Switching in Multisite Phosphorylation Networks

Carsten Conradi, Dietrich Flockerzi, Katharina Holstein

Max-Planck-Institute Dynamics of Complex Technical Systems
Magdeburg

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Overview

1. Dynamical systems defined by mass action networks
2. Switching and multistationarity in mass action networks
3. Conditions for multistationarity
4. Switching in the NFAT – Calcineurin system
5. Summary
Overview

1. Dynamical systems defined by mass action networks

2. Switching and multistationarity in mass action networks

3. Conditions for multistationarity
   - The polynomial system $S \text{diag}(k)\phi(a) = 0$, $S \text{diag}(k)\phi(b) = 0$
   - Adding the linear system
   - The Transformed Equation $Y^T \mu = \ln \frac{E^\nu}{E^\lambda}$
   - The nonlinear constraint $\kappa \in \text{im}_+(\Psi)$

4. Switching in the NFAT – Calcineurin system

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A simple example

Dynamical system with polynomial right hand side

\[
\begin{align*}
\dot{x}_1 &= k_1 x_1 x_2 - k_2 x_1^2 \\
\dot{x}_2 &= -k_1 x_1 x_2 + k_2 x_1^2
\end{align*}
\]

\[
\dot{x} = \begin{bmatrix}
1 & -1 \\
-1 & 1
\end{bmatrix}
\begin{bmatrix}
k_1 & 0 \\
0 & k_2
\end{bmatrix}
\begin{bmatrix}
x_1 x_2 \\
x_1^2
\end{bmatrix}
= : S
= : \phi(x)
\]

Observe: \(\text{rank}(S) = 1 \iff (1, 1) \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} = (0, 0)\)
The dynamical system is defined by two matrices

1. **Stoichiometric matrix**

   \[
   S = \begin{bmatrix}
   1 & -1 \\
   -1 & 1 \\
   \end{bmatrix}
   \]

2. **Rate exponent matrix (defining \( \phi(x) = (x_1, x_2, x_1^2)^T \))**

   \[
   Y = \begin{bmatrix}
   1 & 2 \\
   1 & 0 \\
   \end{bmatrix}
   \]
Mass action networks in general

**Objects defined by mass action networks**
- Dynamical System $\dot{x} = S \text{diag}(k) \phi(x)$
- Stoichiometric matrix $S$
- Monomial vector $\phi(x)$
- Rate exponent matrix $Y$

**Trajectories: confined to affine linear subspaces**
- $S$ does not have full row rank $\Rightarrow Z^T S \equiv 0$
- Trajectory $x(t)$ with initial value $x(0)$ satisfies
  \[ Z^T x(t) = Z^T x(0) \iff x(t) - x(0) \in \text{im}(S) \]
- Trajectories $x(t)$: confined to **affine linear subspace**: $x(0) + \text{im}(S)$
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Switching and multistationarity in mass action networks

- Switching: solutions $x(t)$ end up in different regions of state space (depending on initial conditions)
- Switching occurs in case of

**Bistability**

**Saddle-point (stable manifold as switching surface)**

- Multistationarity may lead to switching!
Trajectories are confined to affine linear subspaces

Steady states of mass action networks

- In general the steady state variety
  \[
  \{(x, k) \in \mathbb{R}^n_0 \times \mathbb{R}^r_0 | S \text{ diag}(k) \phi(x) = 0\}
  \]
  has dimension $> 0$

- A trajectory $x(t)$ does not ‘see’ all of them ($x(t)$ is confined to an affine linear subspace)

- A trajectory $x(t)$ (initial value $x(0)$) only ‘sees’ those contained in $x(0) + \text{im}(S)$

- Interested in
  \[
  x(0) + \text{im}(S) \cap \{x \in \mathbb{R}^n_0 | S \text{ diag}(k) \phi(x) = 0\}
  \]
Definition of multistationarity

Multistationarity
Existence of at least two distinct positive states \( a \) and \( b \) and a positive vector of rate constants \( k \) satisfying

- **polynomial system**
  
  \[
  S \text{ diag}(k) \phi(a) = 0, \quad S \text{ diag}(k) \phi(b) = 0
  \]

- **linear condition**

  \[
  Z^T a = Z^T b \iff b - a \in \text{im}(S)
  \]
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A transformation

- **Goal:** positive solutions $a$, $b$ and $k$ to the polynomials $S \text{diag}(k)\phi(a) = 0$, $S \text{diag}(k)\phi(b) = 0$

- **Transformation:** $(a, b) \rightarrow (a, \mu)$:

  $$\mu_i := \ln \frac{b_i}{a_i}, \quad b_i = e^{\mu_i} a_i$$

- **Observation I:**

  $$b^\gamma = \prod_i b_i^{\gamma_i} = \prod_i (e^{\mu_i} a_i)^{\gamma_i} = \prod_i (e^{\mu_i})^{\gamma_i} \cdot \prod_i a_i^{\gamma_i} = e^{\gamma^T \mu} a^\gamma$$

- And hence

  $$\phi(b) = \text{diag}(e^{\gamma^T \mu}) \phi(a)$$
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A transformation

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$$S \text{ diag}(k) \phi(a) = 0, \ S \text{ diag}(k) \phi(b) = 0$$

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- And hence

$$\phi(b) = \text{diag}(e^{\gamma^T \mu}) \phi(a)$$
Observation II:

\[ S \text{ diag}(k) \phi(x) = 0, \ k, x > 0 \iff \text{diag}(k) \phi(x) \in \text{int} (\ker(S) \cap \mathbb{R}^r_{\geq 0}) \]

Reparameterize \( \text{diag}(k) \phi(a), \text{diag}(k) \phi(b) \) over \( \text{int} (\ker(S) \cap \mathbb{R}^r_{> 0}) \) using finite set of unique generators \( E \) (up to scalar multiplication):

Dividing equations:

\[ e^{Y^T \mu} = \frac{E \nu}{E \lambda} \]

Ultimately (applying \( \ln \)):

Transformed equation

\[ Y^T \mu = \ln \frac{E \nu}{E \lambda} \]
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\[ \text{diag}(k) \phi(a) = E \lambda \]

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\[ S \, \text{diag}(k) \, \phi(x) = 0, \ k, x > 0 \Leftrightarrow \text{diag}(k) \, \phi(x) \in \text{int} \left( \ker(S) \cap \mathbb{R}^r_{\geq 0} \right) \]

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\[ \text{diag}(k) \, \phi(a) = E \, \lambda \]
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Ultimately (applying \( \ln \)):

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\text{diag}(k) \phi(a) &= E \lambda \\
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Ultimately (applying \( \ln \)):

**Transformed equation**

\[ Y^T \mu = \ln \frac{E \nu}{E \lambda} \]
Lemma (Conradi & Flockerzi, 2012)

The following are equivalent:

1. $\exists a, b, a \neq b \ k > 0$ such that
   
   $S \text{diag}(k)\phi(a) = 0$ and $S \text{diag}(k)\phi(b) = 0$

2. $\exists \mu \neq 0$ and $\nu, \lambda > 0$ such that

   $Y^T \mu = \ln \frac{E\nu}{E\lambda}$ (Transformed Equation)

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Adding the linear system

- Assume a solution \((\mu, \nu, \lambda)\) to \(Y^T \mu = \ln \frac{E_\nu}{E_\lambda}\)
- Can we find positive \(a \neq b\) such that

\[
Z^T a = Z^T b \iff b - a \in \text{im}(S)
\]

Feinberg, 1995 & Conradi et. al. 2008

- Desired \(a, b > 0\) exist, if and only if there exists a \(z \in \text{im}(S)\) with \(\text{sign}(z) = \text{sign}(\mu)\)
- Linear inequality condition


Conditions for multistationarity

- The polynomial system $S \text{diag}(k)\phi(a) = 0$, $S \text{diag}(k)\phi(b) = 0$
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Solvability of the Transformed Equation

**Transformed Equation**

\[ Y^T \mu = \ln \frac{E^\nu}{E^\lambda} \]

- Linear left hand side \( Y^T \mu \)
- Nonlinear right hand side
- \( \ln \frac{E^\nu}{E^\lambda} \): In of fractionals
Solvability of the Transformed Equation

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Idea (Conradi & Flockerzi, 2012)

- Necessary and sufficient conditions: existence of \( \mu, \nu, \lambda \)
- Linear inequalities
- Selected network structures (identifiable via \( \ker(Y) \) and \( E \) )
## Solvability of the Transformed Equation

### Transformed Equation

\[ Y^T \mu = \ln \frac{E \nu}{E \lambda} \]

- Linear left hand side \( Y^T \mu \)
- Nonlinear right hand side
- \( \ln \frac{E \nu}{E \lambda} \): \( \ln \) of fractionals

### Idea (Conradi & Flockerzi, 2012)

- Necessary and sufficient conditions: existence of \( \mu, \nu, \lambda \)
- Linear inequalities
- Selected network structures (identifiable via \( \ker(Y) \) and \( E \))

### Based on the Fredholm alternative

- Nonlinear \( \ln \frac{E \nu}{E \lambda} \in \text{im} \left( Y^T \right) \) \( \Leftrightarrow \) \( \ln \frac{E \nu}{E \lambda} \perp \text{im} \left( Y^T \right)^\perp \)
- Transformed Equation is solvable, if and only if

\[ U^T Y^T \equiv 0 \Rightarrow U^T \ln \frac{E \nu}{E \lambda} = 0 \]

- Polynomial condition in \( \nu, \lambda \)
Exploit the structure of ker \((Y)\)

- **Observation III:** ker \((Y)\) often contains vectors \(u_\ell = e_i - e_j\) (differences of elements of the standard basis of \(\mathbb{R}^r\))

**Trivial kernel vectors**

\[ u_\ell = (0, \ldots, 1, 0, \ldots, -1, 0, \ldots)^T \]

- Condition \(u_i^T \ln \frac{E_i^\nu}{E_i^\lambda} = 0\) implies equality of two elements:

\[ \ln \frac{E_i^\nu}{E_i^\lambda} = \ln \frac{E_j^\nu}{E_j^\lambda} \]

- **Observation IV:** equality of two elements implies equality of all elements defined by linear combinations of row vectors \(E_i\) and \(E_j\)

\[ \ln \frac{E_i^\nu}{E_i^\lambda} = \ln \frac{E_j^\nu}{E_j^\lambda} \Rightarrow \ln \frac{E_k^\nu}{E_k^\lambda} = \ln \frac{E_j^\nu}{E_j^\lambda}, \ \forall E_k \in \text{span}(E_i, E_j) \]
Exploit the structure of $\ker(Y)$

- **Observation III**: $\ker(Y)$ often contains vectors $u_\ell = e_i - e_j$ (differences of elements of the standard basis of $\mathbb{R}^r$)

<table>
<thead>
<tr>
<th>Trivial kernel vectors</th>
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  $\ln \frac{E_i}{E_j} = \ln \frac{E_j}{E_i} \Rightarrow \ln \frac{E_k}{E_j} = \ln \frac{E_j}{E_k}, \forall E_k \in \text{span}(E_i, E_j)$
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- **Observation III:** \( \ker(Y) \) often contains vectors \( u_\ell = e_i - e_j \) (differences of elements of the standard basis of \( \mathbb{R}^r \))

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Clusters $J_i$

- Clustering of rows of the generator matrix $E$:

  Cluster $J_i$:

  $$J_i \subseteq \{1, \ldots, r\} \text{ with } \ln \frac{E_j \nu}{E_j \lambda} = \ln \frac{E_\ell \nu}{E_\ell \lambda}, \forall j, \ell \in J_i$$

- ‘Trivial’ kernel vectors induce a clustering of fractionals that evaluate to one and the same real number $\kappa_i$:

  $$\kappa_i = \ln \frac{E_j \nu}{E_j \lambda}, \forall j \in J_i$$

- Every cluster $J_i$ defines a nonlinear function $\psi_i(\nu, \lambda)$:

  Functions $\psi_i(\nu, \lambda)$

  $$\psi_{J_i}(\nu, \lambda) := \ln \frac{E_j \nu}{E_j \lambda}, \forall j \in J_i$$
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Clusters \( J_i \)

- Every cluster defines an **indicator vector** \( \pi^i \):
  
  Indicator vectors \( \pi^i \)
  
  \[
  \pi^i_j = 1, \text{ if } j \in J_i \text{ and } \pi^i_j = 0, \text{ else }
  \]

- **Consequently**: (\( \gamma \) clusters)
  
  ▶ Matrix: \( \Pi := [\pi^1, \ldots, \pi^\gamma] \)
  
  ▶ Vector-valued function: \( \Psi(\nu, \lambda) = (\psi_{J_1}, \ldots, \psi_{J_\gamma})^T \)

- **Reduction**: (based on trivial kernel vectors):
  
  \[
  \ln \frac{E_\nu}{E_\lambda} \in \mathbb{R}^r \text{ to } \Psi(\nu, \lambda) \in \mathbb{R}^\gamma
  \]
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  - **Vector-valued function**: $\Psi(\nu, \lambda) = (\psi_{J_1}, \ldots, \psi_{J_\gamma})^T$

- **Reduction**: (based on trivial kernel vectors):

  $$\ln \frac{E_{\nu}}{E_{\lambda}} \in \mathbb{R}^r \text{ to } \Psi(\nu, \lambda) \in \mathbb{R}^\gamma$$
We have established the following equivalence

**Lemma (Conradi & Flockerzi 2012)**

The following are equivalent:

1. \( \exists a, b, a \neq b \ \ k > 0 \ \text{such that} \)

\[
S \ \text{diag}(k) \phi(a) = 0 \ \text{and} \ S \ \text{diag}(k) \phi(b) = 0
\]

2. \( \exists \mu \neq 0, \nu, \lambda > 0 \ \text{such that} \)

\[
Y^T \mu = \ln \frac{E \nu}{E \lambda}
\]

(\text{Transformed Equation})

3. \( \exists \mu \neq 0, \kappa \ \text{such that} \)

\[
Y^T \mu = \prod \kappa
\]

(\text{linear})

\[
\kappa \in \text{im}_+ (\Psi(\nu, \lambda))
\]

(\text{nonlinear})
Overview

1. Dynamical systems defined by mass action networks

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4. Switching in the NFAT – Calcineurin system

5. Summary
Generator matrix for ERK signaling

(1) Clustering of rows based on the span of the trivial kernel vectors:
Generator matrix for ERK signaling

(2) Occurrence of $\nu_i$, $\lambda_i$ in the clusters:
Generator matrix for ERK signaling

(2) Occurrence of $\nu_i$, $\lambda_i$ in the clusters:

Definition (Isolation Property)

A pair $(\nu_j, \lambda_j)$ has the Isolation Property, if it is used in exactly one function $\psi_{J_i}(\nu, \lambda)$.
Generator matrix for ERK signaling

(2) Occurrence of $\nu_i$, $\lambda_i$ in the clusters:

|\begin{array}{ccccccc}
1 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 1 & 0 \\
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0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{array}|

Definition (Isolation Property)

A pair $(\nu_j, \lambda_j)$ has the *Isolation Property*, if it is used in exactly one function $\psi_{J_i}(\nu, \lambda)$.

Definition (Bridging Property)

A pair $(\nu_j, \lambda_j)$ has the *Bridging Property*, if it is used in exactly two functions $\psi_{J_{i1}}(\nu, \lambda)$ and $\psi_{J_{i2}}(\nu, \lambda)$. 
Lemma (Conradi & Flockerzi 2012)

If all $\nu_i$, $\lambda_i$ have the **Isolation Property** then

- $\text{im}_+ (\Psi) \equiv R^n \iff$ Nonlinear constraint $\kappa \in \text{im}_+ (\Psi)$ is satisfied for every $\kappa \in R^n$

- Only need **nontrivial solutions** to the linear system:

$$ Y^T \mu = \prod \kappa $$

---

Lemma (Conradi & Flockerzi 2012)

If all \( \nu_i, \lambda_i \) have the **Isolation Property** then

- \( \text{im}_+ (\Psi) \equiv \mathbb{R}^\gamma \iff \text{Nonlinear constraint} \ \kappa \in \text{im}_+ (\Psi) \) is satisfied for every \( \kappa \in \mathbb{R}^\gamma \)
- Only need **nontrivial solutions** to the linear system:
  \[
  Y^T \mu = \Pi \kappa
  \]

Theorem (Conradi & Flockerzi 2012)

If all \( \nu_i, \lambda_i \) have either the **Isolation** or the **Bridging Property**, then

- \( \kappa \in \text{im}_+ (\Psi) \iff \text{feasibility of linear} \ \kappa\text{-inequalities} \)
- Only need **nontrivial solutions** to the **augmented** linear system:
  \[
  Y^T \mu = \Pi \kappa, \ A \kappa > 0
  \]

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4. Switching in the NFAT – Calcineurin system
5. Summary
The NFAT – Calcineurin system

- NFAT (Nuclear Factor of Activated T-cells): family of (five) transcription factors
- Play an important role in immune response
- Assist DNA binding (various transcription factors)

Localization

- Localized in nucleus and cytoplasm
- Localization is determined by $n = 13$ phosphorylation sites:
  1. Unphosphorylated NFAT imported to the nucleus (phosphatase
  2. Fully phosphorylated NFAT is exported to the cytoplasm
Mass action network describing phosphorylation and nuclear import/export

**Goal**: Consequences of multistationarity in the phosphorylation networks (K. Holstein)

- Two phosphorylation networks with $n = 13$
- Cytoplasm ($A^{(C)}$) & nucleus ($A^{(N)}$)
- Nuclear import/export reactions

**Two step approach**:  
1. Multistationarity in the phosphorylation network  
2. Coupling by import/export reactions
**Phosphorylation in the cytoplasm:**

\[
A^{(C)} + E_1 \overset{k_1}{\underset{k_2}{\rightleftharpoons}} A^{(C)} E_1 \rightarrow A_p^{(C)} + E_1 \quad \rightarrow \quad A_{pp}^{(C)} + E_1 \quad \rightarrow \quad \cdots \quad A_{(n-1)p}^{(C)} + E_1 \overset{k_{6n-5}}{\underset{k_{6n-4}}{\rightleftharpoons}} A_{(n-1)p}^{(C)} E_1 \rightarrow A_{np}^{(C)} + E_1 \\
A_{np}^{(C)} + E_2 \overset{k_{6n-2}}{\underset{k_{6n-1}}{\rightleftharpoons}} A_{np}^{(C)} E_2 \rightarrow A_{(n-1)p}^{(C)} + E_1 \quad \rightarrow \quad A_{pp}^{(C)} + E_2 \overset{k_{10}}{\rightleftharpoons} A_{pp}^{(C)} E_2 \rightarrow A_p^{(C)} + E_2 \rightarrow A_{np}^{(C)} + E_2 
\]

**Nuclear import/export:**

\[
A^{(C)} \overset{k_{in}}{\rightarrow} A^{(N)} \\
A_{np}^{(N)} \overset{k_{out}}{\rightarrow} A_{np}^{(C)} 
\]

**Phosphorylation in the nucleus:**

\[
A^{(N)} + E_1 \overset{k_1}{\underset{k_2}{\rightleftharpoons}} A^{(N)} E_1 \rightarrow A_p^{(N)} + E_1 \quad \overset{k_7}{\underset{k_8}{\rightleftharpoons}} A_p^{(N)} E_1 \rightarrow A_{pp}^{(N)} + E_1 \quad \rightarrow \quad \cdots \quad A_{(n-1)p}^{(N)} + E_1 \overset{k_{6n-5}}{\underset{k_{6n-4}}{\rightleftharpoons}} A_{(n-1)p}^{(N)} E_1 \rightarrow A_{np}^{(N)} + E_1 \\
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\]
Multistationarity & switching in the phosphorylation networks

**Multistationarity analysis:**

1. Clustering yields $\gamma = 13$ and 13 functions $\psi_i(\nu, \lambda)$
2. All $\nu_i, \lambda_i$ have the Isolation Property $\Rightarrow \text{im}_+ (\Psi) \equiv R^{13}$
3. Multistationarity requires feasibility of (at least one) linear inequality system

**Rate constants:**

1. Solutions define rate constants
2. Obtain realistic values for the rate constants (K. Holstein)

**Switching:**

Numerical analysis shows bistability and hence switching for realistic parameter values
Multistationarity & switching in the phosphorylation networks

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Multistationarity & switching in the simple NFAT – Calcineurin model

- **Multistationarity analysis:**
  
  IFT (for $\epsilon$ sufficiently small)
  
  1. Multistationarity in the phosphorylation networks $\Rightarrow$ multistationarity in the complete network
  2. Multistationarity in the positive orthant, if rate constants describing nuclear import and export satisfy:
     
     \[
     \frac{k_{out}}{k_{in}} = \frac{[A^c]_{ss}}{[A^{13P}]_{ss}}
     \]

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**Summary**

- **Multistationarity:**
  
  positive $a$, $b$ and $k$ with $S \ \text{diag}(k) \ \phi(a) = 0$, $S \ \text{diag}(k) \ \phi(b) = 0$ and $Z^T a = Z^T b$

- **Transformation:**
  
  $\mu = \ln \frac{b}{a}$, $b = \text{diag} \left( e^{\mu} \right) \ a$

- **Reparametrization over $\ker(S) \cap \mathbb{R}^r_{\geq 0}:$**

  **Transformed Equation**
  
  $Y^T \mu = \ln \frac{E^\nu}{E^\lambda}$

- **Equivalently (Fredholm):**

  $Y^T \mu = \prod \kappa$, $\kappa \in \text{im}_+ (\Psi)$
Feasibility of nonlinear $\kappa \in \text{im}_+ (\Psi)$:

(A) If all $\nu_i, \lambda_i$ have the Isolation Property: $\text{im}_+ (\Psi) \equiv \mathbb{R}^\gamma$

(B) If all $\nu_i, \lambda_i$ have either the Isolation Property or the Bridging Property: $\kappa \in \text{im}_+ (\Psi) \iff A \kappa > 0$

- In both cases establishing multistationarity requires only linear algebra computations!

Applied these results to study the consequences of multistationarity in the NFAT – Calcineurin system
Acknowledgments

MPI Magdeburg, Systems- & Control Theory
Dietrich Flockerzi and Katharina Holstein

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Thank you for your attention!!