Equilibrium switching and mathematical properties of nonlinear interaction networks with concurrent antagonism and self-stimulation

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SUPPLEMENTARY MATERIAL

The CDM ODE model:

$$\frac{dX_i}{dt} = F_i(X) = \frac{\beta_i X_i^{c_i}}{K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}} + g_i - \rho_i X_i, \quad i = 1, 2, ..., n. \tag{S1}$$

Table S1: Summary of state variables and parameters.

Variables, Parameters	**Definition**
X_i	value of the i-th component †
$X = (X_1, X_2, ..., X_n)$	temporal state of the CDM ODE model
$X^* = (X_1^*, X_2^*, ..., X_n^*)$	a steady state of the CDM ODE model
β_i	growth constant of unrepressed X_i without decay
ρ_i	degradation rate of X_i ††
$\gamma_{i,j}$	coefficient affecting the inhibition of X_i by X_j
$[\gamma_{i,j}]$	matrix of the interaction (inhibition) coefficients
$g_i = e_i + \alpha_i s_i$	basal growth of X_i and effect of external stimulus
$K_i > 0$	threshold constant
$c_i \geq 1$	exponent affecting the strength of self-stimulation †††
$c_{i,j}$	exponent affecting inhibition of X_i by X_j †††
$[c_{i,j}]$	matrix of the interaction (inhibition) exponents

† can also be interpreted as concentration of protein, population size of species, gain of a community, worth of choices, etc.

†† can also be interpreted as rate of decay of protein, death of species, costs of a community, forgetfulness of memory, etc.

††† these are the exponents that influence the sigmoid growth of X_i.

We assume that all state variables and parameters are non-negative ($X \in \mathbb{R}^{\oplus n}$).

The multivariate sigmoid function H_i:

$$H_i(X_1, X_2, ..., X_n) = \frac{\beta_i X_i^{c_i}}{K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}}. \tag{S2}$$

The univariate sigmoid function H_i^1:

$$H_i^1(X_i) = \frac{\beta_i X_i^{c_i}}{K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}} \tag{S3}$$

where each X_j, $j \neq i$ is taken as a dynamic parameter.

Since the denominator of the sigmoid function (S2) is always positive, then the corresponding polynomial equation to

$$F_i(X) = \frac{\beta_i X_i^{c_i}}{K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}} - \rho_i X_i + g_i = 0 \tag{S4}$$

is

$$\begin{aligned} P_i(X) =& \beta_i X_i^{c_i} + (g_i - \rho_i X_i) \left(K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}} \right) = 0 \\ =& - \rho_i X_i^{c_i+1} + (\beta_i + g_i) X_i^{c_i} - \left(K_i + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}} \right) (\rho_i X_i) \\ &+ g_i \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}} + g_i K_i = 0 \ \forall i. \end{aligned} \tag{S5}$$

The following is the Jacobian of our system:

$$\mathbf{J}F(X) = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \cdots & a_{nn} \end{bmatrix} \tag{S6}$$

where

$$a_{ii} = \frac{\partial F_i}{\partial X_i} = \frac{\left(K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}\right) \beta_i c_i X_i^{c_i - 1} - \beta_i c_i X_i^{2c_i - 1}}{\left(K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}\right)^2} - \rho_i$$

$$= \frac{\left(K_i + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}\right) \beta_i c_i X_i^{c_i - 1}}{\left(K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}\right)^2} - \rho_i \tag{S7}$$

$$a_{ik} = \frac{\partial F_i}{\partial X_k} = \frac{-\beta_i X_i^{c_i} c_{i,k} \gamma_{i,k} X_k^{c_{i,k} - 1}}{\left(K_i + X_i^{c_i} + \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}\right)^2}, \ i \neq k. \tag{S8}$$

Proofs and Notes

SM1. Proof that all state variables are always non-negative.

Proof. Since we are considering only non-negative initial condition and non-negative parameters, if $X_i \to 0$ then either $dX_i/dt|_{X_i=0} = 0$ or $dX_i/dt|_{X_i=0} > 0$ but $dX_i/dt|_{X_i=0} \not< 0$ (where dX_i/dt is given in the ODE system (S1)). That is, if a component of a state variable goes to zero then the component will either stay zero or become positive but never negative. Hence, we are sure that the values of the state variables of the CDM ODE model (S1) are always non-negative. □

Note that the instantaneous rate of change $dX_i/dt|_{X_i=0} > 0$ happens only when $g_i > 0$.

SM2. Property 1: The steady state $X^* = ({X_1}^*, {X_2}^*, ..., {X_n}^*)$ of the CDM ODE system (S1) is stable only if all its components are attracting. In other words, if at least one of the components of X^* is non-attracting, then X^* is unstable. The converse of this statement is not always true.

The proof of Property 1 is straightforward. If at least one of the components of a steady state is non-attracting (say X_i^*) then a perturbation, however small, can cause the solution to X_i to move to a different value of X_i.

We have found some cases showing that the converse of this statement is not always true (e.g., the repressilator-type system).

SM3. Proof of Property 2: Suppose $\rho_i > 0$. The value $\frac{g_i+\beta_i}{\rho_i}$ is the upper bound of, but will never be equal to, X_i^*. The equilibrium points of the ODE system (S1) lie on the hyperspace

$$\left[\frac{g_1}{\rho_1}, \frac{g_1+\beta_1}{\rho_1}\right) \times \left[\frac{g_2}{\rho_2}, \frac{g_2+\beta_2}{\rho_2}\right) \times ... \times \left[\frac{g_n}{\rho_n}, \frac{g_n+\beta_n}{\rho_n}\right). \tag{S9}$$

Proof. The steady states can be found by getting the intersections of the multivariate function H_i (S2) and the decay hyperplane. The minimum and maximum value of H_i is zero and β_i, respectively.

The minimum value of the multivariate function H_i is zero which happens when $\beta_i = 0$ or when $X_i = 0$. If $H_i(X_1, X_2, ..., X_n) = 0$ then $F_i(X) = g_i - \rho_i X_i = 0$, implying $X_i = g_i/\rho_i$.

The upper bound of H_i is β_i. If $H_i(X_1, X_2, ..., X_n) = \beta_i$ then $F_i(X) = \beta_i - \rho_i X_i + g_i = 0$, implying $X_i = \frac{g_i+\beta_i}{\rho_i}$. However, H_i is equal to β_i only when $X_i = \infty$; hence, $X_i = \frac{g_i+\beta_i}{\rho_i}$ is an upper bound but cannot be a component of an equilibrium point. □

Note that the monotonically increasing univariate sigmoid curve $Y = H_i^1(X_i)$ (S3) and $Y = \rho_i X_i$ intersect at infinity when $g_i \to \infty$, $\beta_i \to \infty$ or $\rho_i \to 0$.

SM4. Proof of the statement: If both $g_i > 0$ and $\rho_i > 0$ then $X_i = g_i/\rho_i$ can only be an i-th component of a steady state when $\beta_i = 0$.

Proof. We first show that $X_i = g_i/\rho_i$ cannot be an i-th component of a steady state if $\beta_i > 0$. Suppose $\beta_i > 0$, $g_i > 0$, and g_i/ρ_i is an i-th component of an equilibrium point. Then, from the ODE system (S1),

$$F_i\left(X_1,...,\frac{g_i}{\rho_i},...,X_n\right) = \frac{\beta_i\left(\frac{g_i}{\rho_i}\right)^{c_i}}{K_i+\left(\frac{g_i}{\rho_i}\right)^{c_i}+\sum_{j\neq i}\gamma_{i,j}{X_j}^{c_{i,j}}} - \rho_i\frac{g_i}{\rho_i}+g_i = 0 \tag{S10}$$

$$= \frac{\beta_i\left(\frac{g_i}{\rho_i}\right)^{c_i}}{K_i+\left(\frac{g_i}{\rho_i}\right)^{c_i}+\sum_{j\neq i}\gamma_{i,j}X_j^{c_{i,j}}} = 0$$

implying that $\beta_i\left(g_i/\rho_i\right)^{c_i}=0$. Thus $\beta_i=0$ or $g_i=0$, a contradiction.

Now, if $\beta_i=0$ then solving $F_i(X)=0$ leads to $X_i=g_i/\rho_i$. □

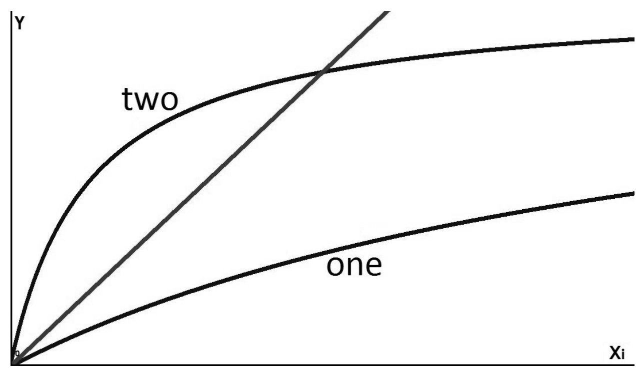

Figure S1: The possible number of intersections of $Y=\rho_iX_i$ and $Y=H_i^1(X_i)+g_i$ where $c_i=1$ and $g_i=0$. The value of $\sum_{j\neq i}\gamma_{i,j}X_j^{c_{i,j}}$ is fixed.

SM5. Proof of Property 3: Suppose $\rho_i>0$ for all i. Then each component of any state of the CDM ODE model (S1) is always attracted by an attracting component.

Proof. Figures (S1) to (S4) illustrate all possible cases showing the topologies of the intersections of $Y=\rho_iX_i$ and $Y=H_i^1(X_i)+g_i$. We employ the geometric analysis shown in Figure (S5) (where we rotate the graph of the curves, making $Y=\rho_iX_i$ the horizontal axis) to each topology of the intersections of $Y=\rho_iX_i$ and $Y=H_i^1(X_i)+g_i$. Given fixed values of X_j, $j\neq i$ (see the definition of "attracting component" in the main text), the univariate sigmoid curve $Y=H_i^1(X_i)$ and $Y=\rho_iX_i$ have the following possible number of intersections (see Figures (S1) to (S4)):

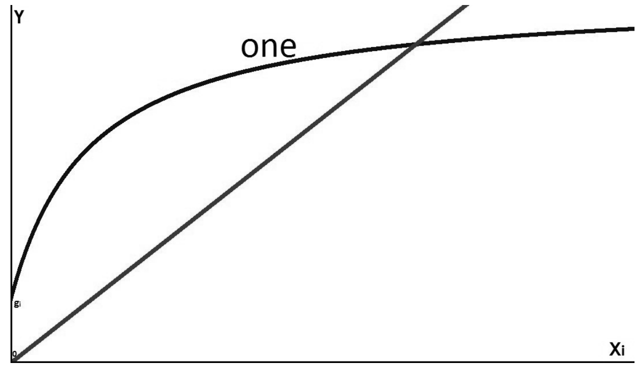

Figure S2: The possible number of intersections of $Y = \rho_i X_i$ and $Y = H_i^1(X_i) + g_i$ where $c_i = 1$ and $g_i > 0$. The value of $\sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}$ is fixed.

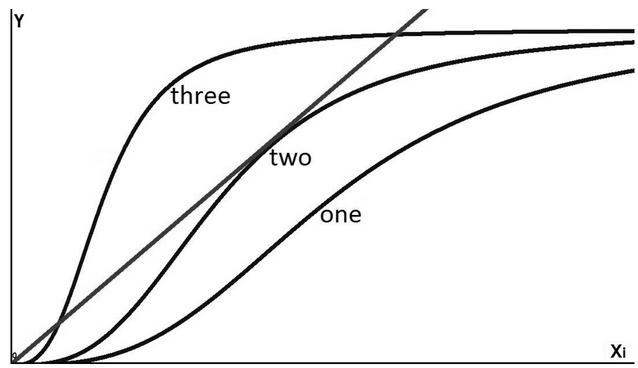

Figure S3: The possible number of intersections of $Y = \rho_i X_i$ and $Y = H_i^1(X_i) + g_i$ where $c_i > 1$ and $g_i = 0$. The value of $\sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}$ is fixed.

- two intersections (where one is attracting);
- one intersection (which is attracting); or
- three intersections (where two are attracting).

We can see that there is always an attracting intersection located in the first quadrant (including the axes) of the Cartesian plane. We can also observe that when there are two or more intersections, the value of one attracting intersection is always greater than the value of the non-attracting intersection — implying that any solution to the ODE is bounded. □

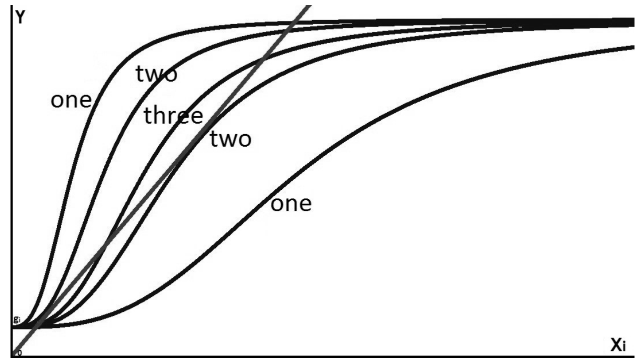

Figure S4: The possible number of intersections of $Y = \rho_i X_i$ and $Y = H_i^1(X_i) + g_i$ where $c_i > 1$ and $g_i > 0$. The value of $\sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}$ is fixed.

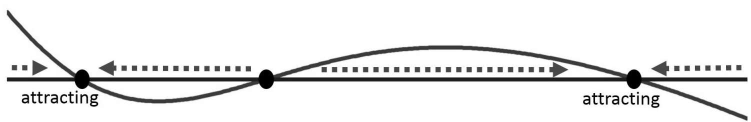

Figure S5: The curves are rotated making the line $Y = \rho_i X_i$ as the horizontal axis. Positive slope means non-attracting, negative slope means attracting. If the slope is zero, we look at the left and right neighboring slopes.

Note: Here we discuss the criterion "Positive slope denotes non-attracting intersection, negative slope denotes attracting intersection." in Figure (S5).

- Suppose $H_i^1 + g_i$ has a positive slope at ${X_i}^*$. This means that for $X_i > {X_i}^*$ in the neighborhood of ${X_i}^*$, dX_i/dt increases away from ${X_i}^*$ because $H_i^1(X_i) + g_i - \rho_i X_i > 0$. It also means that for $X_i < {X_i}^*$ in the neighborhood of ${X_i}^*$, dX_i/dt decreases away from ${X_i}^*$ because $H_i^1(X_i) + g_i - \rho_i X_i < 0$. Hence, ${X_i}^*$ is repelling.

- Suppose $H_i^1 + g_i$ has a negative slope at ${X_i}^*$. This means that for $X_i > {X_i}^*$ in the neighborhood of ${X_i}^*$, dX_i/dt decreases towards ${X_i}^*$ because $H_i^1(X_i) + g_i - \rho_i X_i < 0$. It also means that for $X_i < {X_i}^*$ in the neighborhood of ${X_i}^*$, dX_i/dt increases towards ${X_i}^*$ because $H_i^1(X_i) + g_i - \rho_i X_i > 0$. Hence, ${X_i}^*$ is attracting.

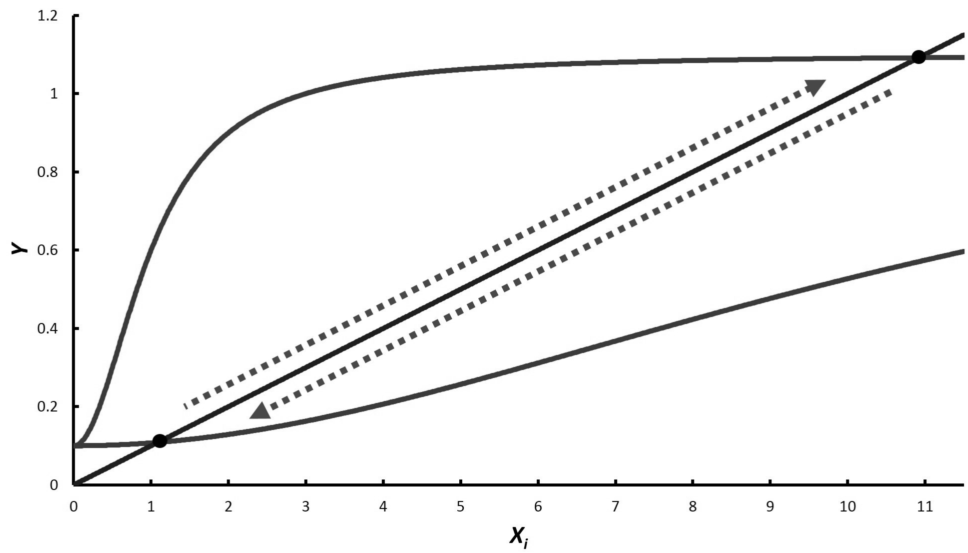

Figure S6: The two sigmoid curves are sample graphs of $Y = H_i^1(X_i)$ with different values of $\sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}$. The denominator of the sigmoid function H_i continuously varies resulting in changing value of the attracting component. The solution to X_i is sequentially attracted by high-valued and low-valued attracting components, which generates oscillatory behavior.

SM6. Property 4: Suppose sustained oscillations exist. The value of $\frac{g_i+\beta_i}{\rho_i}$ is an upper bound of the sustained oscillating solution to X_i. The sustained oscillations of the CDM ODE system (S1) is contained in the hyperspace (S9).

The proof of Property 4 follows from the proofs of Property 2 (there is always an attracting component) and Property 3 (the solution to the ODE is bounded). A high-valued attracting component and a low-valued attracting component alternately attract the solution. This alternate attraction generates oscillations. For visualization, see Figure (S6).

SM7. Property 5: Under the assumption that that there is only a finite number of steady states, the number of steady states of the CDM ODE model (S1) (where c_i and $c_{i,j}$ are integers) is at most

$$\prod_{i=1}^{n} max\{c_i + 1, c_{i,j} + 1 \text{ for all } j \neq i\}. \tag{S11}$$

The proof of Property 5 is by Bézout Theorem. Suppose there is only a finite number of steady states. The degree of P_i (S5) is $max\{c_i + 1, c_{i,j} + 1\ \forall j \neq i\}$. By the Bézout

Theorem, the number of complex-valued solutions to the polynomial system is at most $max\{c_1+1, c_{1,j}+1\ \forall j \neq 1\} \times max\{c_2+1, c_{2,j}+1\ \forall j \neq 2\} \times \ldots \times max\{c_n+1, c_{n,j}+1\ \forall j \neq n\}$. It follows that this is the upper bound of the number of real-valued steady states.

SM8. For the Example (3) in the main text, consider $n = 2$ and $c_i = c_{i,j} = 1$, $i, j = 1, 2$. Solving

$$\frac{dX_i}{dt} = \frac{\beta_i X_i}{K_i + X_i + \gamma_{i,j} X_j} - \rho_i X_i + g_i = 0$$

results in

$$X_i = \frac{\beta_i - \rho_i \hat{K}_i + g_i \pm \sqrt{\left(\beta_i - \rho_i \hat{K}_i + g_i\right)^2 + 4\rho_i g_i \hat{K}_i}}{2\rho_i} \tag{S12}$$

where $\hat{K}_i = K_i + \gamma_{i,j} X_j$, $i, j = 1, 2$. If $g_i = 0$,

$$X_i = 0 \text{ or } X_i = \frac{\beta_i - \rho_i \hat{K}_i}{\rho_i}. \tag{S13}$$

If $\beta_i \leq \rho_i \hat{K}_i$ then zero is the only solution.

- To prove that the zero state is stable when $\beta_i < \rho_i \hat{K}_i$, see SM12.

- To prove that $\left(0, \frac{\beta_i - \rho_i K_i}{\rho_i}\right)$ or $\left(\frac{\beta_i - \rho_i K_i}{\rho_i}, 0\right)$ is stable when $\beta_j < \rho_j \left(K_j + \gamma_{j,i} \frac{\beta_i - \rho_i K_i}{\rho_i}\right)$, we use the Jacobian matrix (S6). Note that $K_i \rho_i < \beta_i$ should be satisfied, because X_i^* is a switched-on steady state. The eigenvalues of the Jacobian evaluated at $X_i^* = \frac{\beta_i - \rho_i K_i}{\rho_i}$ and $X_j^* = 0$ are

$$\lambda_1 = \frac{K_i \beta_i}{(K_i + X_i^*)^2} - \rho_i, \text{ and} \tag{S14}$$

$$\lambda_2 = \frac{\beta_j}{K_j + \gamma_{j,i} X_i^*} - \rho_j. \tag{S15}$$

To have a stable steady state, the eigenvalues should be both negative. Since $X_i^* = \frac{\beta_i - \rho_i K_i}{\rho_i}$, then $\lambda_1 < 0$ when $K_i \rho_i < \beta_i$, which is always true. Now, $\lambda_2 < 0$ if $\beta_j < \rho_j \left(K_j + \gamma_{j,i} \frac{\beta_i - \rho_i K_i}{\rho_i}\right)$.

- From Equation (S13), if both X_1^* and X_2^* are switched-on, we need to solve the following system of equations:

$$X_1 = \frac{\beta_1 - \rho_1 (K_1 + \gamma_{1,2} X_2)}{\rho_1} \text{ and}$$
$$X_2 = \frac{\beta_2 - \rho_2 (K_2 + \gamma_{2,1} X_1)}{\rho_2}. \tag{S16}$$

The solution to this system of equations is

$$\left(\frac{\beta_1 - \rho_1 \left(K_1 + \gamma_{1,2} \left(\frac{\beta_2}{\rho_2} - K_2 \right) \right)}{\rho_1 (1 - \gamma_{1,2}\gamma_{2,1})}, \frac{\beta_2 - \rho_2 \left(K_2 + \gamma_{2,1} \left(\frac{\beta_1}{\rho_1} - K_1 \right) \right)}{\rho_2 (1 - \gamma_{2,1}\gamma_{1,2})} \right). \tag{S17}$$

This steady state is likely to be stable by looking at the graph with two intersections where the high-valued intersection is attracting in Figure (S1).

SM9. Proof of Property 6: Suppose $c_i = c_{i,j} = 1$, $K_i = K > 0$, $\gamma_{i,j} = 1$, $g_i = 0$, $\beta_i = \beta > 0$ and $\rho_i = \rho > 0$ where $\beta > \rho K$ for all i and j (K, β and ρ are constants). Then the polynomial system associated to the CDM ODE model (S1) has a non-constant common factor.

Proof. Recall Equation (S5), we have the corresponding polynomial system $P_i(X) = 0$ ($i = 1, 2, ..., n$):

$$\beta_i X_i^{c_i} - \rho_i K_i X_i - \rho_i X_i^{c_i+1} - \rho_i X_i \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}}$$
$$+ g_i K_i + g_i X_i^{c_i} + g_i \sum_{j \neq i} \gamma_{i,j} X_j^{c_{i,j}} = 0. \tag{S18}$$

Suppose $c_i = c_{i,j} = 1$, $K_i = K > 0$, $\gamma_{i,j} = 1$, $g_i = 0$, $\beta_i = \beta > 0$ and $\rho_i = \rho > 0$. Then the polynomial system can be written as ($i = 1, 2, ..., n$)

$$\beta X_i - \rho K X_i - \rho X_i^2 - \rho X_i \sum_{j \neq i} X_j = 0$$
$$\Rightarrow X_i \left(\beta - \rho K - \rho X_i - \rho \sum_{j \neq i} X_j \right) = 0$$
$$\Rightarrow X_i = 0 \text{ or } \left(\beta - \rho K - \rho X_i - \rho \sum_{j \neq i} X_j \right) = 0. \tag{S19}$$

Notice that the factor

$$\beta - \rho K - \rho X_i - \rho \sum_{j \neq i} X_j$$
$$= \beta - \rho K - \rho \sum_{j=1}^{n} X_j \tag{S20}$$

is common to all equations in the polynomial system. Thus, there are infinitely many complex-valued solutions to the polynomial system. However, note that we have restricted the state variables to be non-negative, so we do further investigation to determine the conditions for the existence of an infinite number of solutions given strictly non-negative variables. We focus our investigation on real-valued solutions.

Let $B = \beta - \rho K$.

Case 1: If $\beta = \rho K$ then $B = 0$. Thus, $B - \rho \sum_{j=1}^{n} X_j$ is never zero except when $X_j = 0$ $\forall j = 1, 2, ..., n$ (since X_j can take only non-negative values). Hence, the only equilibrium point to the system is the zero state.

Case 2: If $\beta < \rho K$ then $B < 0$. Thus, $B - \rho \sum_{j=1}^{n} X_j$ is always negative, and the polynomial equation does not have any zero for any non-negative value of X_j. Hence, the only equilibrium point is the zero state (that is, $X_i = 0$ $\forall i = 1, 2, ..., n$, see Equation (S19)).

Case 3: If $\beta > \rho K$ then $B > 0$. Thus, there exist solutions to the equation $B - \rho \sum_{j=1}^{n} X_j = 0$. Notice that the set of non-negative real-valued solutions to $B - \rho \sum_{j=1}^{n} X_j = 0$ is a hyperplane (e.g., it is a line for $n = 2$ and it is a plane for $n = 3$). Hence, there are infinitely many non-isolated steady states if $\beta > \rho K$. □

This also shows that any CDM ODE model that can be converted to this type of polynomial system has infinitely many steady states.

SM10. Property 7: Suppose $c_i = c_{i,j} = 1$, $K_i = K > 0$, $\gamma_{i,j} = 1$, $g_i = 0$, $\beta_i = \beta > 0$ and $\rho_i = \rho > 0$ for all i and j (K, β and ρ are constants). If $\beta > \rho K$ then the steady states of the ODE system (S1) are the zero state and the non-isolated points lying on the hyperplane with equation

$$\sum_{j=1}^{n} X_j = \frac{\beta}{\rho} - K, \; X_j \geq 0 \text{ for all } j. \tag{S21}$$

In addition, the zero state is an unstable equilibrium point while the hyperplane (S21) is an attractor.

The proof of Property 7 follows from Equation (S19) and the Case 3 in the proof of Property 6.

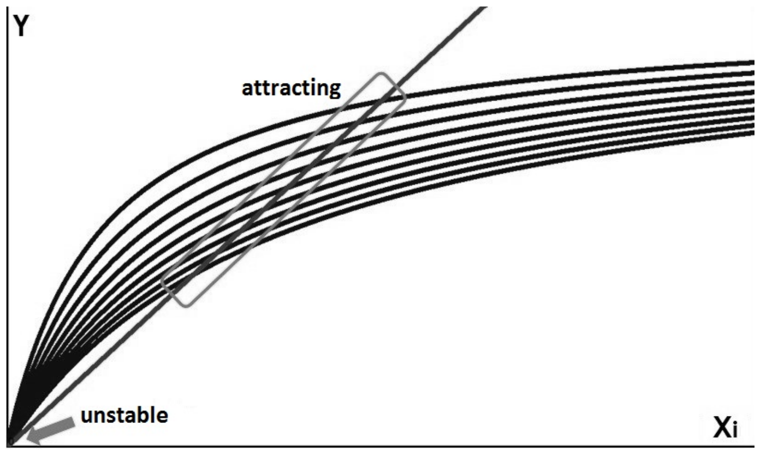

Figure S7: The origin is unstable while the points where $X_i^* = \beta/\rho - K - \sum_{j\neq i} X_j^*$ are attracting.

The graph of the univariate sigmoid function $Y = H_i^1(X_i)$ (S3) with $c_i = 1$ is hyperbolic. Suppose $\sum_{j\neq i} X_j = 0$ in the denominator of H_i^1. At $X_i = 0$, the slope of the sigmoid curve $Y = H_i^1(X_i)$ is

$$\frac{\partial H_i^1}{\partial X_i} = \frac{\beta}{K}. \tag{S22}$$

Since $\beta > \rho K$ then $\beta/K > \rho$. This implies that the slope of $Y = H_i^1(X_i)$ at $X_i = 0$ is greater than the slope of the decay line $Y = \rho X_i$. Therefore, when $\sum_{j\neq i} X_j = 0$ in the denominator of H_i^1, there are two possible intersections of $Y = H_i^1(X_i)$ and $Y = \rho X_i$ (see Figure (S1)). The intersections are at the origin (which is unstable) and at $X_i = \beta/\rho - K$ (which is an attracting component).

Now, suppose $\sum_{j\neq i} X_j$ in the denominator of H_i^1 varies (see Figure (S7) for illustration). Then the intersections of $Y = H_i^1(X_i)$ and $Y = \rho X_i$ are at the origin (which is unstable) and at $X_i = \beta/\rho - K - \sum_{j\neq i} X_j$ (which is attracting). From Figure (S7), the zero state is an unstable equilibrium point and the hyperplane $X_i = \beta/\rho - K - \sum_{j\neq i} X_j$ is an attractor if $\beta > \rho K$.

SM11. Here, we show that the sigmoid curve is always below the decay line.

Proof of Property 8 (part 1): If $c_i > 1$, $g_i = 0$ and

$$\rho_i({K_i}^{1/c_i}) \geq \beta_i \tag{S23}$$

for all i, then the ODE system (S1) has only one equilibrium point which is the zero state.

Proof. Let us first consider the case where $X_j = 0$, for all $j \neq i$. Recall that the upper bound of H_i^1 is β_i. Moreover, recall that when $X_i = K_i^{1/c_i}$ then $H_i^1(X_i) = \beta_i/2$. Note that $(K_i^{1/c_i}, \beta_i/2)$ is the inflection point of the univariate sigmoid curve. We substitute $X_i = K_i^{1/c_i}$ in the decay function $Y = \rho_i X_i$, and if the value of $\rho_i({K_i}^{1/c_i})$ is larger or equal to the value of the upper bound β_i then we are sure that $Y = H_i^1(X_i)$ lies below $Y = \rho_i X_i$. This means that they only intersect at the origin.

Now, as the values of X_j for all $j \neq i$ increase then the univariate sigmoid curve $Y = H_i^1(X_i)$ will just shrink and will definitely not intersect the decay line $Y = \rho_i X_i$ except at the origin. □

Proof of Property 8 (part 2): If $c_i = 1$, $g_i = 0$ and $\beta_i/K_i \leq \rho_i$ for all i, then the ODE system (S1) has only one equilibrium point which is the zero state.

Proof. Let us first consider the case where $X_j = 0$, for all $j \neq i$. Recall that $Y = H_i^1(X_i)$ where $c_i = 1$ is a hyperbolic curve. The partial derivative

$$\frac{\partial H_i^1}{\partial X_i} = \frac{\partial}{\partial X_i}\left(\frac{\beta_i X_i}{K_i + X_i}\right) = \frac{K_i \beta_i}{(K_i + X_i)^2} \tag{S24}$$

means that the slope of the hyperbolic curve is monotonically decreasing as X_i increases. The partial derivative at $X_i = 0$ is

$$\frac{\partial H_i^1}{\partial X_i} = \frac{\beta_i}{K_i} \leq \rho_i, \tag{S25}$$

which means that the slope of $Y = H_i^1(X_i)$ at $X_i = 0$ is less than or equal to the slope of the decay line $Y = \rho_i X_i$ at $X_i = 0$. Hence, the sigmoid curve $Y = H_i^1(X_i)$ lies below the decay line for all $X_i > 0$. □

SM12. Proof of Property 9 (part 1): In the ODE system (S1), suppose $g_i = 0$ and $c_i = 1$ $\forall i$. Then the zero state is a stable equilibrium point when $\rho_i > \beta_i/K_i$ $\forall i$, or an unstable equilibrium point when $\rho_i < \beta_i/K_i$ for at least one i. When $\rho_i = \beta_i/K_i$ for at least one i then we have an attractor only if X_i is restricted to be non-negative and $\rho_j \geq \beta_j/K_j$ $\forall j \neq i$.

Proof. Since $g_i = 0$ for all i then the zero state is an equilibrium point. The characteristic polynomial associated with the Jacobian of the ODE system (S1) when $X = (0, 0, ..., 0)$ is

$$|\mathbf{J}F(\mathbf{0}) - \lambda\mathbf{I}| = \begin{vmatrix} \frac{\beta_1}{K_1} - \rho_1 - \lambda & 0 & \cdots & 0 \\ 0 & \frac{\beta_2}{K_2} - \rho_2 - \lambda & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \frac{\beta_n}{K_n} - \rho_n - \lambda \end{vmatrix} \tag{S26}$$

$$= \left(\frac{\beta_1}{K_1} - \rho_1 - \lambda\right)\left(\frac{\beta_2}{K_2} - \rho_2 - \lambda\right)...\left(\frac{\beta_n}{K_n} - \rho_n - \lambda\right). \tag{S27}$$

The eigenvalues (λ) are $\beta_1/K_1 - \rho_1, \beta_2/K_2 - \rho_2, ..., \beta_n/K_n - \rho_n$. Therefore, the zero state is a stable equilibrium point when $\rho_i > \beta_i/K_i$ $\forall i$. The zero state is an unstable equilibrium point when $\rho_i < \beta_i/K_i$ for at least one i.

If $\rho_j \geq \beta_j/K_j$ $\forall j \neq i$ but $\rho_i = \beta_i/K_i$ (for at least one i) then we have a nonhyperbolic equilibrium point. Geometrically, the decay line $Y = \rho_i X_i$ is tangent to the univariate sigmoid curve $Y = H_i^1(X_i)$ at $X_i = 0$, which implies that $X_i^* = 0$ is a saddle — stable from $X_i^* > 0$ and unstable from $X_i^* < 0$. Hence, if we restrict $X_i \geq 0$ for any value of X_i then this nonhyperbolic equilibrium point is an attractor. □

Proof of Propert 9 (part 2): Suppose $\rho_i > 0$, $g_i = 0$ and $c_i > 1$ $\forall i$, then the zero state is a stable equilibrium point of the ODE system (S1).

Proof. The characteristic polynomial associated with the Jacobian of the ODE system (S1) when $X = (0, 0, ..., 0)$ is

$$|\mathbf{J}F(\mathbf{0}) - \lambda\mathbf{I}| = \begin{vmatrix} -\rho_1 - \lambda & 0 & \cdots & 0 \\ 0 & -\rho_2 - \lambda & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & -\rho_n - \lambda \end{vmatrix} \tag{S28}$$

$$= (-\rho_1 - \lambda)(-\rho_2 - \lambda)...(-\rho_n - \lambda). \tag{S29}$$

The eigenvalues (λ) are $-\rho_1, -\rho_2, ..., -\rho_n$ which are all negative. Therefore, the zero state is a stable equilibrium point. □

SM13. Proof of Remark 2: Suppose $c_i > 1$, $\rho_i > 0$ and $g_i = 0$. Then $X_i^* = 0$ is always an attracting component.

Proof. The ODE system (S1) has an equilibrium point with i-th component equal to zero if and only if $g_i = 0$. The only possible topologies of the intersections of $Y = H_i^1(X_i)$ and $Y = \rho_i X_i$ are shown in Figure (S3). Notice that zero i-th component is always stable. □

Note that if $X_i = 0$ and $g_i = 0$, then the n-dimensional system can be reduced to an $n-1$-dimensional system. The steady states of the form $(X_1^* X_2^*, X_3^*, 0)$ of a system with $n = 4$ and $g_4 = 0$ are the steady states $(X_1^* X_2^*, X_3^*)$ of the corresponding system with $n = 3$.

SM14. Here, we present additional examples of CDM systems with oscillating solution:

- 5-component repressilator with $c_i = c_{i,j} = 1\ \forall i, j$.

$$\begin{aligned} \frac{dX_1}{dt} &= \frac{X_1}{1 + X_1 + 5X_2 + 0.01X_3 + 0.01X_4 + 0.01X_5} - 0.1X_1 \\ \frac{dX_2}{dt} &= \frac{X_2}{1 + 0.01X_1 + X_2 + 5X_3 + 0.01X_4 + 0.01X_5} - 0.1X_2 \\ \frac{dX_3}{dt} &= \frac{X_3}{1 + 0.01X_1 + 0.01X_2 + X_3 + 5X_4 + 0.01X_5} - 0.1X_3 \\ \frac{dX_4}{dt} &= \frac{X_4}{1 + 0.01X_1 + 0.01X_2 + 0.01X_3 + X_4 + 5X_5} - 0.1X_4 \\ \frac{dX_5}{dt} &= \frac{X_5}{1 + 5X_1 + 0.01X_2 + 0.01X_3 + 0.01X_4 + X_5} - 0.1X_5. \end{aligned} \tag{S30}$$

  $X_0 = (1, 1.1, 1.2, 1.3, 1.4)$.

- An oscillator with even number of components.

$$\begin{aligned}
\frac{dX_1}{dt} &= \frac{X_1^2}{1+X_1^2+X_2^2+X_3} - 0.1X_1 + 0.1 \\
\frac{dX_2}{dt} &= \frac{X_2^2}{1+X_2^2+X_3^2+X_4} - 0.1X_2 + 0.1 \\
\frac{dX_3}{dt} &= \frac{X_3^2}{1+X_3^2+X_4^2+X_5} - 0.1X_3 + 0.1 \\
\frac{dX_4}{dt} &= \frac{X_4^2}{1+X_4^2+X_5^2+X_6} - 0.1X_4 + 0.1 \\
\frac{dX_5}{dt} &= \frac{X_5^2}{1+X_5^2+X_6^2+X_7} - 0.1X_5 + 0.1 \\
\frac{dX_6}{dt} &= \frac{X_6^2}{1+X_6^2+X_7^2+X_8} - 0.1X_6 + 0.1 \\
\frac{dX_7}{dt} &= \frac{X_7^2}{1+X_7^2+X_8^2+X_1} - 0.1X_7 + 0.1 \\
\frac{dX_8}{dt} &= \frac{X_8^2}{1+X_8^2+X_1^2+X_2} - 0.1X_8 + 0.1.
\end{aligned} \tag{S31}$$

$X_0 = (5.6931, 5.6932, 5.6933, 5.6934, 0.1, 0.1, 0.1, 0.2)$.

SM15. We add a time-dependent Gaussian white noise (dW) to the ODE model to investigate the effect of additive random fluctuations. This Gaussian white noise term approximates multiple heterogeneous sources of temporal noise. The stochastic differential equation (SDE) that we consider is of the form

$$dX_i = F_i(X)dt + \sigma dW \tag{S32}$$

where $\sigma = 1$ is a parameter representing the amplitude of noise, and W is a Brownian motion (Wiener process).

SM16. The numerical simulations in our paper employed Runge-Kutta 4 for ODEs and Euler-Maruyama for SDEs with step size=0.01. These simulations are carried-out using Berkeley Madonna (www.berkeleymadonna.com).

The phase planes are generated using Scientific WorkPlace (www.mackichan.com).