

S100A4 and its Role in Metastasis - Computational Integration of Data on Biological Networks

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Supplementary Material

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1 Text ESI 1

S100A4 in Cancer

In order to build a reliable network scheme (Figure 1) representing the interactions between S100A4 and its interacting partners as well as the principal pathological processes influenced in the system, manually-curated information was searched in the literature and retrieved from the following references: articles¹⁻³².

2 Text ESI 2

Computational Performance of the Algorithm.

Performance and Parallelization on Multiple CPU Cores. We evaluated the performance of our program on a test network containing 8 nodes and 16 edges. Five of the parameters accounting for basal expression were combinatorially varied over a range of $10^{-3} - 10^{-1}$ in 1.5-fold variation steps. Sampling the so defined parameter space required the simulation of 124,416 different conditions. The computation time required for the simulation of steady-state activities and sensitivity analysis was measured on different architectures and using a variable number of CPU cores (see Figure ESI 5). By increasing the number of cores, the required computing time decreased from about 40 minutes to less than a minute. This demonstrates effective scalability of the model and a drastic reduction of the processing time due to parallelization. We note that the system has been tested up to 16 cores, further increasing the number of cores would not improve the efficiency in this test case because of the small size of the simulated system. It is however clear that more complex systems would benefit substantially from more extensive parallelization, and that very demanding simulations would become tractable upon using a much larger number of cores.

Performance and Network Size. In order to correlate the scaling of our method to the network size, we compared the computing time for simulating and analysing an extended network (see Figure ESI 1 of the companion article³³) where 9 additional nodes and 13 additional reactions were added to the network represented in Figure 1 (corresponding to an increase of 60% and 42% for nodes and reactions, respectively). Five of the parameters accounting for basal expression were combinatorially varied over a range of $10^{-3} - 10^{-1}$ in 2-fold variation steps. Despite the increase in the number of nodes and reactions, the simulations of the larger network did not take significantly longer to converge (Table ESI 5).

3 Text ESI 3

Principal Component Analysis.

Principal component analysis (PCA) was applied to the dataset of globally varying basal activity values and compared to the simulation outcome presented in section "Determination of Parameter Space Regions of Interest". The results of this analysis were very similar to those obtain with a constant value of the basal activity (Figure 4).

In Figure 4, it is shown that at the steady-state activity level, increasing S100A4 causes grouping of *CellDiss* with the variables *OPN* and *uPA_uPAR* in a close-distance cluster. In

addition, this also displaces *S100A4* with a compact group of variables (*EGFR*, *NFKB* and cytoskeletal proteins, *i.e.*, *ECadh*, *Myo9*, *BCat*) through *CapGrowth* towards *CellDiss* proportionally to *S100A4*, bringing the variables *CapGrowth* and *S100A4* closest together at intermediate *S100A4* activity. This analysis separates the network in two subgroups (*S100A4* with *EGFR*, *NFKB* and cytoskeletal proteins, similarly to the steady-state representation; and *CellDiss* with *uPA_uPAR*) whose distances decrease with increasing *S100A4* activity until the two groups merge in a single cluster isolated from *EphrA1* and *ECadh*. (See Figure 4).

When PCA was applied to the dataset of globally varying basal activity values however (section "Global Parameter Variation: Basal Activity (β)"), the analysis of sensitivity values delineates two distinct clusters at low *S100A4* levels composed of *CellDiss* and *CapGrowth* together with *OPN*, *Plasmin uPA_uPAR* separated from *S100A4* with *EGFR* and *NFKB* which merge into a single compact group with increasing *S100A4*. This group does not include the variables *cytoskeletal proteins* and *EphrA1*. (See Figure ESI 2).

4 Supplementary Figures

$$Act(X \rightarrow Y; \alpha, \gamma, \eta) = \alpha \frac{X^\eta}{X^\eta + \gamma^\eta} \quad (1)$$

$$Inh(X \dashv Y; \alpha, \gamma, \eta) = \alpha \frac{\gamma^\eta}{X^\eta + \gamma^\eta} \quad (2)$$

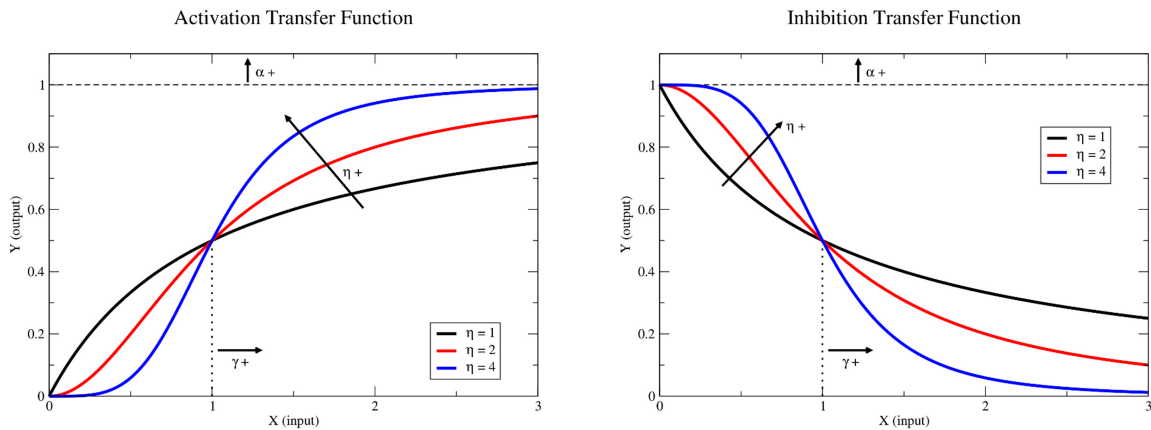


Figure ESI 1: Hill-type regulatory functions. Transfer functions connecting two components of an interaction network (X and Y , considered as input and output of the signal transmission link, respectively, *i.e.*, node X influences node Y). The left part represents activation and the right part inhibition. Hill-type transfer functions connect input to output nodes. The parameters α , γ and η enable the modulation of the function in order to make the output responsive at different ranges and in different modes. The black arrows in the graphical representations indicate the curve shift by the increase of one of the parameters.

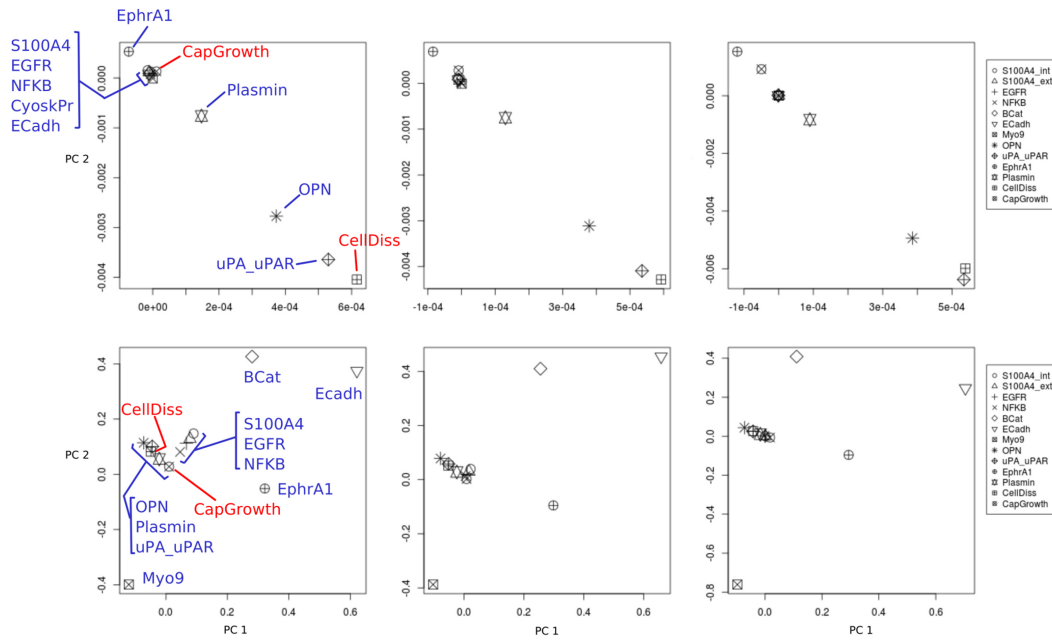


Figure ESI 2: Loading plots of MMPs and TIMPs variation combined with global β variation. Low (left), medium (middle), high (right) S100A4; upper row: steady-state, lower row: sensitivity.

Computational Approach

Automated workflow applicable to activation/inhibition networks

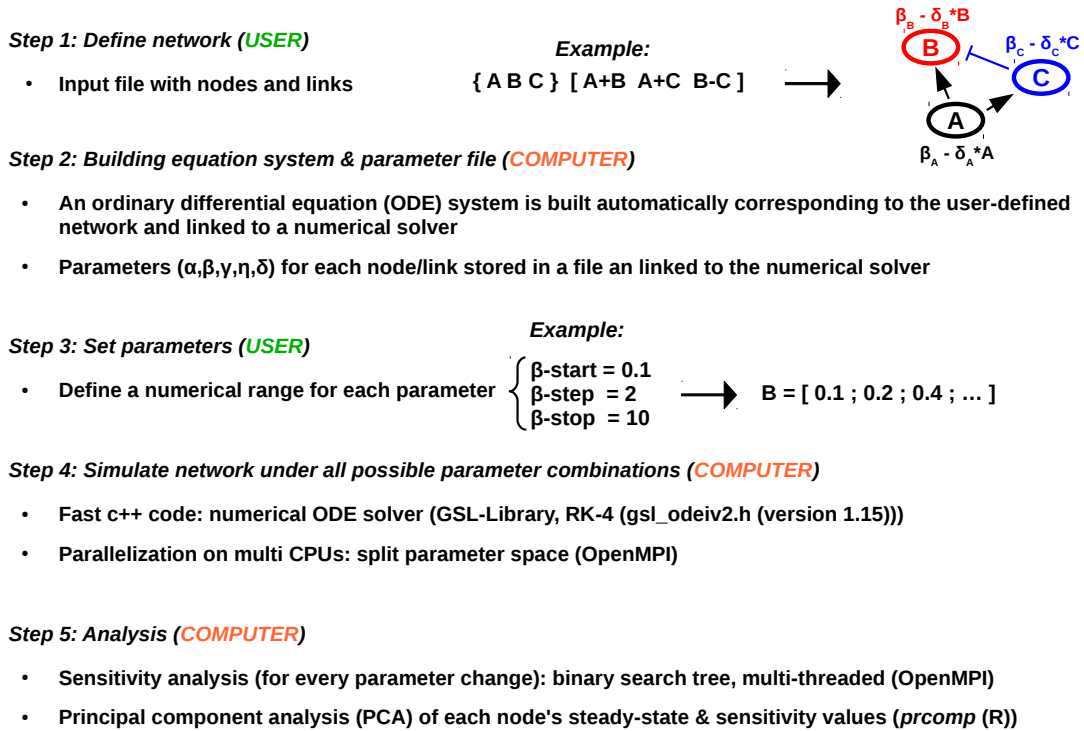


Figure ESI 3: The computational workflow.

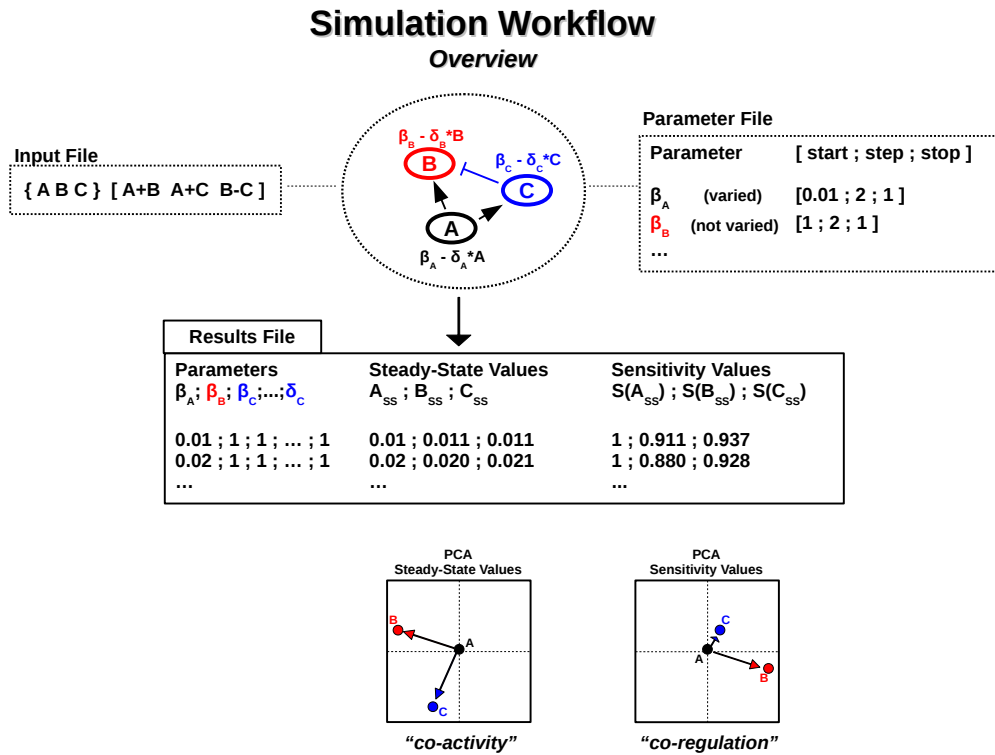


Figure ESI 4: Simulation workflow. The upper part of the scheme represents the information needed to run a simulation on an example network (represented schematically in the middle). The lower part illustrates the outcome of the procedure: user-defined conditions (parameter list corresponding to the screened conditions) are processed to yield steady-state and sensitivity values resulting from the simulation procedure. In addition, PCA plots summarize the simulation results highlighting components of the network that are co-activated (steady-state values, low panel left) or co-regulated (sensitivity values, low panel right).

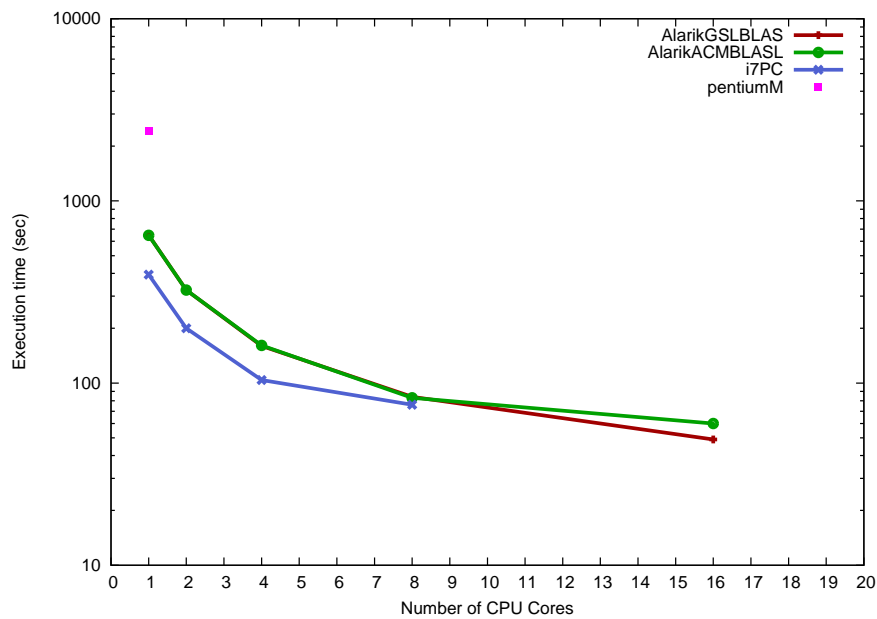


Figure ESI 5: Computational performance and model scalability. The execution time of the same simulation set is compared using different computational architectures and a different number of CPU cores. Two high-performance BLAS (Basic Linear Algebra Subprograms) libraries were compared on a supercomputing unit of the Alarik cluster (LUNARC, Lund University) containing two 64-bit, 8-core AMD6220 (3.0 GHz) CPUs: the CBLAS Library (AlarikGSLBLAS) and the AMD Core Math Library (AlarikACMBLASL). In addition, the performance of two personal computer processors were also tested: 64-bit Intel Core i7 (i7PC) and 32-bit Intel Core Pentium M (pentiumM).

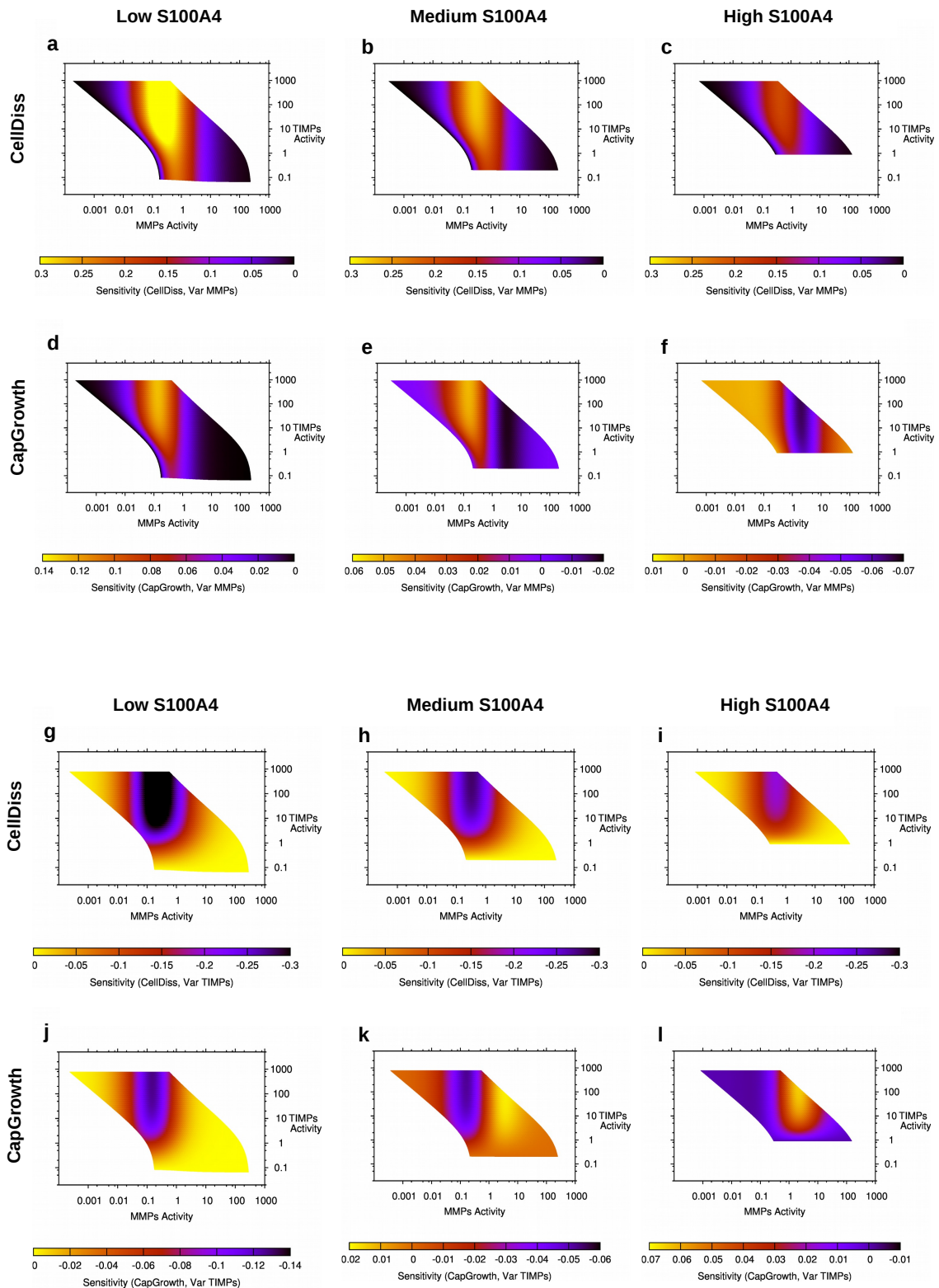


Figure ESI 6: Sensitivity heat maps. (a)-(f): sensitivity to variable MMPs activity. (g)-(l): sensitivity to variable TIMPs activity. (a), (b), (c) and (g), (h), (i) represent the sensitivity of cell dissociation while (d), (e), (f) and (j), (k), (l) represent the sensitivity of capillary growth by increasing S100A4 activity.

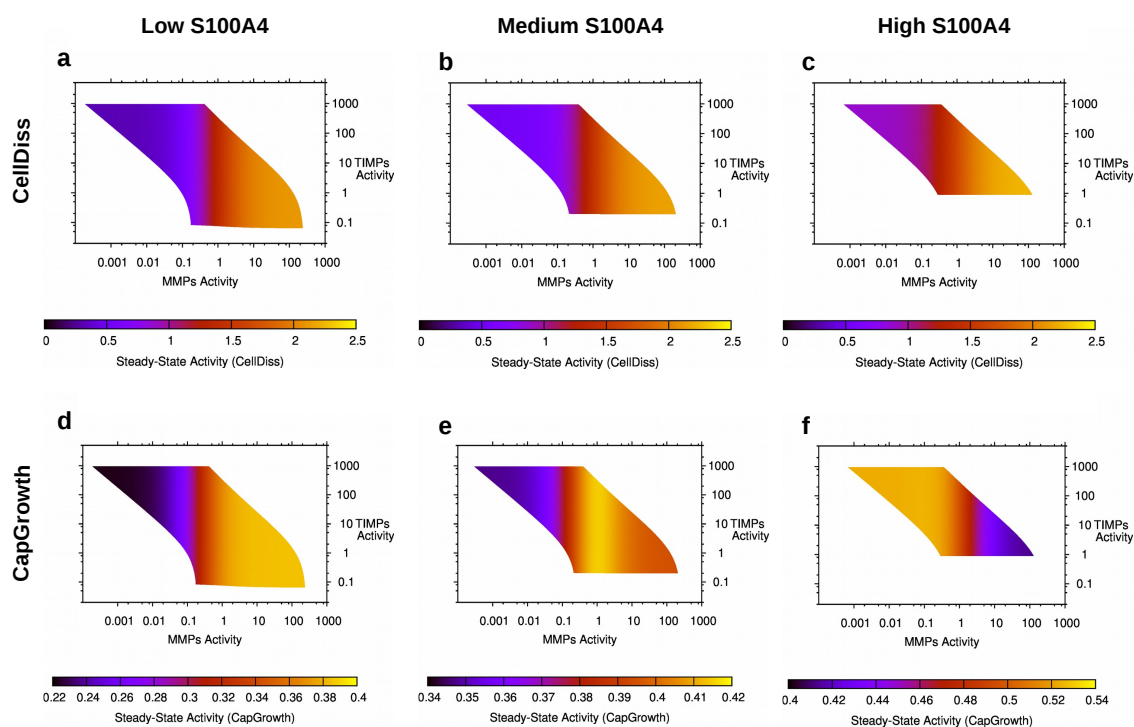


Figure ESI 7: Activity heat maps. Steady-state activities of cell dissociation (a,b, and c) and capillary growth (d,e, and f) are represented by increasing S100A4 activity.

5 Supplementary Tables

Table ESI 1: Average execution times (n=3) for simulation and sensitivity analysis of networks of different sizes.

Number of CPU cores	Network Figure 1 (sec)	Extended Network ³³ (sec)
1	89.3	96.7
2	52.7	55.0
4	33.3	36.3

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