

Text S2. Detailed procedure of multi-model selection

For each of the 108 candidate structures, we initially performed three rounds of parameter estimation whilst changing the starting points for the parameter search. Note that, in the procedure of optimization for model selection, the search space for each parameter is not fixed between 0 and 10 which is used in parameter estimation of the preliminary pathway model mentioned above, but fixed between 0.0001 and 10, because we have assumed that all of the reactions in each candidate structure are not so weak and the corresponding parameters are therefore not so small. As an estimator, we used the Hook-Jeevse algorithm. The error equation (see Figure S1) that is optimized by Hook-Jeevse algorithm, ERR, was defined by the total sum of squares relating the gap between the experimental data and simulated values for all the considered proteins at each time point with combined weight coefficients as follows:

$$\begin{aligned} ERR &= \sum_{i=1}^M \sum_{j=1}^{N_i} \omega_i \left[Y_i^{(\text{th})}(t_{i_j}, X) - Y_i^{(\text{exp})}(t_{i_j}) \right]^2 \\ &= \sum_{\substack{\text{Protein} \\ \in P}} \sum_{\substack{\text{Data Point} \\ \in D}} \text{Weight} \cdot (\text{Experimental Data} - \text{Simulated Value})^2 \end{aligned} \quad (1)$$

Where measured proteins set $P = \{\text{p-p38}, \text{p-AKT}, \text{p-c-Jun}, \text{degraded BCL-XL}\}$, time points set $D = \{0, 5, 10, 30 \text{ and } 90 \text{ minutes}\}$, and all of other symbols have been described in the main text. In the model selection procedure, we do not only minimize the error function for all of the candidate structure, but also introduce some constraints in order to reduce the complexity of computation. From the observation of experimental data, we found that the p-p38 activation is sustained and p-AKT stability is quick for both of normal and MDS cases. Therefore, we evaluated each of the estimated parameters using quantitative criteria (i)-(iii) as outlined below, and selected one that satisfied most of the criteria of the three trials. If the number of satisfied criteria was identical, one that yielded the smallest estimation error was selected. The criteria for model selection were defined as follow:

(i) Estimation error

For each data point $\in D$,

$$|\text{Experimental data} - \text{Simulated value}| \leq \Delta E \quad (2)$$

where

$$\Delta E = \max_D(\text{Experimental data}) \times 0.25 \quad (3)$$

Set D is the time points set described above text. The 25% of the maximum experimental value was used as a threshold since the model describes topological regulation rather than detailed molecular mechanism, and might not result in perfect fitting.

(ii) Sustained p-p38 activation

$$DUR \geq 20(\text{minutes}) \quad (4)$$

Where *DUR* represents the duration time calculated from the time-course data generated using the model for normal and MDS cases, and defined by

$$DUR = t_e - t_s \quad (5)$$

Where t_s represents that time point at which p-p38 activity exceeds 70% of the maximum activity, and t_e represents that time point after t_s at which p-p38 activity becomes lower than 70% of the maximum activity. The detailed diagram of the definition of *DUR* is shown in Figure S2. If *DUR* values are present due to oscillatory behavior, the maximum one is used. From the experimental data for both of normal and MDS cases, the threshold was set to 20 minutes.

(iii) Quick stable for p-AKT

$$STAB \leq 10(\text{minutes}) \quad (6)$$

Where *STAB* represents the duration time from initial time point to stable time point for p-AKT from the time-course data generated using the model for normal and MDS cases, and defined by

$$STAB = t_{stab} - 0 \quad (7)$$

Where t_{stab} represents that time point at which p-AKT concentration tends to be the stable value after transient decrease due to inhibition by p-p53, and 0 is the initial time point. Considering on the effect of oscillation, the stable value is defined as the concentration value at the stable time point after which the oscillation is small, i.e. satisfying the following constraint

$$\text{Oscillation} \leq 10\% \text{ Stable Value} \quad (8)$$

The detailed diagram of the definition of $STAB$ is shown in Figure S3. From the experimental data for both of normal and MDS cases, the threshold was set to 10 minutes.

The following formula is the summary of whole model selection procedure, where all of the three constraints are incorporated into the parameter vector Π .

$$\hat{S} = \arg \min_{S \in \Pi} \left\{ \min_{X \in \Omega} \left\{ \sum_{i=1}^M \sum_{j=1}^{N_i} \omega_i \left[Y_i^{(th)}(t_{ij}, X, S) - Y_i^{(exp)}(t_{ij}) \right]^2 \right\} \right\} \quad (9)$$