COMPUTER-BASED SIMULATION OF THE OBSERVED PHENOMENA

1. Network arquitecture

In order to develop a computer-based simulator of the observed behavior of the modified AKY signaling pathway, an Artificial Neural Network (ANN) was chosen. The choice is justified since neural networks are (given some conditions) general function approximators. In the current case the vector input includes the Zstk concentration, as well as the logical variables corresponding to the pre-treatment/treatment state and the inhibition of mTOR raptor. The output of the network is the concentration of nuclear FOXO1a. The chosen ANN network corresponds to a feedforward one (see Figure 1), with a hidden layer including 10 neurons which transfer function is tan-sigmoid; the differentiability of the transfer function is required when applying backpropagation learning of the network, which is the case here. The output layer includes one neuron (with an-sigmoid transfer function also) and the output range is fixed by the measured observed values for nuclear FOXO1a.

2. Results

The ANN was trained with the measured data and as a result of the application of the backpropagation technique the parameters (weights) of the network are the following ones:

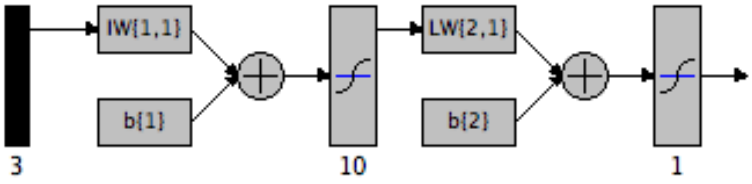

Figure 1. Feed-forward artificial neural network.

- Weight to the hidden layer from the vector input:

$$iw(1,1) = \begin{bmatrix} -0.043251 & -3.4045 & 5.2247 \\ -2.3609 & -3.7818 & -6.7951 \\ 1.7986 & -0.04413 & 4.4177 \\ 0.52742 & -0.60316 & -6.9438 \\ 2.644 & 6.242 & 1.2336 \\ 2.5534 & 5.9924 & 4.8831 \\ -9.2817 & -16.4754 & 7.8842 \\ 1.2283 & 1.613 & 9.3747 \\ -0.064732 & -3.737 & 4.5166 \\ 5.3393 & 5.979 & 9.1011 \end{bmatrix}$$

- Weight to the output layer:
  $lw = [-2.4098\ -1.9233\ 0.3275\ 1.0355\ -1.6458\ 1.8401\ 2.5193\ -2.1186\ 2.748\ 2.9692]$
- The bias to the hidden (b[1]) and the output layer (b[2]) are:

$$b[1] = \begin{bmatrix} -4.1694 \\ 12.2003 \\ -8.8737 \\ 4.0121 \\ -9.2401 \\ -8.917 \\ 6.3892 \\ -6.3462 \\ -0.83211 \\ -3.752 \end{bmatrix}$$

$$b[2] = [0.48205]$$

When applying the network to the given input data (*i.e.* when performing a simulation, in the current case using the Neural Networks Toolbox of Matlab) it results in what is displayed in Figure 2 and Figure 3. In each case the simulator basically reproduces the measured nuclear FOXO1a concentration.

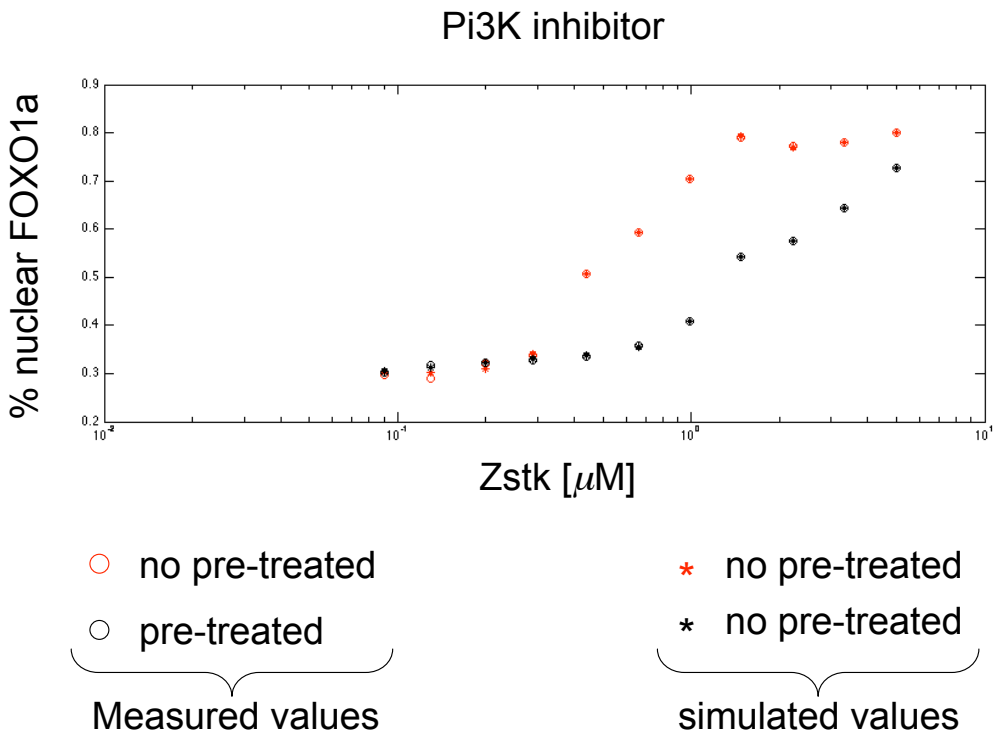

FIGURE 2. Behavior of the AKT signaling pathway when no mTOR inhibitor is considered.

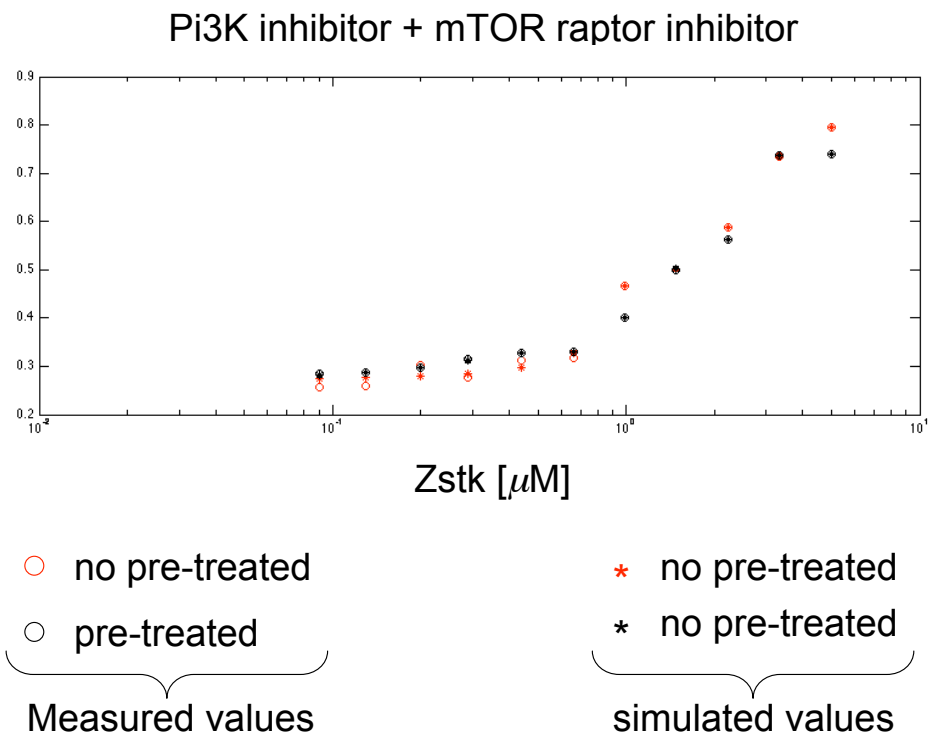

FIGURE 3. Behavior of the AKT signaling pathway when considering mTOR inhibition.