Robustness of Model Predictions under Extension (Supplementary Material)

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This supplementary material contains the material that did not fit into the main paper because of space constraints. A graphical illustration of the causal ordering algorithm applied to the equations of a cyclic model is provided in the first section. The second section contains more details on the signaling cascade model. The third section contains the proofs of the results in the main paper.

A CAUSAL ORDERING ALGORITHM APPLIED TO A CYCLIC MODEL

In this supplementary section we demonstrate how the causal ordering algorithm works on a set of equations for a cyclic model. The algorithm is also presented graphically. Consider the following equations for endogenous variables $X$ and exogenous random variables $U$:

\begin{align}
  f_1 & : \quad g_1(X_{v_1}, U_{w_1}) = 0, \quad (1*) \\
  f_2 & : \quad g_2(X_{v_2}, X_{v_1}, U_{w_2}) = 0, \quad (2*) \\
  f_3 & : \quad g_3(X_{v_3}, X_{v_2}, U_{w_3}) = 0, \quad (3*) \\
  f_4 & : \quad g_4(X_{v_4}, X_{v_3}, U_{w_4}) = 0, \quad (4*) \\
  f_5 & : \quad g_5(X_{v_5}, X_{v_4}, U_{w_5}) = 0. \quad (5*)
\end{align}

The associated bipartite graph in Figure 1*b consists of variable vertices $V = \{v_1, \ldots, v_5\}$ and equation vertices $F = \{f_1, \ldots, f_5\}$. There is an edge between a variable vertex and an equation vertex whenever that variable appears in the equation. The associated bipartite graph has exactly two perfect matchings:

\begin{align}
  M_1 &= \{ (v_1 - f_1), (v_2 - f_2), (v_3 - f_3), (v_4 - f_4), (v_5 - f_5) \}, \\
  M_2 &= \{ (v_1 - f_1), (v_2 - f_3), (v_3 - f_4), (v_4 - f_2), (v_5 - f_5) \}.
\end{align}

Application of the first step of the causal ordering algorithm results either in the directed graph in Figure 1*b or that in Figure 1*c depending on the choice of the perfect matching. The segmentation of vertices into strongly connected components, which takes place in the second step of the algorithm, results in the clusters $\{v_1\}$, $\{f_1, v_2, v_3, v_4, v_5\}$, $\{f_2, f_3, f_4\}$, $\{f_5\}$, and $\{v_5\}$. To construct the clusters of the causal ordering graph we add $S_i \cup M(S_i)$ to a cluster set $V$ for each $S_i$ in the segmentation. The segmentation of vertices into strongly connected components is displayed in Figures 1*d and 1*e. Notice that the segmentation in Figure 1*d is the same as that in Figure 1*e.

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corresponding equilibrium equations of the saturated model are given by:

In this supplementary section we provide more details on the signaling cascade model that is discussed in Section 4.3.

Figure 1*: Graphical illustration of the causal ordering algorithm that was described in Section 1.1. Figure 1*a shows the
bipartite graph that is associated with equations (1*) to (5*). Application of the first step of the causal ordering algorithm
results in the directed graph in Figure 1*b for perfect matching \( M_1 \) and that in Figure 1*c for perfect matching \( M_2 \). The blue and orange edges correspond to the edges in the perfect matchings \( M_1 \) and \( M_2 \), respectively. Figures 1*d and 1*e show that the segmentation into strongly connected components does not depend on the choice of the perfect matching. Exogenous vertices and edges from these vertices to clusters were added to the causal ordering graph in Figure 1*f.

### B EXAMPLE: SIGNALING CASCADE MODEL

In this supplementary section we provide more details on the signaling cascade model that is discussed in Section 4.3.

We denote the concentrations of active (phosphorylated) RAS, RAF, MEK, and ERK proteins, respectively, by \( X_s(t) \), \( X_r(t) \), \( X_m(t) \), and \( X_e(t) \), and denote by \( I(t) \) an external stimulus or perturbation. The system dynamics is modeled by differential equations:

\[
\dot{X}_s(t) = I(t) \frac{k_{Is} (T_s - X_s(t))}{(K_{Is} + (T_s - X_s(t))) \left(1 + \left(\frac{X_s(t)}{K_F}\right)^2\right)} - F_s k_{F,s} \frac{X_s(t)}{K_{F,s} + X_s(t)} \tag{6*}
\]

\[
\dot{X}_r(t) = \frac{X_s(t) k_{sr} (T_r - X_r(t))}{K_{sr} + (T_r - X_r(t))} - F_r k_{F,r} \frac{X_r(t)}{K_{F,r} + X_r(t)} \tag{7*}
\]

\[
\dot{X}_m(t) = \frac{X_r(t) k_{rm} (T_m - X_m(t))}{K_{rm} + (T_m - X_m(t))} - F_m k_{F,m} \frac{X_m(t)}{K_{F,m} + X_m(t)} \tag{8*}
\]

\[
\dot{X}_e(t) = \frac{X_m(t) k_{me} (T_e - X_e(t))}{K_{me} + (T_e - X_e(t))} - F_e k_{F,e} \frac{X_e(t)}{K_{F,e} + X_e(t)} \tag{9*}
\]

These dynamical equations correspond with a signaling pathway that goes from \( I(t) \) to \( X_s(t) \) to \( X_r(t) \) to \( X_m(t) \) to \( X_e(t) \) with negative feedback from \( X_e(t) \) on \( X_s(t) \). We will study this system in a certain saturated regime; specifically, for \( (T_e - X_e(t)) \gg K_{me} \) and \( X_e(t) \gg K_{F,e} \) the following approximation of (9*) holds:

\[
\dot{X}_e(t) = X_m(t) k_{me} - F_e k_{F,e}. \tag{10*}
\]

Thus, the saturated dynamical model that we consider consists of differential equations (6*), (7*), (8*) and (10*). The corresponding equilibrium equations of the saturated model are given by:

\[
0 = I \frac{k_{Is} (T_s - X_s)}{(K_{Is} + (T_s - X_s)) \left(1 + \left(\frac{X_s}{K_F}\right)^2\right)} - F_s k_{F,s} \frac{X_s}{K_{F,s} + X_s} \tag{11*}
\]

\[
0 = \frac{X_s k_{sr} (T_r - X_r)}{K_{sr} + (T_r - X_r)} - F_r k_{F,r} \frac{X_r}{K_{F,r} + X_r} \tag{12*}
\]

\[
0 = \frac{X_r k_{rm} (T_m - X_m)}{K_{rm} + (T_m - X_m)} - F_m k_{F,m} \frac{X_m}{K_{F,m} + X_m} \tag{13*}
\]

\[
0 = X_m k_{me} - F_e k_{F,e}. \tag{14*}
\]
where we also assume the input signal $I$ to be stationary (constant in time).

Figure 2* shows the results of applying the causal ordering procedure to the full model, and to the partial model that treats the equilibrium ERK concentration $X_e$ as unobserved and assumes it to be exogenous with respect to the observed concentrations $X_s$, $X_r$ and $X_m$ of RAS, RAF and MEK, respectively.

Figure 2*: Graphs associated with the saturated protein signaling pathway model, where indices $s, r, m, e$ correspond to concentrations of active RAS, RAF, MEK and ERK respectively, and $I$ is an exogenous input signal. Top row: submodel for RAS, RAF and MEK only. Bottom row: model extension with ERK.

C PROOFS

Theorem[1] Consider model equations $F$ containing endogenous variables $V$ with bipartite graph $B$. Suppose $F$ is extended with equations $F_+$ containing endogenous variables in $V \cup V_+$, where $V_+$ contains endogenous variables that are added by the model extension (which may include parameters or exogenous variables that appear in $F$ and become endogenous in the extended model). Let $B_{ext}$ be the bipartite graph associated with $F_{ext} = F \cup F_+$ and $V_{ext} = V \cup V_+$, and $B_+$ the bipartite graph associated with the extension $F_+$ and $V_+$, where variables in $V$ appearing in $F_+$ are treated as exogenous variables (i.e. they are not added as vertices in $B_+$). If $B$ and $B_+$ both have a perfect matching then:

1. $B_{ext}$ has a perfect matching,
2. ancestral relations in CO($B$) are also present in CO($B_{ext}$),
3. $d$-connections in MO($B$) are also present in MO($B_{ext}$).

Proof. The causal ordering graph CO($B$) is constructed from a perfect matching $M$ for the bipartite graph $B = (V, F, E)$. Let $M_+$ be a perfect matching for $B_+$. Note that $M_{ext} = M \cup M_+$ is a perfect matching for $B_{ext} = (V \cup V_+, F \cup F_+, E_{ext})$. Following the causal ordering algorithm for $B$, $M$ and $B_{ext}$, $M_{ext}$, we note that $G(B, M)$ is a subgraph of $G(B_{ext}, M_{ext})$ and hence clusters in CO($B$) are fully contained in clusters in CO($B_{ext}$). Therefore ancestral relations in CO($B$) are also present in CO($B_{ext}$).

It follows directly from the definition[?] that $\sigma$-connections in a graph remain present if the graph is extended with additional vertices and edges. The directed graphs $G(B, M)$ and $G(B_{ext}, M_{ext})$ can be augmented with exogenous variables by adding exogenous vertices to these graphs with directed edges towards the equations in which they appear. The $\sigma$-connections in the augmentation of $G(B, M)$ must also be present in the augmentation of $G(B_{ext}, M_{ext})$. By [Corollary 2.8.4, ?] and [Lemma 43, Blom et al. [2021] we have that $d$-connections in MO($B$) must also be present in MO($B_{ext}$).

Theorem[2] Let $F$, $F_+$, $F_{ext}$, $V$, $V_+$, $V_{ext}$, $B$, $B_+$, and $B_{ext}$ be as in Theorem[1] If $B$ and $B_+$ both have perfect matchings and no vertex in $V_+$ is adjacent to a vertex in $F$ in $B_{ext}$ then:

1. ancestral relations absent in CO($B$) are also absent in CO($B_{ext}$),
2. $d$-connections absent in MO($B$) are also absent in MO($B_{ext}$).
Proof. Since $\mathcal{B}$ and $\mathcal{B}_+$ both have perfect matchings the results of Theorem 1 hold. Let $\mathcal{G}(\mathcal{B}, M)$, and $\mathcal{G}(\mathcal{B}_{\text{ext}}, M_{\text{ext}})$ be as in the proof of Theorem 1. Note that in $M_{\text{ext}}$ vertices in $F_+$ are matched to vertices in $V_+$ and therefore edges between $f_+ \in F_+$ and $v \in \text{adj}_{\text{ext}}(F_+) \setminus V_+$ are oriented as $(f_+ \leftarrow v)$ in $\mathcal{G}(\mathcal{B}_{\text{ext}}, M_{\text{ext}})$. By assumption, we therefore have that vertices in $V_+$ are non-ancestors of vertices in $V \cup F$ in $\mathcal{G}(\mathcal{B}_{\text{ext}}, M_{\text{ext}})$. Since $M \subseteq M_{\text{ext}}$ we know that the same directed edges between vertices in $V$ and $F$ appear in both $\mathcal{G}(\mathcal{B}, M)$ and $\mathcal{G}(\mathcal{B}_{\text{ext}}, M_{\text{ext}})$. Notice that the subgraph of $\mathcal{G}(\mathcal{B}_{\text{ext}}, M_{\text{ext}})$ induced by the vertices $V \cup F$ coincides with $\mathcal{G}(\mathcal{B}, M)$. Hence CO($\mathcal{B}$) is the induced subgraph of CO($\mathcal{B}_{\text{ext}}$) and MO($\mathcal{B}$) is the induced subgraph of MO($\mathcal{B}_{\text{ext}}$). \qed

Lemma 1. Consider a first-order dynamical model in canonical form for endogenous variables $V$ and let $F$ be the equilibrium equations of the model. If all variables in $V$ are self-regulating then $\mathcal{B}$ has a perfect matching.

Proof. Recall that the equilibrium equation constructed from the derivative of a variable $i$ is labelled $f_i$ according to the natural labelling. When a variable in $v_i \in V$ is self-regulating then it can be matched to its equilibrium equation $f_i$. If this holds for all variables in $V$ then $\mathcal{B}$ has a perfect matching. \qed

Lemma 2. Let $\mathcal{B}$ be a bipartite graph and let $M$ and $M'$ be two distinct perfect matchings. The associated directed graphs $\mathcal{G}(\mathcal{B}, M)$ and $\mathcal{G}(\mathcal{B}, M')$ that are obtained in step 4 of the causal ordering algorithm differ only in the direction of cycles.

Proof. This follows directly from the fact that the output of the causal ordering algorithm does not depend on the choice of the perfect matching. This result is a direct consequence of Theorem 4 and Theorem 6 in Blom et al. [2021]. \qed

Theorem 3. Consider a first-order dynamical model in canonical form for endogenous variables $V$ and an extension consisting of canonical first-order differential equations for additional endogenous variables $V_+$. Let $F$ and $F_{\text{ext}} = F \cup F_+$ be the equilibrium equations of the original and extended model respectively. Let $\mathcal{B} = (V, F, E)$ be the bipartite graph associated with $F$ and $\mathcal{B}_{\text{ext}} = (V_{\text{ext}}, F_{\text{ext}}, E_{\text{ext}})$ the bipartite graph associated with $F_{\text{ext}}$. Assume that $\mathcal{B}$ and $\mathcal{B}_{\text{ext}}$ both have perfect matchings. If the model extension does not introduce a new feedback loop with the original dynamical model, then $d$-connections in $\text{MO}(\mathcal{B})$ are also present in $\text{MO}(\mathcal{B}_{\text{ext}})$.

Proof. Let $E_{\text{nat}}$ be the set of edges $(v_i - f_i)$ associated with the natural labelling of the equilibrium equations of the extended dynamical model. Note that the feedback loops in the dynamical model coincide with cycles in the directed graph $\mathcal{G}(\mathcal{B}_{\text{nat}}, M_{\text{nat}})$ that is obtained by applying step 4 of the causal ordering algorithm to the bipartite graph $\mathcal{B}_{\text{nat}} = (V_{\text{ext}}, F_{\text{ext}}, E_{\text{ext}} \cup E_{\text{nat}})$ using the perfect matching $M_{\text{nat}} = E_{\text{nat}}$.

By Theorem 1 we know that if $\mathcal{B}$ and $\mathcal{B}_+$ (the subgraph of $\mathcal{B}_{\text{ext}}$ induced by $V_+ \cup F_+$) both have perfect matchings then $d$-connections in $\text{MO}(\mathcal{B})$ must also be present in $\text{MO}(\mathcal{B}_{\text{ext}})$. Therefore, if there exists a perfect matching $M_{\text{ext}}$ for $\mathcal{B}_{\text{ext}}$ so that each $f \in F$ is $M_{\text{ext}}$-matched to a vertex $v \in V$ and each $f_+ \in F_+$ is $M_{\text{ext}}$-matched to a vertex $v_+ \in V_+$ in $\mathcal{B}_{\text{ext}}$, $d$-connections in $\text{MO}(\mathcal{B})$ are also present in $\text{MO}(\mathcal{B}_{\text{ext}})$.

We will prove the contrapositive of the theorem, so we start with the assumption that the $d$-connections in $\text{MO}(\mathcal{B})$ are not preserved in $\text{MO}(\mathcal{B}_{\text{ext}})$. In that case, there must exist a perfect matching $M_{\text{ext}}$ for $\mathcal{B}_{\text{ext}}$ so that there is an $f \in F$ that is $M_{\text{ext}}$-matched to a $v_+ \in V_+$ and a $v \in V$ that is $M_{\text{ext}}$-matched to a $f_+ \in F_+$. Note that since $\mathcal{B}_{\text{ext}}$ is a subgraph of $\mathcal{B}_{\text{nat}}$, this perfect matching $M_{\text{ext}}$ is also a perfect matching for $\mathcal{B}_{\text{nat}}$. Lemma 2 says that $\mathcal{G}(\mathcal{B}_{\text{nat}}, M_{\text{nat}})$ and $\mathcal{G}(\mathcal{B}_{\text{nat}}, M_{\text{ext}})$ only differ in the direction of cycles. We know that vertices in $V$ are only $M_{\text{nat}}$-matched to vertices in $F$, while vertices in $V_+$ are only $M_{\text{nat}}$-matched to vertices in $F_+$. Therefore, the vertices $v_+$ and $f_+$ must be on a directed cycle in both directed graphs, as well as $v$ and $f_+$. Hence the model extension $F_+$ introduced a new feedback loop that includes variables in the original model. \qed