# Supplementary Material S4:
# Graphical Cell Differentiation Model

In our model of human epidermis (Grabe and Neuber, 2005) we distinguish proliferating (stem cells, TA cells) and differentiating (spinosum cells, granulosum cells) keratinocytes. The graphical cell differentiation model depicted in figure 1 shows how sub-cellular model behaviour can be linked to cell states using EPISIM Modeller. Based on their age, TA cells differentiate to early spinosum cells (Fig. 4 (1a)). Early spinosum cells in turn become late spinosum cells depending on the epidermal Ca2+ gradient (Fig. 4 (1b)). Spinosum cells finally differentiate to granulosum cells according to the lipids concentration in the outermost layers of the tissue (Fig. 4 (1c)). TA cell differentiation to early spinosum cells corresponds to a cell state transition from proliferation to differentiation. Tyson's cell cycle model can operate in three modes. The model's parameter k6 (named sbml_k6 after im-port) can be used to change between these modes. By setting sbml_k6 = 2 (Fig. 4 (2)) the model behaviour changes from oscillation to steady state. Hence, proliferation stops as cell division is triggered by high active MPF concentrations. Threshold MT is never reached in the cell cycle model's steady state mode.

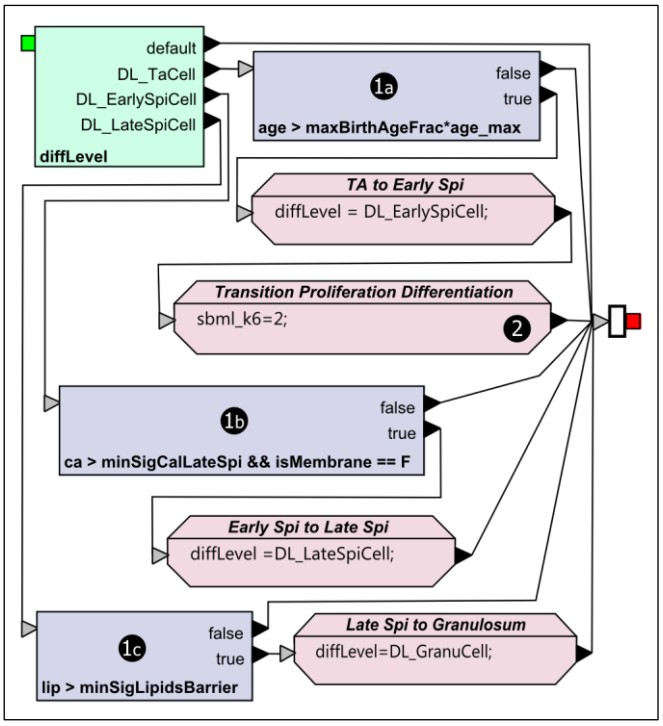


**Fig. 1.** Linking of sub-cellular model behaviour to a cell's differentiation stage. TA cells differentiate to early spinosum cells after a number of cell divisions (1a). Early spinosum cells become late spinosum cells depending on the epidermal Ca2+ gradient. Differentiation from a late spinosum cell to a granulosum cell is coupled to the lipid production in the outermost layers of the in silico tissue (1c). The cell cycle model behaviour is linked to a cell's differentiation stage (2). By setting sbml_k6=2 the behaviour switches from oscillation to steady state.

## References

Grabe,N. and Neuber,K. (2005) A multicellular systems biology model predicts epidermal morphology, kinetics and Ca2+ flow. *Bioinformatics (Oxford, England)*, **21**, 3541–7.