A tug-of-war mechanism for pattern formation in a genetic network

Marcella M Gomez[1*], Murat Arcak[1]

1 Electrical Engineering and Computer Sciences, UC Berkeley, Berkeley, CA, USA

* mmgomez@berkeley.edu (MMG)

S1 Steady state solutions of the representative model

In this section we present a derivation of steady state solutions of the simplified system to show the existence of non-homogeneous solutions. For ease of notation, we redefine $u \equiv u_1$ and $v \equiv u_2$. Consider the following two state PDE

$$\frac{\partial}{\partial t}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = D\,\frac{\partial^2}{\partial x^2}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} + \begin{bmatrix} f(u_2) \\ f(u_1) \end{bmatrix} - \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}, \tag{S1}$$

where $f(-u) = -f(u)$. To show that the system admits a non-homogeneous solution we consider the steady-state by setting $\frac{\partial u}{\partial t} = 0$. By introducing a second variable we write the steady-state system as

$$\begin{aligned} \frac{d}{dx}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} &= \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \\ \frac{d}{dx}\begin{bmatrix} v_1 \\ v_2 \end{bmatrix} &= -D^{-1}\begin{bmatrix} f(u_2) \\ f(u_1) \end{bmatrix} + D^{-1}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \end{aligned} \tag{S2}$$

In order to find a non-homogeneous solution we need to consider an invariant manifold that connects the two equilibrium points of the bistable system. Naturally, only one such manifold exists and it is the unstable manifold that crosses the saddle point. We wish to investigate solutions along this invariant manifold, which in this example is described by $u_1 = -u_2$. Then we have $v_2 = -v_1$ and

$$
\begin{aligned}
\frac{d}{dx}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} &= \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \\
\frac{d}{dx}\begin{bmatrix} v_1 \\ -v_1 \end{bmatrix} &= -D^{-1}\begin{bmatrix} -f(u_1) \\ f(u_1) \end{bmatrix} + D^{-1}\begin{bmatrix} u_1 \\ -u_1 \end{bmatrix}.
\end{aligned}
\tag{S3}
$$

Therefore, the steady-state system solutions constrained to this manifold are described by

$$
\begin{aligned}
\frac{d\,u_i}{dx} &= v_i \\
\frac{d\,v_i}{dx} &= \frac{1}{D}(f(u_i) + u_i)
\end{aligned}
\tag{S4}
$$

We can remove the diffusion term in equation (S4) through the change of variables $\tilde{x} = x/\sqrt{D}$ and $\tilde{v} = v\sqrt{D}$

$$
\frac{d\,u_i}{d\tilde{x}} = \tilde{v}_i \tag{S5}
$$

$$
\frac{d\,\tilde{v}_i}{d\tilde{x}} = (f(u_i) + u_i) \tag{S6}
$$

Note that along this manifold, the system is Hamiltonian. By definition the Hamiltonian function $H(u, v)$ satisfies the properties

$$
\frac{\partial H(u_i)}{\partial v_i} = \dot{u}_i \tag{S7}
$$

$$
\frac{\partial H(v_i)}{\partial u_i} = -\dot{v}_i. \tag{S8}
$$

System (S6) is uniquely defined by the Hamiltonian

$$
\begin{aligned}
H(v, u) &= \sum_{i=1}^{2} \frac{1}{2} v_i^2 - \sum_{i=1}^{2} G(u_i) \\
&= \frac{1}{2} v^T v - \sum_{i=1}^{2} G(u_i)
\end{aligned}
\tag{S9}
$$

where $G(u_i) = \int_0^{u_i} g(u_i)\mathrm{d}u_i$ and $g(u_i) = (f(u_i) + u_i)$. Then

$$G(u_i) = \left(\int_0^{u_i} f(u_i)\mathrm{d}u_i + \frac{1}{2}u_i^2 \right) \tag{S10}$$

and plugging in $u_1 = -u_2$ we get

$$\begin{aligned} H(v,u) &= v_1^2 - u_1^2 - 2\,F(u_1) \\ &= \left(\frac{du_1}{dx}\right)^2 - u_1^2 - 2\,F(u_1) \end{aligned} \tag{S11}$$

where $F(u) = \int_0^u f(u)\mathrm{d}u$. Solutions are given by the contours of $H(v,u) = E$ for different E. From now on to simplify notation we replace u_1 with u.

We consider the case where $f(u) = -\alpha\, \tan^{-1}(u)$, Then

$$F(u) = \alpha\frac{1}{2}\ln(1+u^2) - \alpha\, u \tan^{-1}(u) \tag{S12}$$

and the contours of Hamiltonian function are given by plotting $\frac{du}{dx}$ as a function of u through the following relation

$$\frac{du}{dx} = \pm\sqrt{E - 2\alpha\, u \tan^{-1}(u) + \alpha \ln(1+u^2) + u^2}. \tag{S13}$$

The contours are plotted in Fig. 3 for $\alpha = 2$ and different values of E. Given the zero flux boundary conditions $v(0) = v(L) = \frac{du}{dx} = 0$, we look for solutions that satisfy the constraints

$$H(0, u(0)) = H(0, u(L)) = E. \tag{S14}$$

Consider as a reference point the case where a state is at different equilibrium points on opposing ends. That is the boundary conditions correspond to the non-trivial solution of the algebraic equation

$$-\alpha\, \tan^{-1}(-\alpha\, \tan^{-1}(u^*)) = u^*. \tag{S15}$$

This corresponds to the solution of the system with a domain of infinite length. The total energy is given by

$$E_{cr} = -{u^*}^2 - 2\,F(u^*). \tag{S16}$$

We can find the domain length corresponding to each solution provided by the Hamiltonian through the integration

$$\tilde{L} = \int_{u(0)}^{u(L)} \frac{du}{du/dx} \tag{S17}$$

and plugging in terms we get

$$\tilde{L} = 2\int_0^{u_{0,L}} \frac{1}{\sqrt{E_{sol} - 2\alpha\,u\tan^{-1}(u) + \alpha\ln(1+u^2) + u^2}}du, \tag{S18}$$

where

$$E_{sol} = -{u_{0,L}}^2 - 2\,F(u_{0,L}). \tag{S19}$$

Then our domain length for a non-homogeneous steady-state solution is $L = \tilde{L}\sqrt{D}$.

S2 Stability analysis of the discretized representative model

To evaluate stability of the different solutions we consider the discrete-space model

$$\begin{aligned}
\frac{du^1}{dt} &= d(u^2 - u^1) + f(v^1) - u^1 \\
\frac{du^k}{dt} &= d(u^{k-1} + u^{k+1} - 2\,u^k) + f(v^k) - u^k \qquad \text{for} \quad k = 1, \dots, n-1 \\
\frac{du^n}{dt} &= d(u^{n-1} - u^n) + f(v^n) - u^n \\
\frac{dv^1}{dt} &= d(v^2 - v^1) + f(u^1) - v^1 \\
\frac{dv^k}{dt} &= d(v^{k-1} + v^{k+1} - 2\,v^k) + f(u^k) - v^k \qquad \text{for} \quad k = 1, \dots, n-1 \\
\frac{dv^n}{dt} &= d(v^{n-1} - v^n) + f(u^n) - v^n
\end{aligned} \tag{S20}$$

Here we define $u^k(t) = u(k\,\Delta x, t)$ and so we have $d \equiv D/(\Delta x)^2$. We choose Δx small enough to approximate the partial differential equation presented earlier and choose $n = \lfloor L/\Delta x \rfloor$. Again, we look for solutions of the system along the unstable steady-state manifold $u = -v$. Solutions are obtained by solving the following set of equations

$$\begin{aligned}
d(u^2 - u^1) &= f(u^1) + u^1 \\
d(u^{k-1} - u^k) + d(u^{k+1} - u^k) &= f(u^k) + u^k \qquad \text{for} \quad k = 2, \dots, n-1 \\
d(u^{n-1} - u^n) &= f(u^n) + u^n.
\end{aligned} \tag{S21}$$

Note that we can express states $u^2, \dots, u^n$ as a function of u^1. Substituting expressions for u^{n-1} and u^n into the last line of equation (S21), one can solve for u^1. Finally, u^1 is used to calculate steady solutions $u^2, \dots, u^n$.

We determine stability by examining the eigenvalues of the Jacobian of system (S20)

$$\tilde{A} = \begin{bmatrix} A & K1 \\ K2 & A \end{bmatrix} \tag{S22}$$

where

$$A = \begin{bmatrix} -d-1 & d & & & & \\ d & -2\,d-1 & d & & & \\ & d & -2\,d-1 & d & & \\ & & \ddots & \ddots & \ddots & \\ & & & d & -2\,d-1 & d \\ & & & & d & d-1 \end{bmatrix}, \tag{S23}$$

$$K1 = \mathrm{diag}\left(\left.\frac{\partial f}{\partial v}\right|_{v^1=-u^1_{eq}}, \left.\frac{\partial f}{\partial v}\right|_{v^2=-u^2_{eq}}, \ldots, \left.\frac{\partial f}{\partial v}\right|_{v^n=-u^n_{eq}} \right), \tag{S24}$$

$$K2 = \mathrm{diag}\left(\left.\frac{\partial f}{\partial u}\right|_{u^1=u^1_{eq}}, \left.\frac{\partial f}{\partial u}\right|_{u^2=u^2_{eq}}, \ldots, \left.\frac{\partial f}{\partial u}\right|_{u^n=u^n_{eq}} \right), \tag{S25}$$

and $A, K1, K2 \in \mathbb{R}^{n\times n}$.

We find solutions to (S21) with parameters $\alpha = 2\,\mathrm{nM}/\min$, $D = .1mm^2/\min$,and $\Delta x = .01\,mm$. We then determine stability of the solution from the eigenvalues of matrix (S22). We find the maximum eigenvalue corresponding to each initial condition that gives a solution.

S3 Linear stability analysis of PDE

Stability analysis of the linearized system about the saddle point shows that system (1) is type-III unstable. We present the derivation of stability conditions. For a two-dimensional system with mutual repression we have

$$\frac{\partial}{\partial t}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = D\frac{\partial^2}{\partial x^2}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} + \begin{bmatrix} f_1(u_2) \\ f_2(u_1) \end{bmatrix} - \gamma \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}. \tag{S26}$$

We analyze stability of the linearized system about the homogeneous equilibrium point. First, we derive stability criteria for a general linear PDE.

Consider the linearized general PDE system

$$\frac{\partial \vec{\tilde{u}}}{\partial t} = \mathbf{D}\frac{\partial^2 \vec{\tilde{u}}}{\partial x^2} + \mathbf{A}\,\vec{\tilde{u}} \tag{S27}$$

where $\mathbf{A} \in \mathbb{R}^{(n\times n)}$, $\vec{\tilde{u}} \in \mathbb{R}^n$, and $\mathbf{D} \in \mathbb{R}^{(n\times n)}$ is a diagonal matrix. We apply a method of separation of variables. We assume the solution can be written as $\vec{\tilde{u}} = \phi(x)\,\vec{g}(t)$, where $\phi(x) \in \mathbb{R}$ and $\vec{g}(t) \in \mathbb{R}^n$. The assumption that all states share the same space-varying function $\phi(x)$ holds in this case because the differences arise in only a linear scaling given by $\mathbf{D}$. For the purpose of analysis, we rewrite the solution as $\vec{\tilde{u}} = \phi(x)\mathbf{G}\,\vec{q}$, where $\mathbf{G}$ is a diagonal matrix with entries of $\vec{g}(t)$ along the diagonal, $\mathbf{G} = \mathrm{diag}(g_1, g_2, \ldots, g_n)$ and $\vec{q} = [1, \ldots, 1]^T \in \mathbb{R}^n$. Substituting $\vec{\tilde{u}}$ into equation (S27) gives

$$\phi(x)\frac{\partial \mathbf{G}}{\partial t}\,\vec{q} = \mathbf{D}\frac{\partial^2\phi(x)}{\partial x^2}\mathbf{G}\,\vec{q} + \mathbf{A}\,\phi(x)\mathbf{G}\,\vec{q} \tag{S28}$$

$$= \mathbf{G}\,\mathbf{D}\frac{\partial^2\phi(x)}{\partial x^2}\vec{q} + \mathbf{A}\,\phi(x)\mathbf{G}\,\vec{q} \tag{S29}$$

where the last equality holds because $\mathbf{D}$ and $\mathbf{G}$ commute. Rearranging terms we get

$$\mathbf{G}^{-1}\left(\frac{\partial \mathbf{G}}{\partial t} - \mathbf{A}\,\mathbf{G}\right)\vec{q} = \mathbf{D}\frac{1}{\phi(x)}\frac{\partial^2\phi(x)}{\partial x^2}\vec{q} = [\lambda_1, \lambda_2, \ldots, \lambda_n]^T \tag{S30}$$

We assume $\mathbf{G}$ is an invertible matrix. This implies $\vec{g} \succ 0$. Assuming the time-varying function is exponential, then we will have that $\vec{q} \succeq 0$ and $\vec{q} = 0$ only in the limit as $t \to \infty$. We can solve for the eigenvalues by solving for $\phi(x)$. With the eigenvalues known, we can then solve for the time-varying functions.

$$\mathbf{G}^{-1}\left(\frac{\partial \mathbf{G}}{\partial t} - \mathbf{A}\,\mathbf{G}\right)\vec{q} = [\lambda_1, \lambda_2, \ldots, \lambda_n]^T \tag{S31}$$

$$\left(\frac{\partial \mathbf{G}}{\partial t} - \mathbf{A}\,\mathbf{G}\right)\vec{q} = \mathbf{G}[\lambda_1, \lambda_2, \ldots, \lambda_n]^T \tag{S32}$$

$$\left(\frac{\partial \mathbf{G}}{\partial t} - \mathbf{A}\,\mathbf{G}\right)\vec{q} = \mathbf{G}\,\mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n)\,\vec{q} \tag{S33}$$

$$\left(\frac{\partial \mathbf{G}}{\partial t} - \mathbf{A}\,\mathbf{G}\right)\vec{q} = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n)\,\mathbf{G}\,\vec{q} \tag{S34}$$

$$\frac{\partial \vec{g}}{\partial t} - \mathbf{A}\,\vec{g} = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n)\,\vec{g} \tag{S35}$$

We denote $\mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n)$ by $\mathbf{\Lambda}$. Therefore, for instability we look for unstable eigenvalues of the matrix $\mathbf{A} + \mathbf{\Lambda}$. Assuming Neumann boundary conditions

$$\frac{\partial u}{\partial x}(0, t) = 0 \tag{S36}$$

$$\frac{\partial u}{\partial x}(L, t) = 0, \tag{S37}$$

for $\mathbf{D} = \mathrm{diag}(d_1, d_2, \ldots, d_n)$, the corresponding eigenvalues are $\lambda_i(k) = -d_i\left(\frac{k\pi}{L}\right)^2$ with eigenfunctions $\phi(x) = \cos\left(\frac{k\pi x}{L}\right)$. Just as presumed, the different scaling terms in $\mathbf{D}$ do not change the eigenfunction. The linear scaling appears in the eigenvalues . The general solution is given by

$$\vec{\tilde{u}} = \sum_{k=0}^{\infty} A_n \cos\left(\frac{k\pi x}{L}\right)\vec{g}(t, k). \tag{S38}$$

Therefore, $\phi(x)$ is bounded and so we look for instability of $\vec{g}(t, k)$ for the different spacial modes.

For the bistable toggle we have

$$\mathbf{A} + \mathbf{\Lambda} = \begin{bmatrix} -\gamma - D\left(\frac{k\pi}{L}\right)^2 & \frac{\partial f_1}{\partial u_2}\Big|_{u_2 = u_2^*} \\ \frac{\partial f_2}{\partial u_1}\Big|_{u_1 = u_1^*} & -\gamma - D\left(\frac{k\pi}{L}\right)^2 \end{bmatrix}. \tag{S39}$$

The system must satisfy the following properties for stability of the various modes:

$$\text{trace}(\mathbf{A}+\mathbf{\Lambda}) = 2\left(-\gamma - D\left(\frac{k\pi}{L}\right)^2\right) < 0 \tag{S40}$$

$$\det(\mathbf{A}+\mathbf{\Lambda}) = \left(-\gamma - D\left(\frac{k\pi}{L}\right)^2\right)^2 - \left.\frac{\partial f_1}{\partial u_2}\right|_{u_2=u_2^*}\left.\frac{\partial f_2}{\partial u_1}\right|_{u_1=u_1^*} > 0. \tag{S41}$$

This can be simplified to the following condition

$$\gamma > \sqrt{\left.\frac{\partial f_1}{\partial u_2}\right|_{u_2=u_2^*}\left.\frac{\partial f_2}{\partial u_1}\right|_{u_1=u_1^*}} - D\left(\frac{k\pi}{L}\right)^2. \tag{S42}$$

For the toy model $f(u) = -\alpha \tan^{-1}(v)$ stability of each mode is determined by satisfaction of the following inequality

$$\gamma > \alpha - D\left(\frac{k\pi}{L}\right)^2. \tag{S43}$$

Therefore, the zeroth mode is unstable but as k increases we move closer towards the threshold for stability.

S4 Extended analysis of asymmetric circuits

We already showed that initial conditions biased towards one steady state cause all points to converge towards that steady state. However, adding noise helps to push the state in random parts of space across this separatrix, helping to balance initial conditions and resulting in non-homogeneous profiles again.

Figure S1 shows simulations of system (11) with varying standard deviation σ on the stochastic initial condition

$$\begin{aligned} u(0,x,y) &= 100 + \mathrm{randn}(\sigma,x,y)\,[\mathrm{nM}] \\ v(0,x,y) &= 100 + \mathrm{randn}(\sigma,x,y)\,[\mathrm{nM}]. \end{aligned} \tag{S44}$$

The term $\mathrm{randn}(\sigma,x,y)$ represents a pseudo-random number selected from a normal distribution with standard deviation σ and zero mean at point (x,y) in space. In Figure S1A, the production rate for species u is reduced by only .1% but this is sufficient to eliminate patterns. However, adding increased levels of noise at the initial condition allows non-homogeneous profiles to emerge.

We can achieve a balanced system again by tuning other parameters in the model. In other words, we can balance the system without setting all parameters equal. In Figure S1B, we show how severe asymmetry in the parameters can be tolerated by a balancing of overall strength. The production rate of u is significantly reduced but by increasing its diffusion coefficient and increasing the degradation rate of species v, we can see non-homogeneous profiles. Stochastic initial conditions, which provide a more realistic scenario in the evolution of the patterns, can be helpful against inbalanced systems.

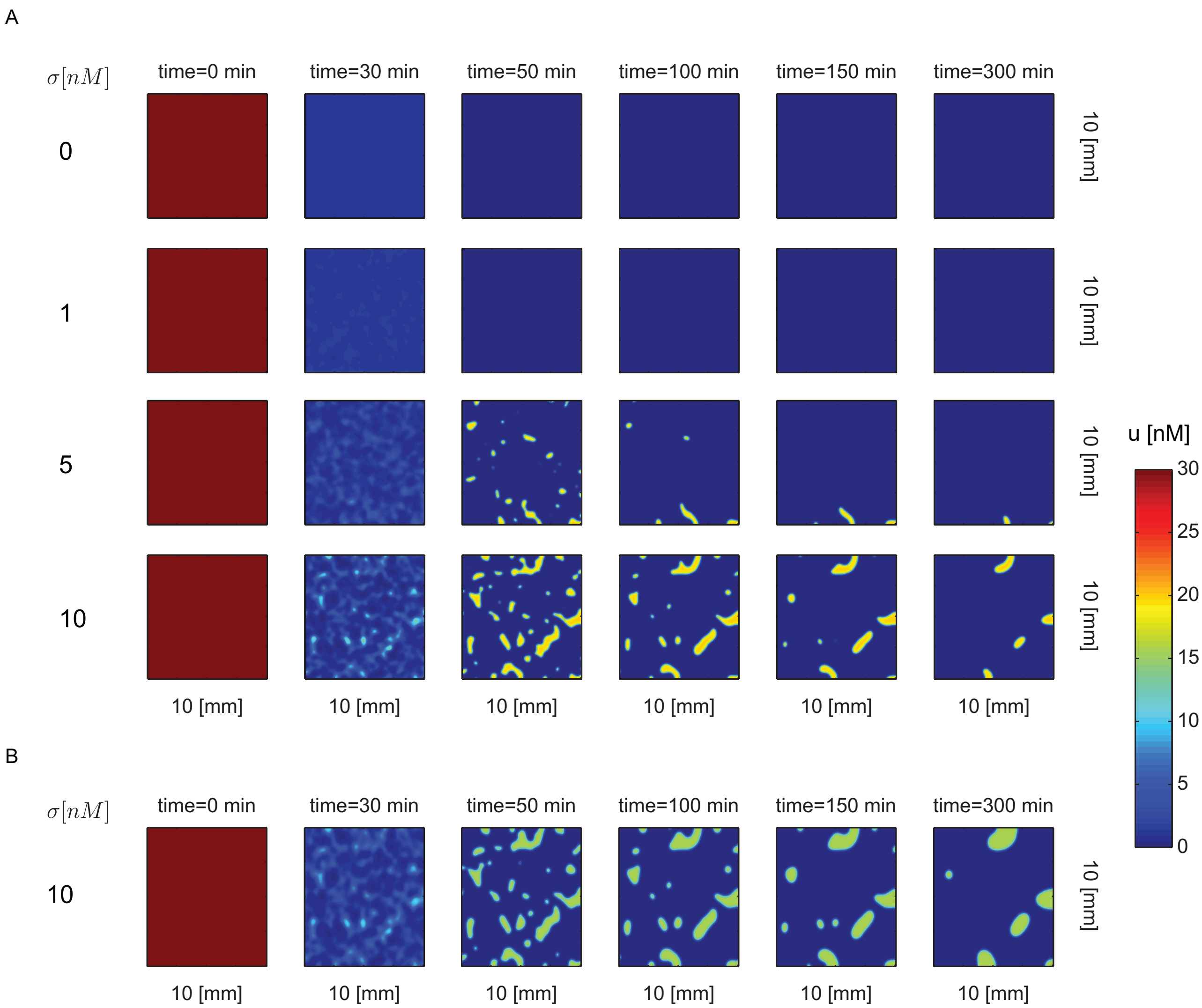

Figure S1: **Stochastic initial conditions are conducive to patterns in asymmetric systems.** (A)-(B): Simulations of system (11) with initial conditions $u(0,x,y) = v(0,x,y) = 100 + \mathrm{randn}(\sigma,x,y)\,\mathrm{nM}$. The term $\mathrm{randn}(\sigma,x,y)$ represents spatial noise. Values are selected from a normal distribution with standard deviation σ at each point in space (x,y). (A) The parameter values are $D_{u,v} = .001\,mm^2/\,\mathrm{min}$, $\alpha_v = 10\,\mathrm{nM}/\,\mathrm{min}$, $\alpha_u = 9.9\,\mathrm{nM}/\,\mathrm{min}$, and $\gamma_{u,v} = .5\ \mathrm{min}^{-1}$.(B) The changed parameter values are $D_u = .0015\,mm^2/\,\mathrm{min}$, $\alpha_u = 8.1\,\mathrm{nM}/\,\mathrm{min}$, and $\gamma_v = .53\ \mathrm{min}^{-1}$.