

Supplementary Information

A Monte Carlo method for *in silico* modeling and visualization of Waddington's epigenetic landscape with intermediate details

Xiaomeng Zhang ^{1,†}, Ket Hing Chong ^{1,†}, Lin Zhu ² and Jie Zheng ^{2,*}

[†]These authors contributed equally to this work.

¹ School of Computer Science and Engineering

Nanyang Technological University, 639798 Singapore

² School of Information Science and Technology, ShanghaiTech University, Pudong District, Shanghai 201210, China

*Correspondence: zhengjie@shanghaitech.edu.cn

1 Drawing Waddington's epigenetic landscape using ODEs

1.1 Introduction

Our algorithm for quantifying Waddington's epigenetic landscape was implemented in MATLAB. The source codes are distributed in different folders for different models of gene regulatory network (GRN) (as discussed in our paper). This document explains how you can run the MATLAB code to plot the Waddington's epigenetic landscape.

This MATLAB code package in the folder named "ODEs" can be modified according to user's own GRN model in ordinary differential equations (ODEs), which can be encoded in the `equations.m` file. For details please read Section 1.4 titled "Using the code to plot potential landscapes for your gene networks in ODEs."

1.2 Usage

For different GRNs the model equations are different, so there are 5 folders for the 5 models presented in the main text. Open a model folder and you can run the MATLAB code to plot the Waddington's epigenetic landscape. Each folder contains 2 MATLAB files:

1. `Setting_and_running.m`
2. `equations.m`

Five common MATLAB files are located at a common code folder.

1. `GetAllInitialConditions.m`
2. `GetAllTrajectories.m`
3. `GetPositionProbabilities.m`
4. `GetOneTrajectory.m`
5. `DrawLandscape.m`

To run and plot the Waddington's epigenetic landscape, open the `Setting_and_running.m` file in MATLAB editor and click the Run button in the menu bar or press F5.

Alternatively, you can run and plot the landscape in the MATLAB Command Window. Type the filename and then press Enter at the command line as below:

```
>>Setting_and_running
```

After the calculation is finished with N trajectories (N is set to 100,000 by default but user can set N to a different integer number that is nonnegative in the file `Setting_and_running.m`), you will obtain two graphs: the 3D view and top view of the landscape.

1.3 Case Studies

Case Study 1: Bistable synthetic toggle switch from [1]

The GRN is given in Fig. S1. According to the Hill function formulation, the two equations for the GRN are:

$$\frac{du}{dt} = \frac{\alpha_1 \cdot S^3}{S^3 + v^3} - k_1 u, \quad (S1)$$

$$\frac{dv}{dt} = \frac{\alpha_2 \cdot S^3}{S^3 + u^3} - k_2 v, \quad (\text{S2})$$

We used the model parameters given in [2, 3] where $\alpha_1 = 3$, $\alpha_2 = 3$, $S = 1$, $k_1 = 1$ and $k_2 = 1$.



Figure S1: The network interactions for the model in Case Study 1, which is a simple synthetic toggle switch that contains two genes u and v . The two genes inhibit each other.

To plot the landscape, open the folder `Gardner_2000_2_genes_model`. Type the filename at the command line as below:

```
>>Setting_and_running
```

After the calculation completes with $N = 100,000$ trajectories, the 3D view and top view of the Waddington's epigenetic landscape will be plotted. Finally, the time taken for the calculation and plotting of the landscape will be printed in the command window. The potential landscape displays 2 attractors as shown in Fig. S2.

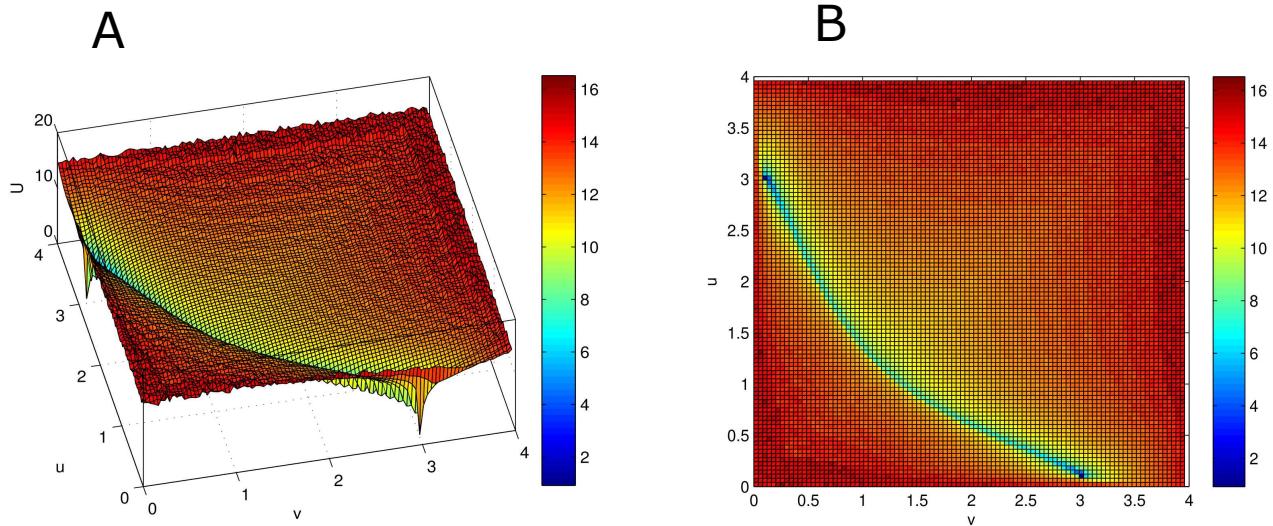


Figure S2: Plots of the landscape of the bistable synthetic toggle switch from [1]. (A) 3D view (B) Top view

Case Study 2: Quantification of Waddington's epigenetic landscape of the GRN model of cancer attractors [4]

The model of GRN from Li and Wang (2015) [4] is shown in Fig. S3. We used model equations given in [4] as listed below:

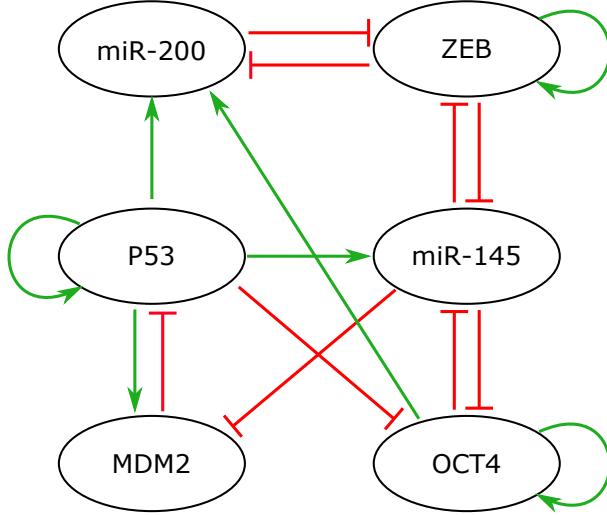


Figure S3: The GRN model of Case Study 2 from [4] contains 7 activations and 9 inhibitions, which are represented by green arrows and red lines with a short bar respectively.

$$\frac{dP53}{dt} = \frac{sa \cdot P53^4}{S^4 + P53^4} + \frac{b \cdot S^4}{S^4 + MDM2^4} - k \cdot P53 \quad (S3)$$

$$\frac{dMDM2}{dt} = \frac{a \cdot P53^4}{S^4 + P53^4} + \frac{b \cdot S^4}{S^4 + (miR145)^4} - k \cdot MDM2 \quad (S4)$$

$$\frac{dOCT4}{dt} = \frac{sa_1 \cdot (OCT4)^4}{S^4 + (OCT4)^4} + \frac{b \cdot S^4}{S^4 + P53^4} + \frac{b \cdot S^4}{S^4 + (miR145)^4} - k \cdot OCT4 \quad (S5)$$

$$\frac{d(miR145)}{dt} = \frac{a \cdot P53^4}{S^4 + P53^4} + \frac{b \cdot S^4}{S^4 + (OCT4)^4} + \frac{b \cdot S^4}{S^4 + ZEB^4} - k \cdot miR145 \quad (S6)$$

$$\frac{d(ZEB)}{dt} = \frac{sa_2 \cdot ZEB^4}{S^4 + ZEB^4} + \frac{b \cdot S^4}{S^4 + (miR145)^4} + \frac{b \cdot S^4}{S^4 + (miR200)^4} - k \cdot ZEB \quad (S7)$$

$$\frac{d(miR200)}{dt} = \frac{a \cdot P53^4}{S^4 + P53^4} + \frac{a \cdot (OCT)^4}{S^4 + (OCT)^4} + \frac{b \cdot S^4}{S^4 + (ZEB)^4} - k \cdot (miR200) \quad (S8)$$

where $a = 0.5$, $sa = 0.8$, $sa_1 = 0.8$, $sa_2 = 0.8$, $b = 0.1$, $S = 0.5$ and $k = 1$.

Open the folder `Li_2015_6_genes_model`, and type the filename at the command line as below:

```
>>Setting_and_running
```

After the calculation finishes, the 3D and top views of the Waddington's epigenetic landscape will be plotted. The potential landscape is shown to have four pairs of attractors as shown in Fig. S4.

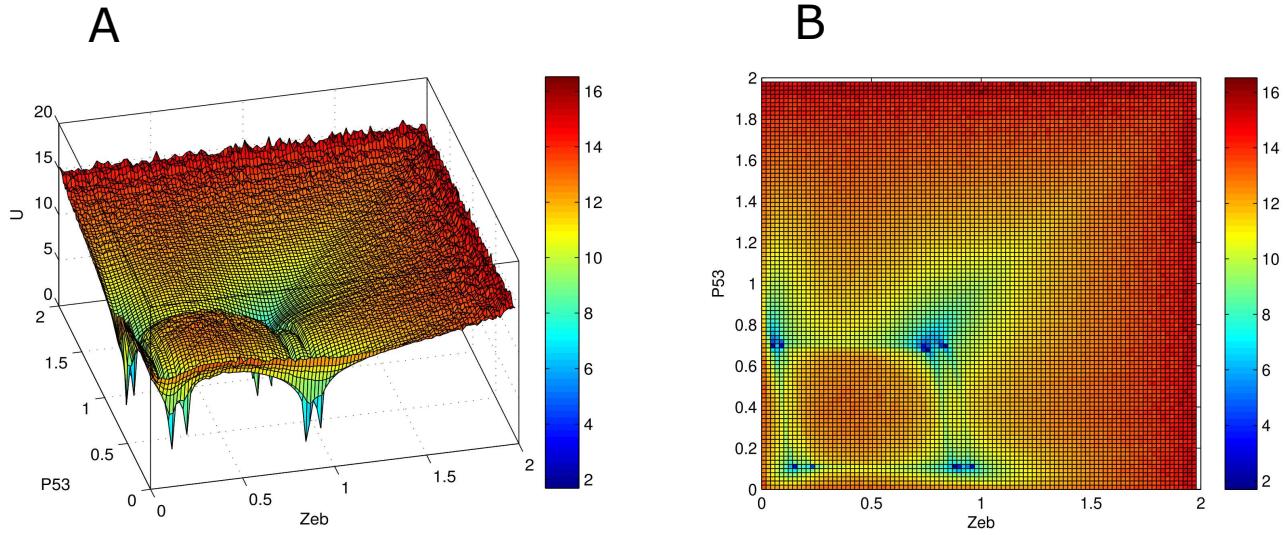


Figure S4: Plots of Waddington's epigenetic landscape of the GRN model of Li and Wang (2015) [4]. (A) 3D view (B) Top view

1.3.1 Case Study 4: Spiral attractors from [5]

The third example was selected to demonstrate the capability of our method to capture the dynamical features of spiral attractors. This model is an artificial network of two variables proposed by [5]. The original landscape shows four attractors, four saddle points and one repeller in the center. The potential landscape generated using our method is shown in Figures S5A and S5B. There are four attractors on the four corners of the landscape and one repeller in the middle. However, the basins of attractor are unique in that they are formed by a counterclockwise spiral (Figure S5A). The landscape also shows four valleys (or kinetic paths) connecting the four attractors. The valleys are formed by the unstable manifolds of saddle points as discussed in Case Study 1.

The conventional phase plane analysis can illustrate the vector field and the flows of the trajectories (Figure S5C), but it can only show the flows in terms of the counterclockwise spiral in a two-dimensional plane. Here, our potential landscape can quantify and depict the spiral attractors in a three-dimensional view of the potential landscape. The formulation of the potential $U = -\ln P$ which includes the probability of non-equilibrium state enables the quantitative description of the detailed transient behavior of the dynamical system.

1.3.2 Case Study 5: Cell cycle modeling by limit cycle oscillator from [6]

The fourth example is used to test the capability of our method to investigate another type of attractors, namely limit cycle attractor. This example is a 3-gene network model of limit cycle oscillator for modeling cell cycle control proposed by [6]. A few key proteins for controlling cell cycle were observed to oscillate [7], and [6] proposed an ODE model of gene network to explain why these proteins can oscillate in a limit cycle. Based on this 3-gene network we used our method to generate a potential landscape. The resulting potential landscape in Figures S6A-B shows a limit cycle attractor (in blue color).

The limit cycle is a unique feature of dynamical systems for describing trajectories attracted to a closed-form cycle from inside and outside the closed orbit [8]. It is traditionally illustrated as a closed-form orbit (with no intersection or crossing) in a two-dimensional diagram as shown in the top view of the potential landscape (Figure S6B). Limit cycle oscillations can be viewed as time-course simulations with a fixed periodic form of oscillation. The potential landscape constructed by our method can capture the limit cycle attractor in a 3D view (Figure S6A).

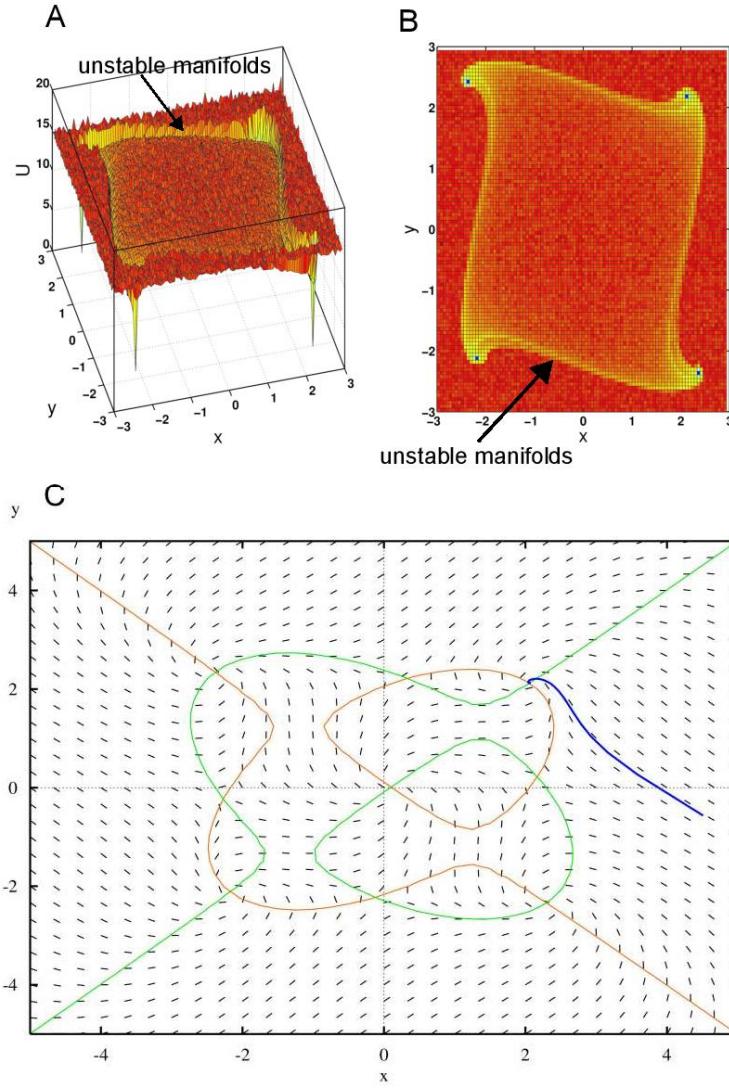


Figure S5: Potential landscape for Case Study 4. The Waddington's epigenetic landscape displays four basins of attraction. (A) 3D view: The Waddington's epigenetic landscape contains four spiral attractors (four blue dots) and the directions of the spirals are all counterclockwise. (B) Top view: There are unstable manifolds connecting any two attractors. (C) A conventional phase plane analysis shows the two nullclines where x or y does not change (green for y -nullcline and brown for x -nullcline) and the vector field. Intersections of the nullclines indicate the steady states. In this phase plane there are 9 intersection points corresponding to the 9 steady states: 5 unstable and 4 stable. The stability of the steady state can be determined by checking the eigenvalues of the eigenvectors: negative eigenvalues indicate stable steady states whereas positive eigenvalues indicate unstable steady states. Also shown is an example of a trajectory (blue line) being attracted to the stable steady state (one of the intersections between the nullclines at the top right). (Figure S5C was generated using XPPAUT, which can be downloaded from <http://www.math.pitt.edu/~bard/xpp/xpp.html>)

The potential landscape for using **Monte Carlo method with PCA dimensionality reduction** is given in Fig. S7. In order to run the MATLAB code for the Monte Carlo method with PCA dimensionality reduction set the `exe_dr=true` in the filename `Setting_and_running.m`. (To run the Monte Carlo method without PCA dimensionality reduction set the `exe_dr=false` in the filename `Setting_and_running.m`)

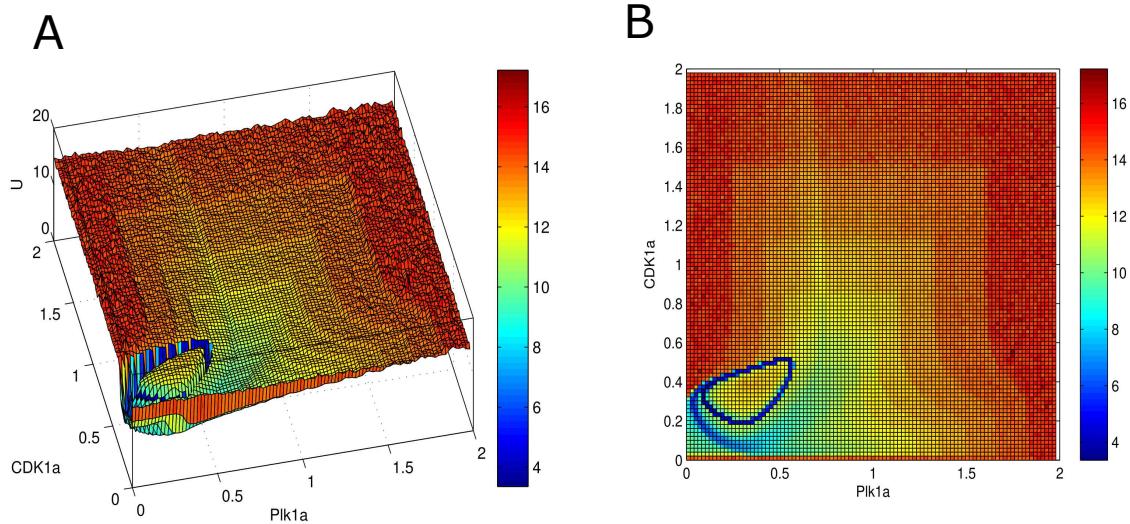


Figure S6: Potential landscapes for Case Study 5. (A) 3D view of the Waddington's epigenetic landscape for the 3-gene ODE model of cell cycle control which demonstrates the limit cycle attractor (Case Study 5). (B) Top view of the Waddington's epigenetic landscape for the ODE model of cell cycle control demonstrates the limit cycle oscillator, which corresponds to the limit cycle attractor.

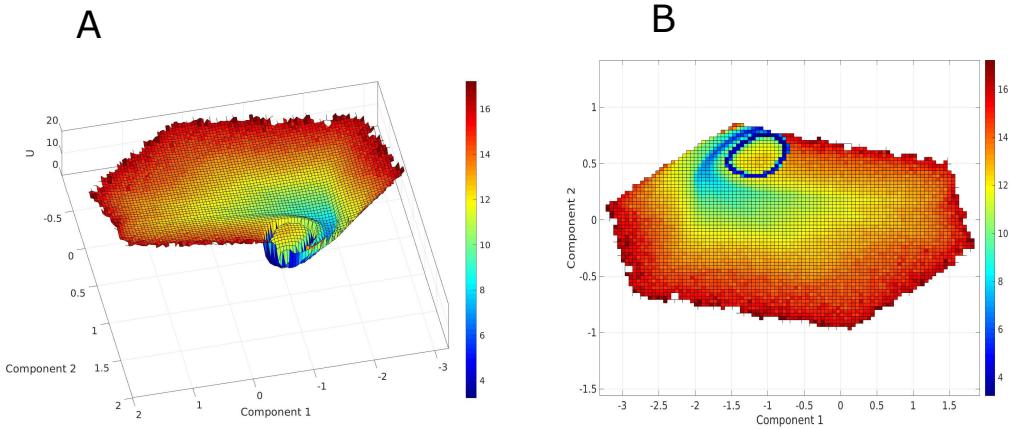


Figure S7: Potential landscape for Case Study 5 using Monte Carlo method with PCA dimensionality reduction. (A) 3D view of the Waddington's epigenetic landscape using Monte Carlo method with PCA dimensionality reduction where the landscape was plotted based on the first two principal components. The landscape shows there are two attractors which is consistent with the potential landscape obtained using the two selected genes GATA6 and NANOG as shown in Figure S6A. (B) Top view of the landscape.

1.4 Computational time

For existing models of Waddington's epigenetic landscape in the literature, most authors did not report computational time for obtaining potential landscapes. Here, we record the computational time for generating each of the landscapes using our Monte Carlo method (Table 1). We used MATLAB R2012b software installed on a Dell desktop computer running Windows 7 (64-bit) operating system with 8 GB memory (RAM). Table 1 shows the benchmark computational time in generating Waddington's epigenetic landscape. For example, even for the 52-gene model of [9], our method needs only 33 minutes and 50 seconds. One key factor that might affect the computational time is the non-linearity in the model equations. The 2-gene model from [5] contains four cubic terms, whereas the 52-gene model from [9] is composed of Hill functions and as such takes much less time. Moreover, Ferrell et al. (2011) [6] model with

non-linearity terms of multiplication between one variable and Hill functions required the third longest time although it contains only 3 variables.

Table 1: Benchmark computational time for generating Waddington’s epigenetic landscape

No.	Model	No. variables	No. interactions	Computational time
1	Gardner et al. (2000)	2	2	10 min 5 sec
2	Li and Wang (2015)	6	16	12 min 0 sec
3	Li and Wang (2013)	52	123	33 min 50 sec
4	Zhou et al. (2012)	2	8	39 min 21 sec
5	Ferrell et al. (2011)	3	3	20 min 22 sec

1.5 Using the code to plot potential landscapes for your gene networks in ODEs

In order to plot a potential landscape of your own model, you only need to edit two files: `equations.m` and `Setting_and_running.m`.

First, define your gene network model in ODEs in the file of `equations.m`. Secondly, change the model setting in the file of `Setting_and_running.m`. Set the variable names (`variableNames`) as the order of the equations according to the ODEs (e.g. for the Example 1, the `variableNames = {'u', 'v'}`). Then, you need to set a different maximum range of the state space for your gene network. For example, based on the prior knowledge from time-course simulations the maximum value of the level of a protein is say 3, then you may enter the maximum value as 4 (`range_max = 4`). We added a margin of 1 such that the landscape will cover enough values for getting a complete landscape. Because each GRN model equations and landscape is different, user may need to adjust and add a suitable margin value.

In order to set the state space for the random initial conditions, change the dimension of your model equations in ODEs. For example, if your ODEs contain n variables, then set:

```
initialRange = [zeros(1,n)+range_min; zeros(1,n)+range_max];
```

Also, you need to change the `index = [variable_1 variable_2]` to the two indices of genes (or proteins) of interest to you. If your model equations contain only 2 variables, then set the index to:

```
index = [1 2] where variable_1 = 1 and variable_2 = 2.
```

Finally, you can run the calculation to plot the Waddington’s epigenetic landscape as in the two aforementioned examples.

2 Drawing Waddington’s epigenetic landscape using stochastic method of CLE

2.1 Introduction

This section explains how to run the MATLAB code to generate the Waddington’s epigenetic landscape using a stochastic approach with Chemical Langevin Equation (CLE). The CLE implementation was adapted from [10].

This MATLAB code package in the folder named “CLE” can be modified according to your GRN model in ODEs. The ODEs can be converted into CLE with different rate constants and stoichiometric

matrix \mathbf{V} which should be defined in the `GetTrajectory.m` file. The definition of CLE and the explanation of how to convert ODEs into CLE are given in Section 2.4. For details read Section 2.4 titled “Using the code to plot potentials landscape for your gene networks in CLE.”

2.2 Usage

Open the folder of the model that you wish to run to plot the Waddington’s epigenetic landscape. In our package, we have provided files for two models, Example 1 and Example 2 which correspond to the two examples of ODE model in the preceding section. Each folder contains 2 MATLAB files:

1. `Setting_and_running_CLE.m`
2. `GetTrajectory.m`

Three common MATLAB files are located at a common code folder for CLE.

1. `GetPositionProbabilities.m`
2. `GetAllTrajectories.m`
3. `DrawLandscape.m`

To plot the Waddington’s epigenetic landscape, open the first m file `Setting_and_running_CLE.m` in MATLAB editor and click the Run button on the menu bar.

After the calculation finishes with N simulated trajectories, user should obtain two graphs: the 3D view and the top view of the landscape. The default value of N is 100,000 but user can modify the code to set the value of N .

2.3 Case Studies

Case Study 1: Bistable synthetic toggle switch from [1]

We use the ODE model equations given in Eqn (S1) and Eqn (S2) [2].

Open the folder `Gardner_2000`. Type the filename at the command line as below:

```
>>Setting_and_running_CLE
```

After the calculation finishes with $N = 100,000$ simulated trajectories, the 3D and top views of the Waddington’s epigenetic landscape will be plotted. Moreover, the time taken for the calculation and plotting of the landscape will be displayed in the command line.

In the potential landscape there are two attractors (see Fig. S8), which is consistent with the ODE-based landscape in Fig. S2.

Case Study 2: Cancer attractor landscape of from [4]

We use the ODE model equations given in Eqn (S3-S8) [4]. Open the folder `Li_2015_6_genes_model`. Type the filename at the command line as below:

```
>>Setting_and_running_CLE
```

After the calculation finishes, the 3D and top views of the Waddington’s epigenetic landscape will be plotted. The resulting potential landscape (see Fig. S9) will display four pairs of attractors which is

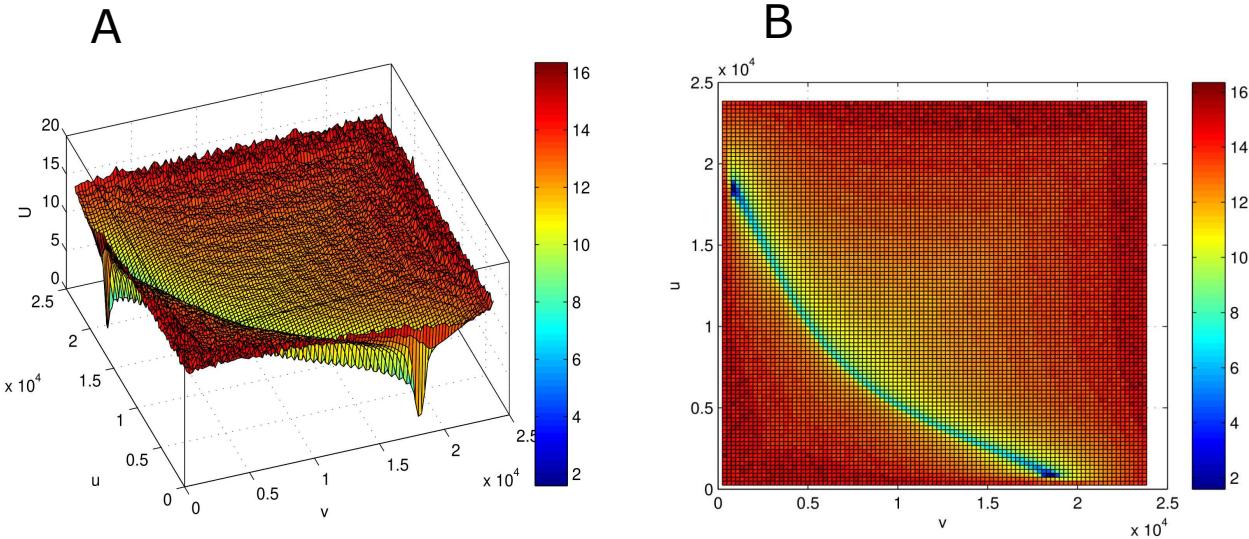


Figure S8: Plots of the landscape for the bistable synthetic toggle switch from [1] using CLE.
(A) 3D view (B) Top view

consistent with that in Fig. S4.

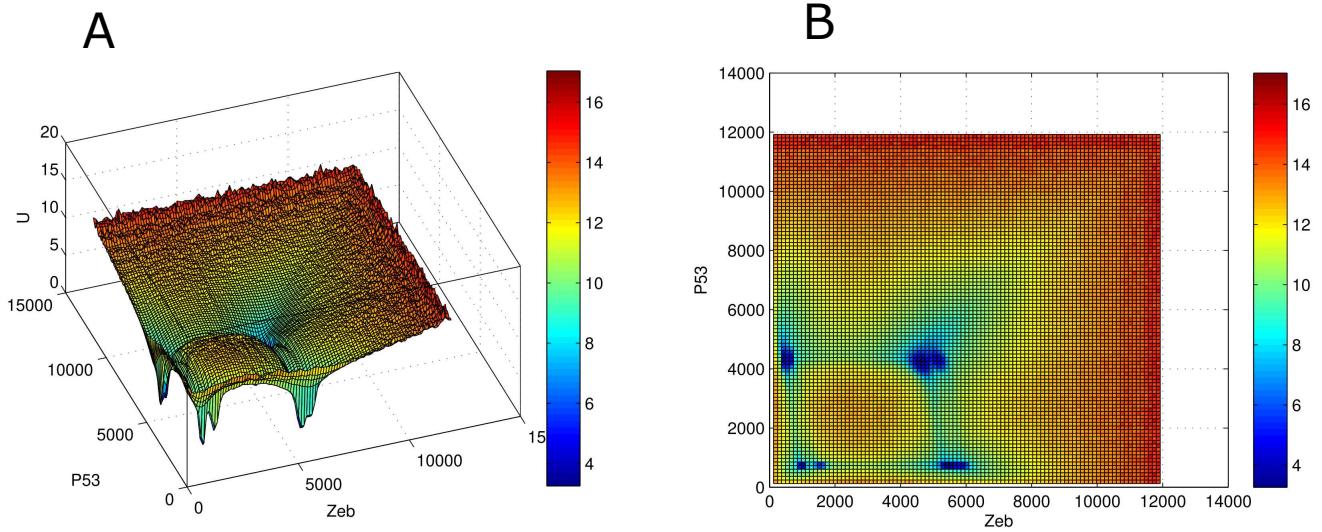


Figure S9: Plots of Waddington's epigenetic landscape of the GRN model in [4] using CLE.
(A) 3D view (B) Top view

2.4 Using the code to plot potential landscapes for your gene networks in CLE

In order to plot the potential landscape of your model, you need modify two files: `GetTrajectory.m` and `Setting_and_running_CLE.m`. For a basic understanding of CLE, readers are referred to a guide with MATLAB code given by Higham [10]. Here, we list the formula for CLE and discuss how to implement the model from [1]. The formula for CLE as given in [10] is:

$$Y(t + \tau) = Y(t) + \tau \sum_{j=1}^m \nu_j a_j(Y(t)) + \sqrt{\tau} \sum_{j=1}^m \nu_j \sqrt{a_j(Y(t))} Z_j \quad (\text{S9})$$

where $Y(t)$ is the state vector, τ is the leap time, and ν_j is the state-change vector for the j th type of reaction, for $1 \leq j \leq m$, $\nu_j \in \mathbb{R}^n$ for m reactions and n molecular species. \mathbf{V} is the stoichiometric matrix, which is an $n \times m$ matrix, where ν_j is the j th column. $a_j(Y(t))$ is the propensity function for the j th reaction, which means the probability of the j th reaction occurring in the infinitesimal time interval $[t, t + \tau]$ is given by $a_j(Y(t))\tau$. Z_j is a random number generated from the uniform distribution.

2.4.1 Defining model equations into reactions

First define your gene network model reactions in CLE in the file `GetTrajectory.m`. A model in ODEs can be converted into CLE with the different rate constants c_i from the ODEs rate constants k_i and stoichiometric matrix \mathbf{V} .

For instance, let us look at the model with ODEs from [1] given below:

$$\frac{du}{dt} = k_1 \frac{k_2^3}{(k_2^3 + v^3)} - k_3 u \quad (\text{S10})$$

$$\frac{dv}{dt} = k_4 \frac{k_2^3}{(k_2^3 + u^3)} - k_5 v \quad (\text{S11})$$

In the first ODE, it contains two reactions: the inhibition by v and the self-degradation of u . Similarly the second ODE also contains two reactions. Correspondingly, there are 4 reactions (R1-R4) and 5 rate constants: k_1 , k_2 , k_3 , k_4 and k_5 .

$$R1 =: k_1 \frac{k_2^3}{(k_2^3 + v^3)},$$

$$R2 =: -k_3 u,$$

$$R3 =: k_4 \frac{k_2^3}{(k_2^3 + u^3)},$$

$$R4 =: -k_5 v.$$

From the formulas of R1-R4, we can determine the stoichiometric matrix \mathbf{V} and the stochastic rate constants.

2.4.2 Defining stoichiometric matrix

The stoichiometric matrix \mathbf{V} for this example contains 4 columns, each representing one reaction. User can key in column by column of the matrix \mathbf{V} . From the ODEs in Eqn (S10) and Eqn (S11) the term with a positive rate means synthesis of protein and a negative rate means degradation of protein. If a reaction is positive put 1 (meaning that the number of molecule is increased by one), and if the reaction is negative put -1 (meaning the number of molecule is reduced by one). In this example, each row represents one molecular species where row 1 represents u and row 2 represents v .

R1: u increases by 1, first column $\nu_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$;

R2: u decreases by 1, second column $\nu_2 = \begin{pmatrix} -1 \\ 0 \end{pmatrix}$;

R3: v increases by 1, third column $\nu_3 = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$;

R4: v decreases by 1, fourth column $\nu_4 = \begin{pmatrix} 0 \\ -1 \end{pmatrix}$.

Thus, the stoichiometric matrix \mathbf{V} is given by:

$$\mathbf{V} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}.$$

2.4.3 Defining stochastic rate constants c_i in CLE

Based on our paper Methods in Section 4.2 we can determine the relationship between deterministic rate constants k_i and stochastic reaction rate constants c_i . The stochastic reaction rate constants c_i are:

$$\begin{aligned} c_1 &= N_A \cdot V \cdot k_1 \\ c_2 &= N_A \cdot V \cdot k_2 \\ c_3 &= k_3 \\ c_4 &= N_A \cdot V \cdot k_4 \\ c_5 &= k_5 \end{aligned}$$

where N_A is the Avogadro's number $N_A = 6.023 \times 10^{23}$ and V is the volume of the system.

Once we know how to convert the rate constants from k_i to c_i we can use c_i to implement into MATLAB code. Here, we illustrate the implementation of it.

In ODEs rate constants (k_i) are:

$$\begin{aligned} k_1 &= 3; \\ k_2 &= 1; \\ k_3 &= 1; \\ k_4 &= 3; \\ k_5 &= 1; \end{aligned}$$

Thus, in CLE rate constants (c_i) are:

$$\begin{aligned} nA &= 6.023e23; \quad \% \text{ Avogadro's number} \\ vol &= 1e-20; \quad \% \text{ system's volume} \\ c(1) &= 3*(nA*vol); \\ c(2) &= 1*nA*vol; \\ c(3) &= 1; \\ c(4) &= 3*(nA*vol); \\ c(5) &= 1; \end{aligned}$$

In Higham's paper [5], the volume of the system is $vol=10^{-15}$. To mimic a higher level of noise, however, we use a smaller value of volume by setting $vol = 10^{-20}$ and obtained consistent landscape (Fig. S9).

2.4.4 Defining $a(j)$ the propensity function

The propensity function for the j th reaction is given by $a_j(Y(t))$. Thus, the expressions of $a(j)$ are given by:

$$a(1) = \frac{c(1)*c(2)^3}{c(2)^3+Y(2)^3},$$

$$a(2) = c(3) * Y(1),$$

$$a(3) = \frac{c(4)*c(2)^3}{c(2)^3+Y(1)^3},$$

$$a(4) = c(5) * Y(2).$$

2.4.5 Implementing the CLE

When all the model reactions and rate constants have been defined, the CLE formula given in Eqn (S9) above is translated into MATLAB code (particularly the line of code highlighted in yellow) as below:

```
tfinal = 30; % simulation time
L = 250; % stepsize
tau = tfinal/L;
for k=1:L
    a(1) = c(1)*c(2)^3/(c(2)^3+Y(2)^3);
    a(2) = c(3)*Y(1);
    a(3) = c(4)*c(2)^3/(c(2)^3+Y(1)^3);
    a(4) = c(5)*Y(2);
    d(1) = tau*a(1) + sqrt(abs(tau*a(1)))*randn;
    d(2) = tau*a(2) + sqrt(abs(tau*a(2)))*randn;
    d(3) = tau*a(3) + sqrt(abs(tau*a(3)))*randn;
    d(4) = tau*a(4) + sqrt(abs(tau*a(4)))*randn;
    % Y(t+tau)= Y(t) + tau*(aj*vj) + sqrt(tau*aj)*Zj*vj
    Y = Y + d(1)*V(:,1) + d(2)*V(:,2) + d(3)*V(:,3)+ d(4)*V(:,4);
    Yvals(:,k+1) = Y; % store all the state values into matrix Yvals
end
```

2.4.6 Initializing the model setting

Finally, modify the model setting in the file of `Setting_and_running_CLE.m`. Set the variable names (`variableNames`) as the order of the variables (or proteins) according to the CLE in the stoichiometric matrix. Then, you need set a different range of the state space for your gene network. For example, based on the prior knowledge from ODEs time-course simulations the maximum value of the protein level is say 3, then you may set the range to 4 (`range_max = 4`).

You need to change the dimension of your model in CLE. For example, if your CLE contain 2 variables, then set:

```
initialRange = [zeros(1,2) + range_min;% set the minimum range
                zeros(1,2) + range_max];% set the maximum range
```

Also, you may change the index [`variable_1 variable_2`] as the two genes or proteins of interest to you. If your model equations only contain 2 variables, then `variable_1 = 1` and `variable_2 = 2`. Then, you can run the calculation to plot the Waddington's epigenetic landscape as given in the example above.

3 Contact information

The MATLAB codes were written by Xiaomeng Zhang and Ket Hing Chong.

For any question or comments, please contact Jie Zheng <zhengjie@shanghaitech.edu.cn>

References

1. Gardner TS, Cantor CR, Collins JJ: Construction of a genetic toggle switch in escherichia coli. *Nature* 2000, 403(6767):339–342.
2. Segel L, Edelstein-Keshet L: *A Primer in Mathematical Models in Biology*. Philadelphia: SIAM; 2013.
3. Chong KH, Samarasinghe S, Kulasiri D, Zheng J: Computational techniques in mathematical modelling of biological switches. In: Weber, T., McPhee, M.J. and Anderssen, R.S. (eds). *21st International Congress on Modelling and Simulation (MODSIM 2015)* 578–584; 2015.
4. Li C, Wang J: Quantifying the landscape for development and cancer from a core cancer stem cell circuit. *Cancer Res.* 2015, 75(13):2607–2618.
5. Zhou JX, Aliyu MDS, Aurell E, Huang S: Quasi-potential landscape in complex multi-stable systems. *Soc. Interface* 2012, 9(77):3539–3553.
6. Ferrell JE, Tsai TY-C, Yang Q: Modeling the cell cycle: Why do certain circuits oscillate? *Cell* 2011, 144(6):874–885.
7. Murray AW, Kirschner MW: Cyclin synthesis drives the early embryonic cell cycle. *Nature* 1989, 339(6222):275–280.
8. Edelstein-Keshet L: Mathematical models in biology. Philadelphia: *SIAM* 2005.
9. Li C, Wang J: Quantifying cell fate decisions for differentiation and reprogramming of a human stem cell network: landscape and biological paths. *PLoS Comp. Biol.* 2013, 9(8):e1003165.
10. Higham DJ: Modeling and simulating chemical reactions. *SIAM Rev Soc Ind Appl Math* 2008, 50(2):347–368.