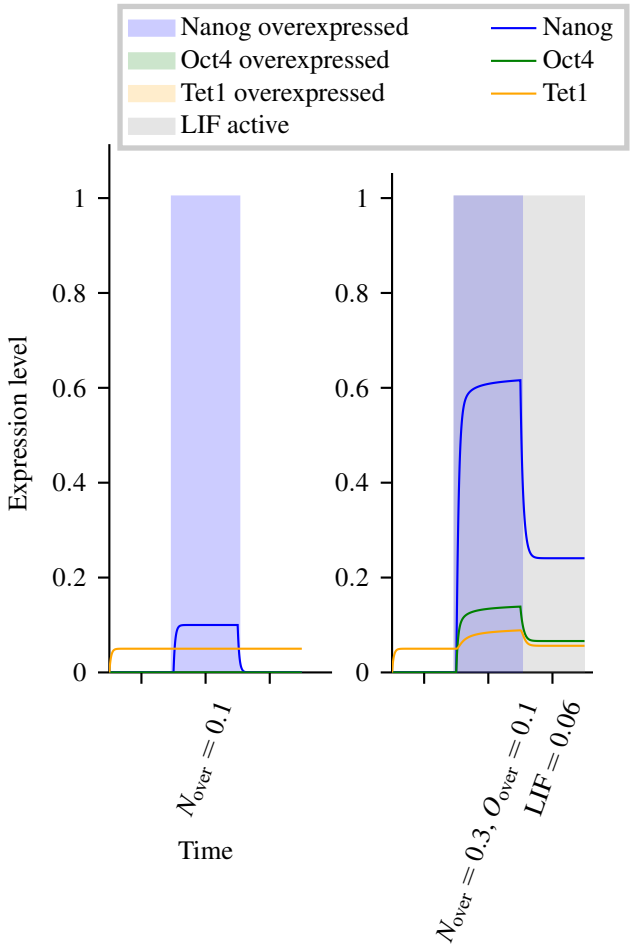

Figure 6: Nanog and Oct4 active.

Inducing Pluripotency with Nanog and Oct4

Our next experiment deals with the fact that according to [1] Nanog and low levels of Oct4 are sufficient to reach pluripotency even though the same levels of Nanog and of Oct4 seperately are insufficient. For this we set O_{over} to 0.1 and N_{over} to 0.4. The results are shown in figure **??**.

Withdrawing LIF

In a final experiment we simulated how a cell in pluripotent state reacts under withdrawal of LIF. Our first

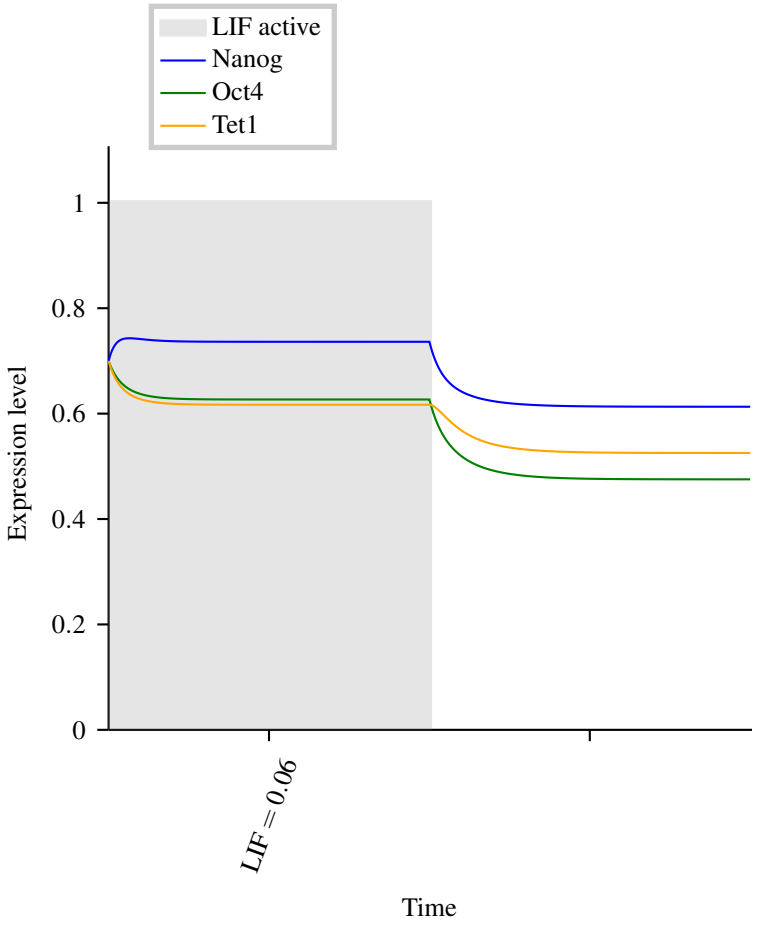

Figure 7: Withdrawing LIF.

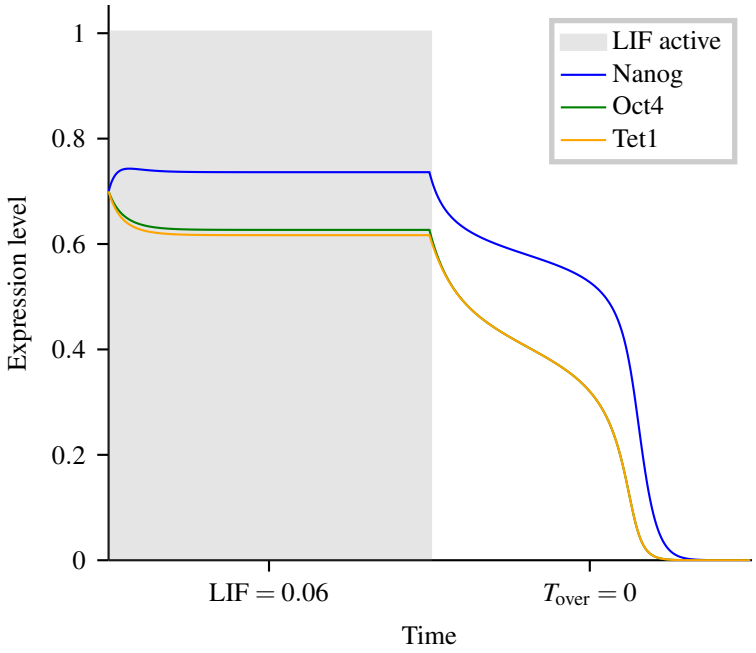

Figure 8: Withdrawing LIF.

Conclusion

Bibliography

[1] V. Olariu, C. Lövkvist, and K. Sneppen, "Nanog, oct4 and tet1 interplay in establishing pluripotency," *Scientific Reports*, vol. 6, no. 1, p. 25 438, May 2016, ISSN: 2045-2322. DOI: 10.1038/srep25438. [Online]. Available: https://doi.org/10.1038/srep25438.

[2] computational-science-HT23, *Github repository to the project.* Online, 2023. [Online]. Available: https://github.com/TheoKoppenhoefer/computational-science-HT23.

[3] V. Olariu, *Modelling in computational science, bern01, 7.5hp, Practical and theoretical knowledge of numerical methods used for solving ode modells for real life science problems.* BERN01, University of Lund, Sep. 2023.