Supplementary material

The model used, based on piecewise-linear differential equations (see Glass and Kauffmann, 1973), defines the derivative of a given variable as an expression containing a combination of synthesis and degradation parameters, each possibly under the control of one or more step-functions. A given step-function $s^+(varN, \theta_{varN})$ evaluates to 1 whenever the variable $varN$ reaches the value θ_{varN}.

For each variable in the model, *FLR1*, *PDR3*, *YRR1*, *RPN4*, *YAP1* and the predicted *FactorX*, a basal mRNA synthesis rate κ^b_{varN} and a degradation rate γ_{varN} of the corresponding protein were assumed (where $varN$ is the given variable). Additionally, we denote by $\kappa^{i,j,k,...}_{varN}$ the rate of $varN$ synthesis, under the influence of the variables i, j, k,..., where mancozeb has index 0, yap1 has index 1, yrr1 has index 2, pdr3 has index 3, rpn4 has index 4 and FactorX has index 5.

For each variable $varN$, the continuous values are discretized into a set of partitions, defined by the variable thresholds θ^i_{varN}, such that $\theta^i_{varN} < \theta^{i+1}_{varN}$. Also, taking into account the known interactions between the network elements (described in section "Revisiting the structure of the *FLR1* gene regulatory network operating in yeast cells exposed to mancozeb stress, through qualitative modeling and simulation"), we have considered for each variable the corresponding synthesis parameters $\kappa^{i,j,k,...}_{varN}$ different from zero (*e.g.*, the variable *flr1* has synthesis parameters $\kappa^{0,1}_{flr1}$, $\kappa^{0,1,3}_{flr1}$ and $\kappa^{0,1,2}_{flr1}$.

The relationships between the thresholds values θ^i_{varN} and the ratios of synthesis to degradation $\kappa^{i,j,...}_{varN}/\gamma_{varN}$ involved in the expression that control each variable (Supplementary Table) were obtained by tunning the model, taking into account the observed time courses and the effects of the relations between these parameters on the behavior of the system.

The model was validated by comparing the experimental time-course data, obtained with single and double mutants (Figure 3), with the simulation of the model, with knockout variables forced to zero (Figure 2A and 2B).

$$\dot{u}_{mancozeb} = 0$$

$$0 < \theta_{mancozeb} < max_{mancozeb}$$

$$\begin{aligned}
\dot{x}_{flr1} &= \kappa^{b}_{flr1} \\
&+ \kappa^{0,1}_{flr1}\ s^{+}(x_{yap1}, \theta^{1}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&+ \kappa^{0,1,3}_{flr1}\ s^{+}(x_{pdr3}, \theta^{1}_{pdr3})\ s^{+}(x_{yap1}, \theta^{1}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&+ \kappa^{0,1,2}_{flr1}\ s^{+}(x_{yrr1}, \theta^{2}_{yrr1})\ s^{+}(x_{yap1}, \theta^{3}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&- \gamma_{flr1}\ x_{flr1}
\end{aligned}$$

$$0 < \kappa^{b}_{flr1}/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1,3}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1}_{flr1} + \kappa^{0,1,3}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1,2}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1}_{flr1} + \kappa^{0,1,2}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1,3}_{flr1} + \kappa^{0,1,2}_{flr1})/\gamma_{flr1} < (\kappa^{b}_{flr1} + \kappa^{0,1}_{flr1} + \kappa^{0,1,3}_{flr1} + \kappa^{0,1,2}_{flr1})/\gamma_{flr1} < max_{flr1}$$

$$\begin{aligned}
\dot{x}_{pdr3} &= \kappa^{b}_{pdr3} \\
&+ \kappa^{0,1,2}_{pdr3}\ s^{+}(x_{yrr1}, \theta^{1}_{yrr1})\ s^{+}(x_{yap1}, \theta^{1}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&- \gamma_{pdr3}\ x_{pdr3}
\end{aligned}$$

$$0 < \kappa^{b}_{pdr3}/\gamma_{pdr3} < \theta^{1}_{pdr3} < (\kappa^{b}_{pdr3} + \kappa^{0,1,2}_{pdr3})/\gamma_{pdr3} < max_{pdr3}$$

$$\begin{aligned}
\dot{x}_{yrr1} &= \kappa^{b}_{yrr1} \\
&+ \kappa^{0,1}_{yrr1}\ s^{+}(x_{yap1}, \theta^{1}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&+ \kappa^{3}_{yrr1}\ s^{+}(x_{pdr3}, \theta^{1}_{pdr3}) \\
&+ \kappa^{0,1\prime}_{yrr1}\ s^{+}(x_{yap1}, \theta^{3}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&- \gamma_{yrr1}\ x_{yrr1}
\end{aligned}$$

$$0 < \kappa^{b}_{yrr1}/\gamma_{yrr1} < \theta^{1}_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{0,1}_{yrr1})/\gamma_{yrr1} < \theta^{2}_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{3}_{yrr1})/\gamma_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{0,1}_{yrr1} + \kappa^{3}_{yrr1})/\gamma_{yrr1} < \theta^{3}_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{0,1}_{yrr1})/\gamma_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{0,1}_{yrr1} + \kappa^{0,1}_{yrr1})/\gamma_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{3}_{yrr1} + \kappa^{0,1}_{yrr1})/\gamma_{yrr1} < (\kappa^{b}_{yrr1} + \kappa^{0,1}_{yrr1} + \kappa^{3}_{yrr1} + \kappa^{0,1}_{yrr1})/\gamma_{yrr1} < max_{yrr1}$$

$$\begin{aligned}
\dot{x}_{rpn4} &= \kappa^{b}_{rpn4} \\
&+ \kappa^{0,1,2}_{rpn4}\ s^{+}(x_{yrr1}, \theta^{1}_{yrr1})\ s^{+}(x_{yap1}, \theta^{1}_{yap1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&- \gamma_{rpn4}\ x_{rpn4}
\end{aligned}$$

$$0 < \kappa^{b}_{rpn4}/\gamma_{rpn4} < \theta^{1}_{rpn4} < (\kappa^{b}_{rpn4} + \kappa^{0,1,2}_{rpn4})/\gamma_{rpn4} < max_{rpn4}$$

$$\begin{aligned}
\dot{x}_{yap1} &= \kappa^{b}_{yap1} \\
&+ \kappa^{0}_{yap1}\ s^{+}(u_{mancozeb}, \theta_{mancozeb}) \\
&+ \kappa^{4}_{yap1}\ s^{+}(x_{rpn4}, \theta^{1}_{rpn4}) \\
&+ \kappa^{5}_{yap1}\ \boldsymbol{s^{+}(x_{factorX}, \theta^{1}_{factorX})} \\
&- \gamma_{yap1}\ x_{yap1}
\end{aligned}$$

$$0 < \kappa^{b}_{yap1}/\gamma_{yap1} < \theta^{1}_{yap1} < (\kappa^{b}_{yap1} + \kappa^{0}_{yap1})/\gamma_{yap1} < (\kappa^{b}_{yap1} + \kappa^{4}_{yap1})/\gamma_{yap1} < (\kappa^{b}_{yap1} + \kappa^{0}_{yap1} + \kappa^{4}_{yap1})/\gamma_{yap1} < \theta^{2}_{yap1} < (\kappa^{b}_{yap1} + \kappa^{5}_{yap1})/\gamma_{yap1} < (\kappa^{b}_{yap1} + \kappa^{0}_{yap1} + \kappa^{5}_{yap1})/\gamma_{yap1} < (\kappa^{b}_{yap1} + \kappa^{4}_{yap1} + \kappa^{5}_{yap1})/\gamma_{yap1} < \theta^{3}_{yap1} < (\kappa^{b}_{yap1} + \kappa^{0}_{yap1} + \kappa^{4}_{yap1} + \kappa^{5}_{yap1})/\gamma_{yap1} < max_{yap1}$$

$$\begin{aligned}
\boldsymbol{\dot{x}_{factorX}} &= \boldsymbol{\kappa^{b}_{factorX}} \\
&+ \boldsymbol{\kappa^{0,1}_{factorX}\ s^{+}(x_{yrr1}, \theta^{1}_{yrr1})\ s^{+}(u_{mancozeb}, \theta_{mancozeb})} \\
&- \boldsymbol{\gamma_{factorX}\ x_{factorX}}
\end{aligned}$$

$$\boldsymbol{0 < \kappa^{b}_{factorX}/\gamma_{factorX} < \theta^{1}_{factorX} < (\kappa^{b}_{factorX} + \kappa^{0,1}_{factorX})/\gamma_{factorX} < max_{factorX}}$$

Supplementary Table: Piecewise-linear differential equations and parameters inequalities for the *FLR1* gene mancozeb response network in *S. cerevisiae*. The model has five state variables corresponding to the concentrations of the transcription factors and the regulated *FLR1* gene, as well as one input variable denoting the presence of the fungicide mancozeb in the cell.