Modelling and experimental validation of signalling pathways with relevance to homologous mammalian systems

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Budding yeast *Saccharomyces cervisiae* exists in either haploid or diploid states that possess one or two copies of each chromosome, respectively. Haploid cells are of two mating types MAT**a** or MATα. Two haploid cells can mate, fuse, and form a single diploid cell of MAT**a**/α type. Haploids use special proteins, called pheromones, for communication in order to mate efficiently. Each haploid type produces a mating type-specific pheromone and is also able to sense the pheromone of the opposite mating type. The type of receptor that recognizes the pheromone in yeast belongs to a well-described family of so called GPCRs (G protein-coupled receptors). GPCRs are present in mammalian cells enabling the sense of smell, the immune system response, etc. In this work, we present a mechanism for tuning the receptor sensitivity. The receptor activity is regulated in a feedback mechanism by the Sst2 protein. It has been shown that mutants lacking Sst2 exhibit hypersensitivity to pheromone, see Yi et al. (2003). We introduced a simple mathematical model of the corresponding mechanism in the yeast pheromone pathway and we show that it is possible to dynamically tune the sensor sensitivity by varying the feedback strength corresponding to Sst2 protein expression levels.

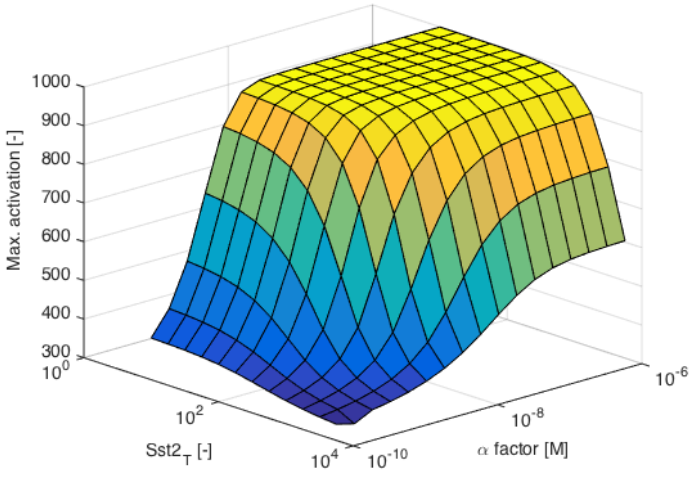

Figure 1: Simulation results show that the maximum receptor activation increases with decreasing levels of Sst2 and leads to ”hepersensitive” receptor responses at the low levels. In contrary, increasing the Sst2 levels will decrease the receptor sensitivity and increase the level of pheromone (α factor) necessary for the receptor activation.

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References

Yi, T.M., Kitano, H., and Simon, M.I., 2003. A quantitative characterization of the yeast heterotrimeric G protein cycle. *Proceedings, The National Academy of Sciences of the USA,* Vol. 100, pp 10764–10769.