論文の内容の要旨

論文題目

Extraction of simple relation in growth factor-specific multiple-input and multiple-output system in cell-fate decision by backward elimination PLS regression

細胞運命決定機構多入力多出力経路における

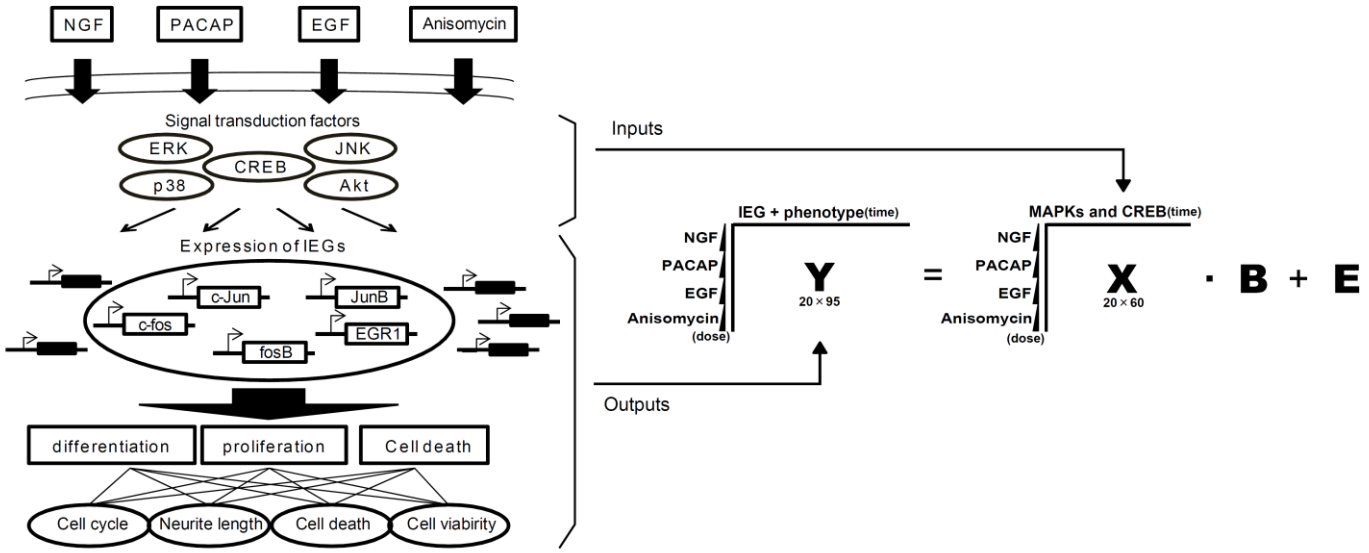
backward elimination PLS regression 法を用いた解析

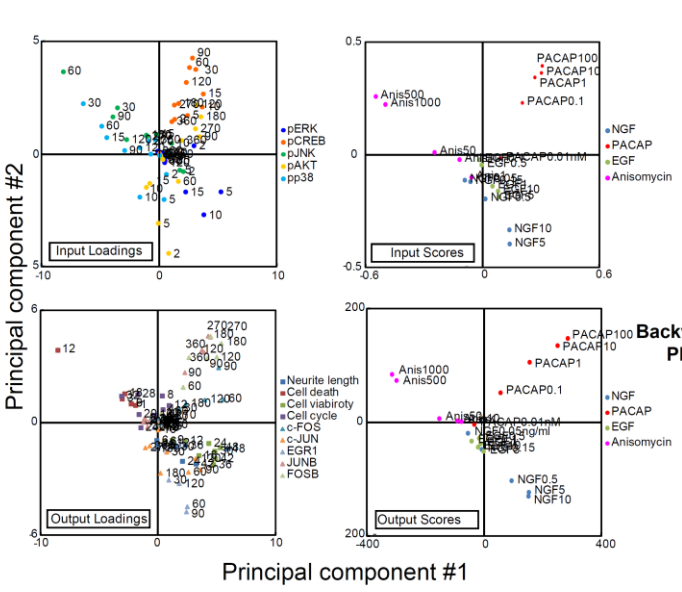
氏　名　　秋元　勇輝

Cells use common signaling molecules for the selective control of downstream gene expression and cell-fate decisions. The relationship between signaling molecules and downstream gene expression and cellular phenotypes is a multiple-input and multiple-output (MIMO) system and is difficult to understand due to its complexity. For example, it has been reported that, in PC12 cells, different types of growth factors activate MAP kinases (MAPKs) including ERK, JNK, and p38, and CREB, for selective protein expression of immediate early genes (IEGs) such as c-FOS, c-JUN, EGR1,

JUNB and FOSB, leading to cell differentiation, proliferation and cell death; however, how multiple-inputs such as MAPKs and CREB regulate multiple-outputs such as expression of the IEGs and cellular phenotypes remains unclear. To address this issue, we employed a statistical method called partial least squares (PLS) regression, which involves a reduction of the dimensionality of the inputs and outputs into latent variables and a linear regression between these latent variables. We measured 1,200 data points for MAPKs and CREB as the inputs and 1,900 data points for IEGs and cellular phenotypes as the outputs, and we constructed the PLS model from these data. The PLS model highlighted the complexity of the MIMO system and growth factor-specific input-output relationships of cell-fate decisions in PC12 cells. Furthermore, to reduce the complexity, we applied a backward elimination method to the PLS regression, in which 60 input variables were reduced to 5 variables, including the phosphorylation of ERK at 10 min, CREB at 5 min and 60 min, AKT at 5 min and JNK at 30 min. The simple PLS model with only 5 input variables demonstrated a predictive ability comparable to that of the full PLS model. The 5 input variables effectively extracted the growth factor-specific simple relationships within the MIMO system in cell-fate decisions in PC12 cells.

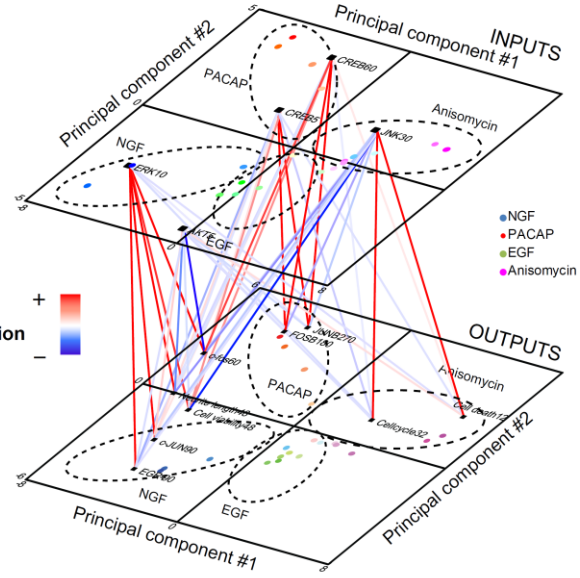
<Summary figure>





The full PLS model

Backward elimination
PLS regression



The simple PLS model