Potential Landscapes

Theory and applications in developmental biology

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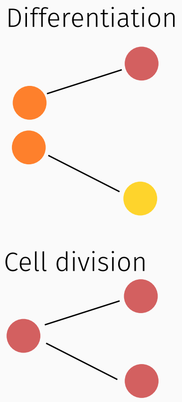
Talk outline

1. Stem cell development and epigenetic landscapes
2. Minimum action paths and landscape formation
3. A toy model example
4. Developmental example
5. Sum-of-squares decomposition
6. Conclusions

Stem cell development and epigenetic landscapes

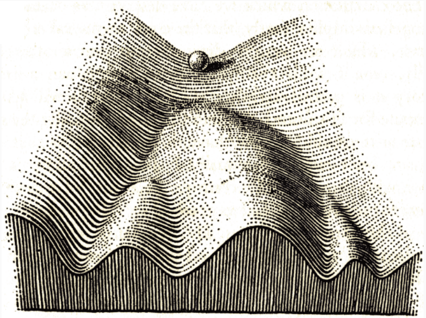
Stem cell development

- Pluripotent stem cells develop into tens of thousands of distinct cell types
- Each cell contains identical genetic information
- As cells divide, information on their phenotype must be stored *epigenetically*
- Many analogies have been provided for this process, one of which is the epigenetic landscape



Waddington's landscapes

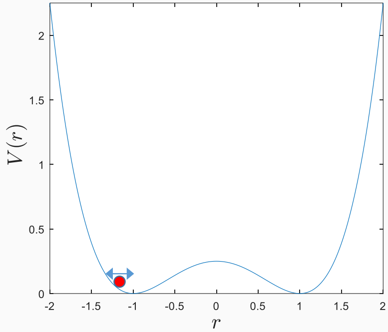
- Waddington proposed a qualitative landscape model[1]
- Cells pictured as marbles moving down the landscape
- Cells face sequential binary fate choices
- Final valleys are distinct cell states - phenotypes
- Shape of the landscape governed by gene regulatory network



[1] Waddington, (1957)[5]

Mathematical interpretations

- Epigenetic landscapes are similar to *potential* functions
- Some stochastic systems can be expressed in terms of a potential
- Waddington's landscapes also display bifurcations
- There are now many quantitative models for development
- It is desirable to reconcile these approaches



$$\dot{r} = -\frac{\mathrm{d}V}{\mathrm{d}r} + \sigma\xi(t) \tag{1}$$

Developmental models

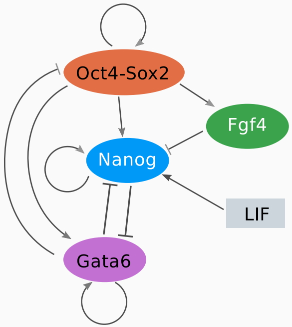
- Models for stem cell development describe systems of chemical reactions, each with propensity a_j
- Propensities depend on concentration of other species
- Each reaction causes copy number changes according to stoichiometry factor S_{ij}
- The time evolution may be approximated by the Chemical Langevin Equation[2]

$$\mathrm{d}X = \mathbf{S}a(X)\,\mathrm{d}t + \mathbf{S}\mathrm{diag}(a(X))\,\mathrm{d}W_t. \tag{2}$$

Reactions

Production: $\varnothing \xrightarrow{a_j(X)} \mathrm{m}_i$

Degradation: $\mathrm{m}_i \xrightarrow{k_i} \varnothing$



[2] Gillespie, (2000)[3]

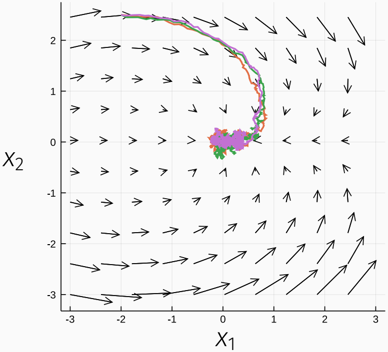
Minimum action paths and landscape formation

A general stochastic model may be written as,

$$dX = f(X;\theta)\,dt + g(X;\eta)\,dW_t. \tag{3}$$

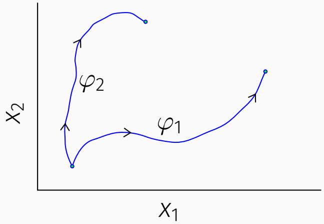
In the limit of low noise (high copy numbers), such models may be written as,

$$\frac{dX}{dt} = f(X;\theta). \tag{4}$$



The minimum action path

- MAP gives most probable path between any two points
- Provides relative probability of different trajectories[3]



[3] Freidlin & Wentzell, (2012)[2]

Minimum action path

Probability of trajectory $X(t) = \varphi$, is related to the *action* according to,

$$P(\varphi) \propto \exp(-S(\varphi)). \tag{5}$$

S is the action functional, evaluated as,

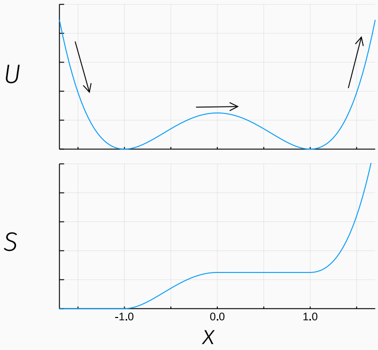
$$S(x,T) = \int_0^T \sum_i (\dot{x}_i - f_i(x))^2 / g_i^2(x)\, \mathrm{d}t. \tag{6}$$

The MAP is found as

$$\min_T \min_\varphi S(\varphi, T) \tag{7}$$

The minimum action path

- Action zero for deterministic trajectories
- Action positive only for "uphill" motion
- Regulated by noise intensity



Minimum action path

Probability of trajectory $X(t) = \varphi$, is related to the *action* according to,

$$P(\varphi) \propto \exp(-S(\varphi)). \tag{8}$$

S is the action functional, evaluated as,

$$S(x, T) = \int_0^T \sum_i (\dot{x}_i - f_i(x))^2 / g_i^2(x)\, \mathrm{d}t. \tag{9}$$

The MAP is found as

$$\min_T \min_\varphi S(\varphi, T) \tag{10}$$

Landscape formation

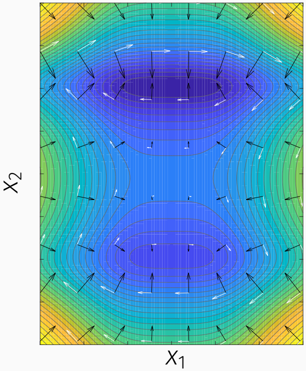
$$\mathrm{d}X = f(X)\,\mathrm{d}t + g(X)\,\mathrm{d}W_t$$

The deterministic forcing vector may be decomposed into a gradient and curl contribution as,

$$f(X;\theta) = -\nabla U(X;\theta) + f_U(X;\theta). \tag{11}$$

The quasi-potential U is analogous to the epigenetic landscape. The remainder f_U is the curl component. Key requirements for a potential landscape[4]:

1. Lyapuov function for the deterministic system
2. Provides the action of the MAP between points



[4] Zhou *et al.* (2012)[6]

Probability flux method

The Fokker-Planck equation for the probability distribution is,

$$\frac{\partial P}{\partial t} = -\nabla \cdot (fP) + \nabla \cdot (D \cdot \nabla P). \tag{12}$$

$$\mathrm{d}X = f(X)\,\mathrm{d}t + g(X)\,\mathrm{d}W_t,$$
$$f = -\nabla U + f_U$$

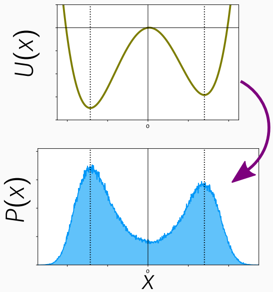
At steady state $\frac{\partial P_s}{\partial t} = 0$ and so,

$$\nabla \cdot (fP_s - D \cdot \nabla P_s) = \nabla \cdot J_s = 0. \tag{13}$$

The flux J_s is therefore a divergence free vector field. Rearranging (13),

$$f = -D \cdot \nabla(-\ln P_s) + J_s/P_s. \tag{14}$$

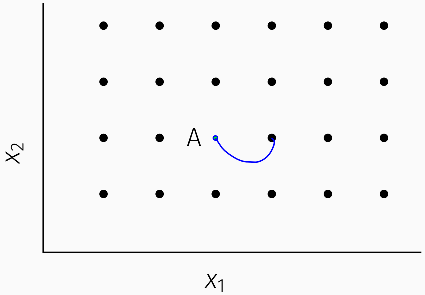
This provides a decomposition of f as the gradient of a quasi-potential $U = -\ln P_s$, and a divergence-free flux term.



Action based method

$$dX = f(X)\,dt + g(X)\,dW_t,$$
$$f = -\nabla U + f_U$$

- Forms a landscape based on the minimum action between points
- Space must be discretized and potential computed in grid
- Computationally expensive



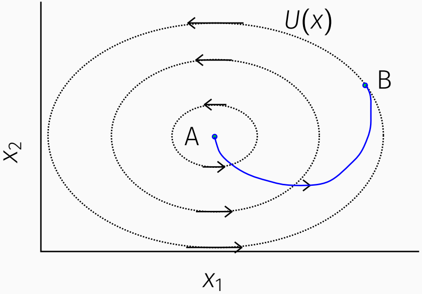
Vector field decomposition

$$dX = f(X)\,dt + g(X)\,dW_t,$$
$$f = -\nabla U + f_U$$

Try to form a landscape such that the decomposition is orthogonal:

$$f_U \cdot \nabla U = 0. \tag{15}$$

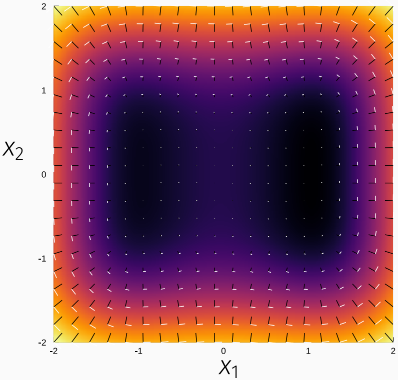
- Gives a landscape directly proportional to the action:
  - $S_{A\to B} = 2(U_B - U_A)$
- Landscape is a Lyapunov function
- May not always be possible



A toy model example

The toy model

Vector field consisting of gradient and curl component



Model equations

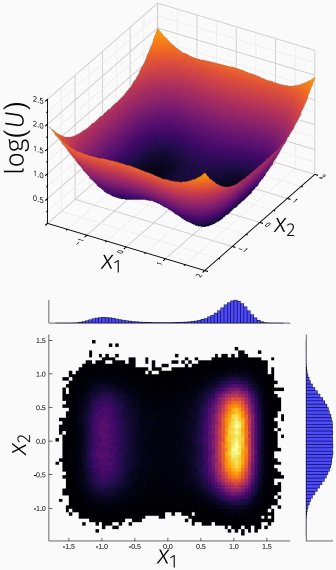
$$\mathrm{d}X = (-\nabla U + f_U)\,\mathrm{d}t + \sigma\,\mathrm{d}W_t$$

$$U(x_1, x_2) = \lambda(x_1^4 + x_2^4) - \alpha x_1^2 + \beta x_1$$

$$-\nabla U = \begin{bmatrix} 2\alpha x_1 - 4\lambda x_1^3 - \beta \\ -4\lambda x_2^3 \end{bmatrix},$$

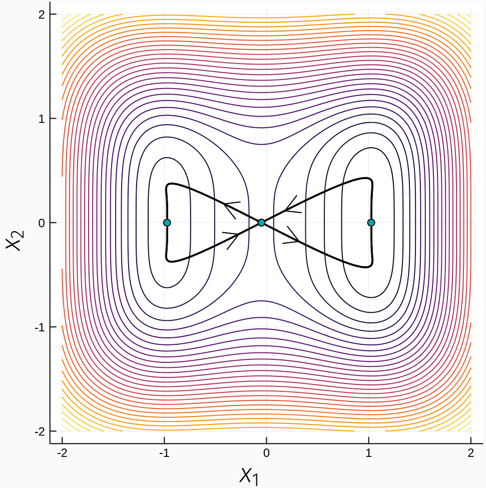
$$f_U = C(X)\begin{bmatrix} 4\lambda x_2^3 \\ 2\alpha x_1 - 4\lambda x_1^3 - \beta \end{bmatrix},$$

- Distribution strongly determined by landscape
- Curl component unobservable from static data



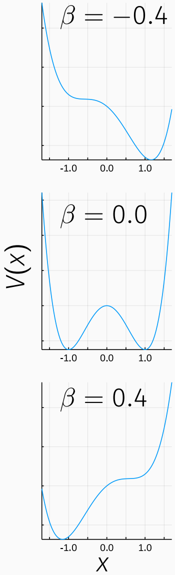
Minimum action paths

- MAP does not directly follow landscape
- MAP follows $\dot{x} = \pm\nabla U + f_{\perp}$
- Shared "transition state" at saddle point



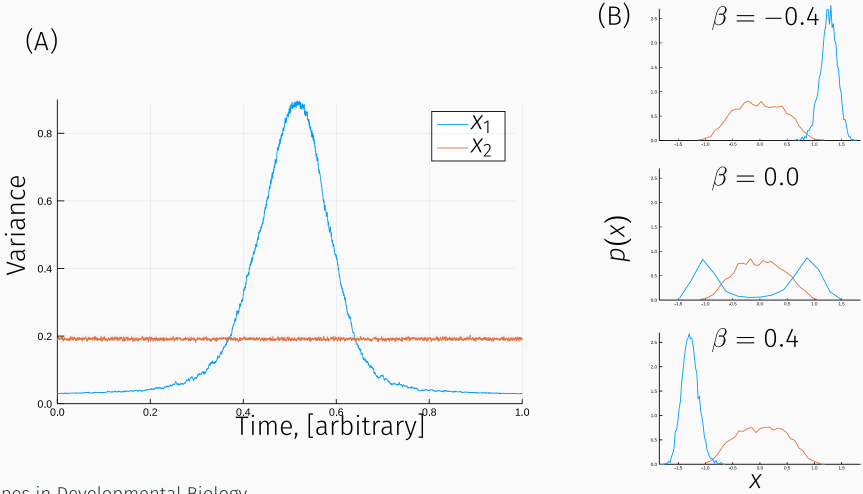
Forming a transitory landscape

- The system is determined by the landscape $U(X, \theta)$, parametrized by $\theta = [\alpha, \lambda, \beta]$
- If the parameters are time-varying, the landscape is *transitory*
- We simulate a transitory landscape with changing β



The transition state

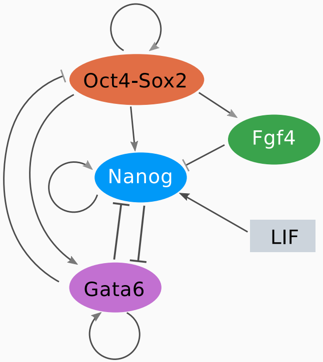
Transition state observed as period of high heterogeneity.



Developmental example

Chickarmane model

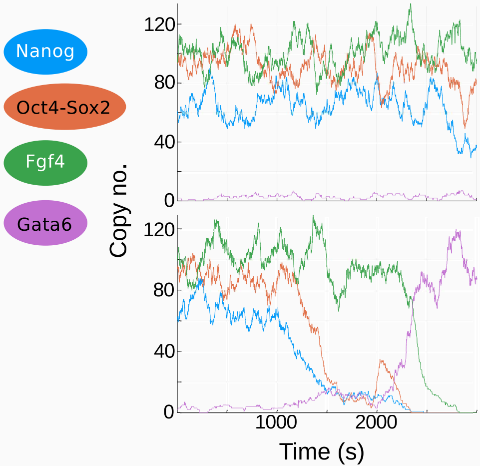
- Developmental model for ES cells[5]
- Based on a mutual inhibition between Nanog and Gata6
- Behaviour may be modified by LIF concentration
- May be interpreted in terms of a static or transitory landscape.



[5]Chickarmane *et al.* (2012)[1]

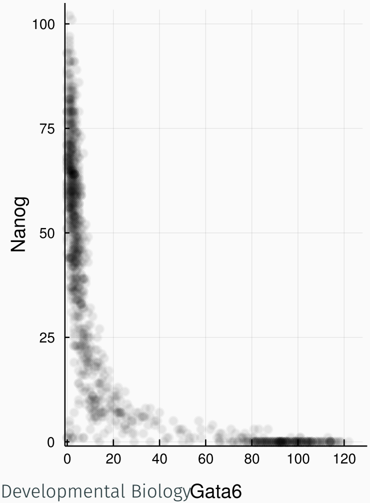
Typical behaviour

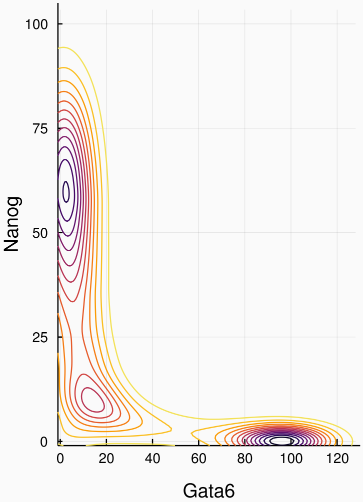
- Cells start out in stem cell state:
  - High Nanog, Oct4, Fgf4. Low Gata6
- Spontaneously transition to differentiated state
  - Low Nanog, Oct4, Fgf4. High Gata6
- Once differentiated cells never return



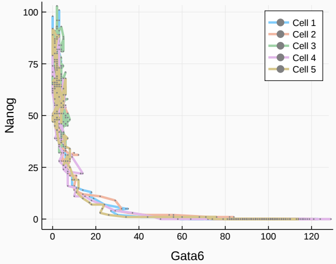
Probabilistic landscape

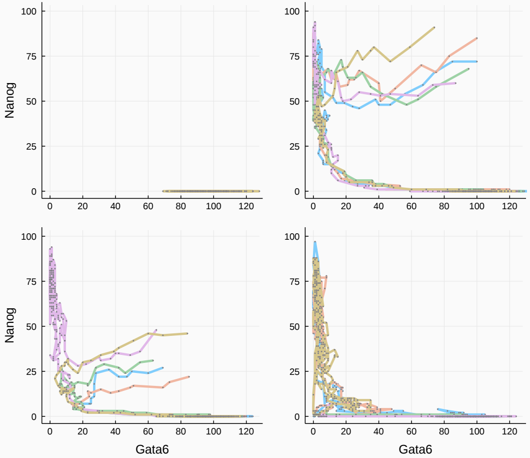
Obtain probabilistic landscape from large number of simulations:





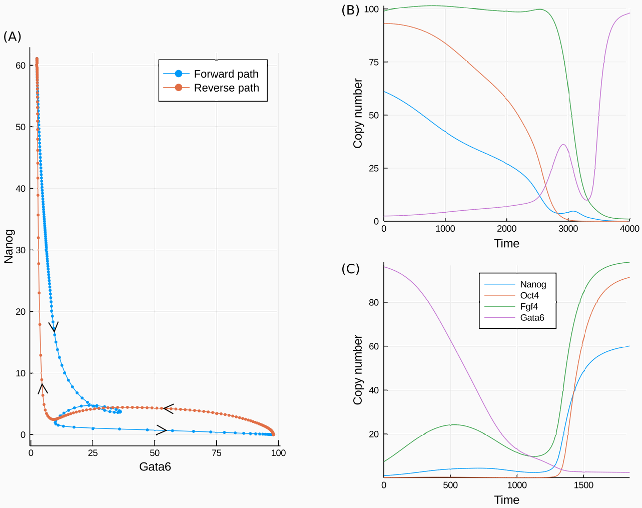
Simulations with various starting conditions





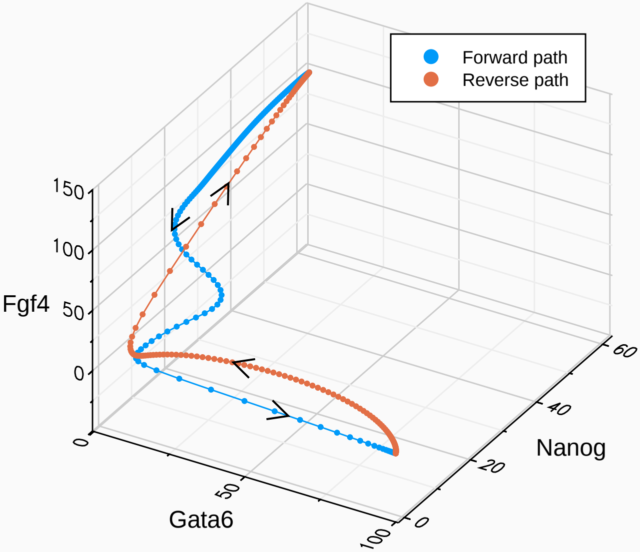
Minimum action paths

- Forward and reverse paths are different
- Paths follow valley of probabilistic landscape
- Also involve oscillatory behavior

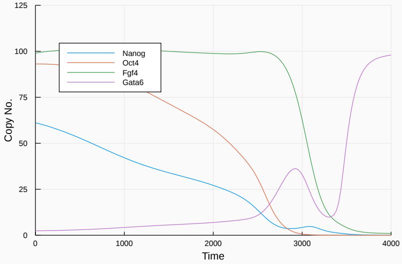


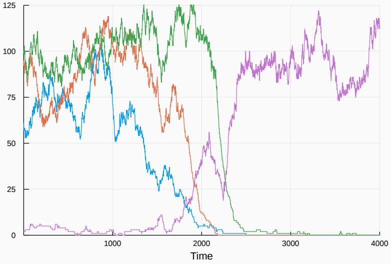
Minimum action paths

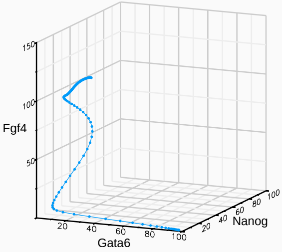
- Paths share start and end points
- Paths also come very close at an intermediate point
  - The static transition state

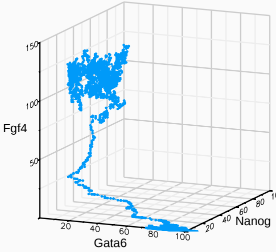


Minimum action paths



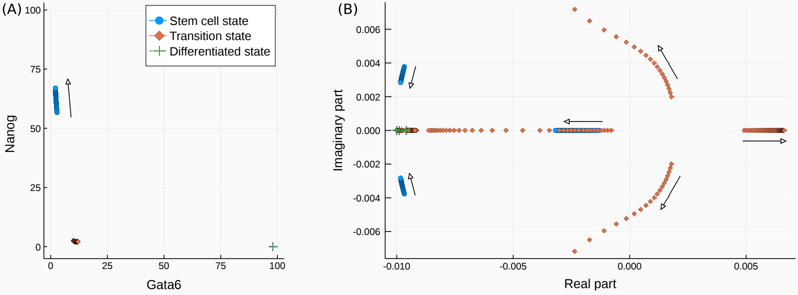






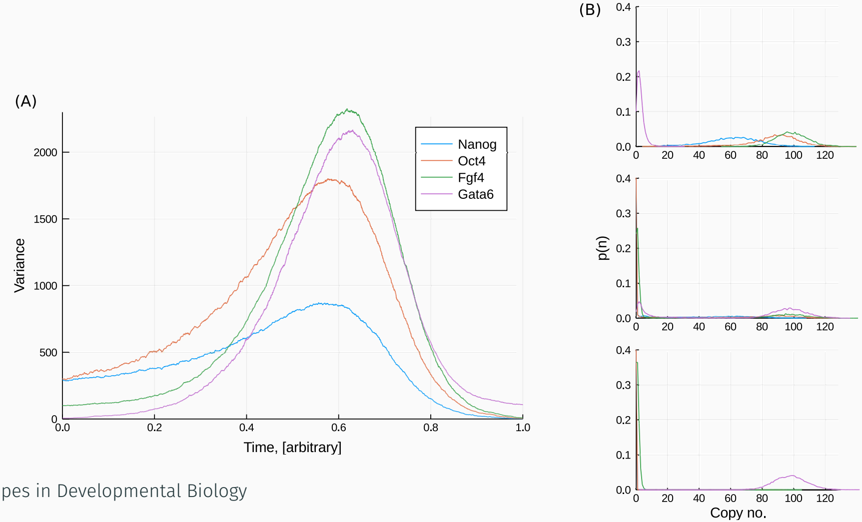
Forming a transitory landscape

- The system may be modified by changing the LIF concentration
- Properties of the landscape vary with L
- Quantified by local eigenvalues at fixed points



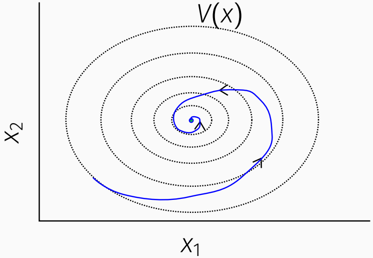
The transitory transition state

We simulate a transitory landscape with changing L.



Sum-of-squares decomposition

A positive definite function that is decreasing along the deterministic trajectories of $f(x)$.



Lyapunov functions

Given an ODE $\dot{x} = f(x)$ and a fixed point X_i, a Lyapunov function $V : \mathbb{R}^n \to \mathbb{R}$ may prove local or global stability provided that:

$$V(X_i) = 0,$$
$$V(x) \geq 0,$$
$$\dot{V}(x) = \nabla V \cdot \dot{x} \leq 0.$$

Sum-of-squares method

- Finding a Lyapunov function is generally difficult
- Positive definite polynomials can be found as a *sum-of-squares*[6]

$$H(x) = \sum_{i}^{M} h_i^2(x),$$

- Enables Lyapunov functions to be found via semi-definite programming

Lyapunov functions

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$$V(X_i) = 0,$$
$$V(x) \geq 0,$$
$$\dot{V}(x) = \nabla V \cdot \dot{x} \leq 0.$$

[6] Papachristodoulou *et al*, (2002)[4]

Landscape formation

- The SOS method gives a Lyapunov function
- The potential from an orthogonal decomposition is also a Lyapunov function
- Therefore, by enforcing orthogonality of the SOS output, we can obtain this decomposition

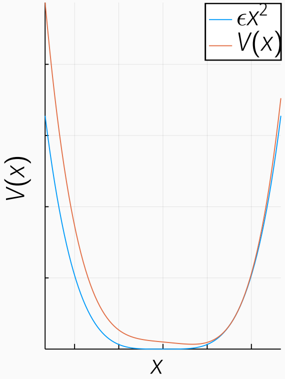
Orthogonalisation method

Orthogonality is enforced via two optimisations.

Step one

For a polynomial $V_1 : \mathbb{R}^n \to \mathbb{R}$ solve:

$$\begin{aligned} \underset{V_1}{\text{maximise}} \quad & \epsilon \\ \text{subject to} \quad & V_1 \geq \epsilon \sum_i x_i^2, \\ & M_{V_1} = \begin{bmatrix} -\nabla V_1 \cdot f & \nabla V_1 \\ \nabla V_1 & I_n \end{bmatrix} \succeq 0.^7 \end{aligned}$$



[7] $M_V \succeq 0$ enforces $\nabla V \cdot f_V \leq 0$ via a Schur Complement argument.

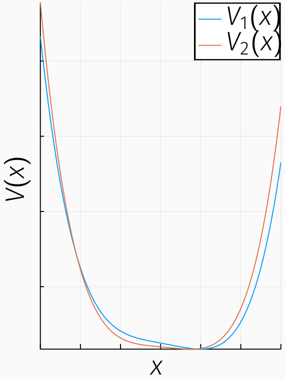
Orthogonalisation method

Orthogonality is enforced via two optimisations.

Step two

For a polynomial $V_2 : \mathbb{R}^n \to \mathbb{R}$ solve:

$$
\begin{aligned}
\underset{V_2}{\text{minimise}} \quad & \alpha \\
\text{subject to} \quad & V_2 \geq \epsilon \sum_i x_i^2, \\
& M_{V_2} \succeq 0, \\
& \nabla V_2 \cdot (f + 2\nabla V_1) \geq \alpha (f \cdot \nabla V_1) + (1+\alpha)||\nabla V_1||^2, \\
& \alpha, \epsilon > 0.
\end{aligned}
$$

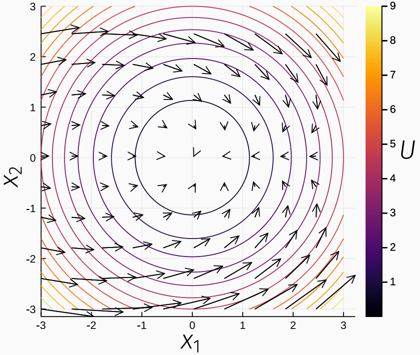


Example

First example is a two-dimensional field with one attractor[8]

$$f(X) = \begin{bmatrix} -x_1 + x_2^2 \\ -x_2 - x_1 x_2. \end{bmatrix}$$

$$= -\nabla[\underbrace{0.5(x_1^2 + x_2^2)}_{U}] + \begin{bmatrix} x_2^2 \\ -x_1 x_2 \end{bmatrix}.$$



[8]Zhou *et al.* (2012)[6]

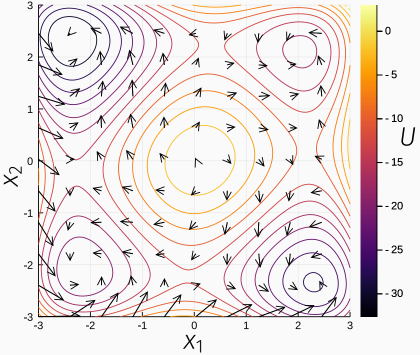
Example

Second example is a two-dimensional field with five fixed points[9]

$$f(X) = \begin{bmatrix} -1 + 9x_1 - 2x_1^3 + 9x_2 - 2x_2^3 \\ 1 - 11x_1 + 2x_1^3 + 11x_2 - 2x_2^3 - x_1x_2. \end{bmatrix}$$

$$= -\nabla[\underbrace{-5(x_1^2 + x_2^2) + 0.5(x_1^4 + x_2^4) + x_1x_2 + x_1}_{U}]$$

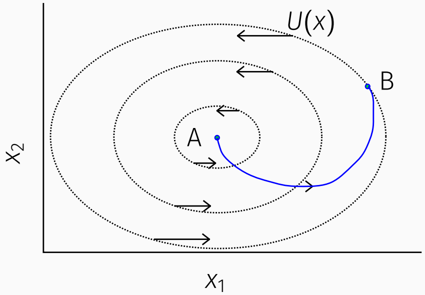
$$+ \begin{bmatrix} -x_1 + 10x_2 - 2x_2^3 \\ 1 - 10x_1 + 2x_1^3 + x_2 \end{bmatrix}.$$



[9] Zhou *et al.* (2012)[6]

Sub-orthogonality

- In the previous examples a known orthogonal solution existed:
  - $\nabla U \cdot f_U = 0$
  - $S_{A \to B} = 2(U_B - U_A)$
  - Curl vectors parallel to contours of U
- In other cases orthogonality may not be achieved:
  - $\nabla U \cdot f_U < 0$
  - $S_{A \to B} > 2(U_B - U_A)$
  - Curl vectors point slightly "downhill"



Conclusions

- Automatic method to orthogonalise vector fields
  - Functions must be polynomial
  - Only seems possible in some cases
- Orthogonal potential gives the action between points
- Sub-orthogonal potential provides a lower bound on the action
- Unclear if this is useful

Results

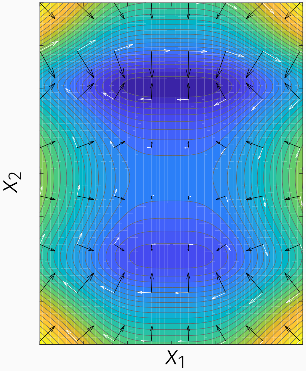
$f = -\nabla U + f_U$

$$\begin{aligned} \text{Either:} \quad & \nabla U \cdot f_U = 0, \\ & S_{A\to B} = 2(U_B - U_A) \\ \text{Or:} \quad & \nabla U \cdot f_U < 0 \\ & S_{A\to B} > 2(U_B - U_A). \end{aligned}$$

Conclusions

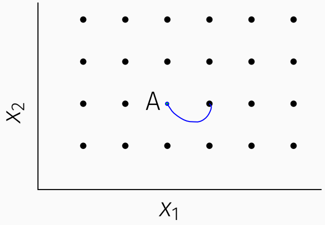
Summary

- Models for stem-cell differentiation may be decomposed into a potential landscape and curl component
- Curl component is likely unidentifiable from snapshot data
- Landscapes may be viewed as static or transitory
- Orthogonal and sub-orthogonal decompositions may be achieved using an optimisation approach



Future work

- Rewrite MAP method to be time independent
- Use MAP and Gaussian Processes for efficient landscape computation
- Use Gaussian Processes to estimate non-parametric developmental models
- Find a problem for which the orthogonal (or sub-orthogonal) decomposition provides useful insight



References i

V. Chickarmane, V. Olariu, and C. Peterson.
Probing the role of stochasticity in a model of the embryonic stem cell - heterogeneous gene expression and reprogramming efficiency.
BMC Systems Biology, 6(98), 2012.

M. I. Freidlin, A. D. Wentzell, and J. Szücs.
Random perturbations of dynamical systems.
Number 260. Springer, Heidelberg [u.a], 3. ed edition, 2012.

D. T. Gillespie.
The chemical Langevin equation.
The Journal of Chemical Physics, 113(1):297–306, 2000.

A. Papachristodoulou and S. Prajna.
On the construction of Lyapunov functions using the sum of squares decomposition.
volume 3, pages 3482–3487. IEEE, 2002.

C. H. Waddington.
The strategy of the genes: a discussion of some aspects of theoretical biology.
Allen & Unwin, London, 1957.

J. X. Zhou, M. D. S. Aliyu, E. Aurell, and S. Huang.
Quasi-potential landscape in complex multi-stable systems.
Journal of The Royal Society Interface, 9(77):3539–3553, 2012.

MAP optimisation approach

- Form a discretised path between 2 points
- Use expression for gradient of the action with respect to each point
- Optimise path with a gradient based approach
- Outer loop performs a line search in the time T