S1 The shuffling parameter β and ensemble size

In addition to the extensions of the artificially reduced draft networks of *E. coli* with $\beta = 0.04$, we have repeated the calculations with exactly the same networks using different values of β. As stated in the main article, this parameter controls the degree of diversity in the resulting extensions. A value of $\beta = \infty$ leads to only one solution that is completely determined by the scores that are assigned to the reactions. The only degree of randomness may result from different reactions with identical scores. The quality of this solution depends only on the quality of the score.
The qualities are depicted in Fig 1 for different values of β. One can clearly see that, as a tendency, the quality of

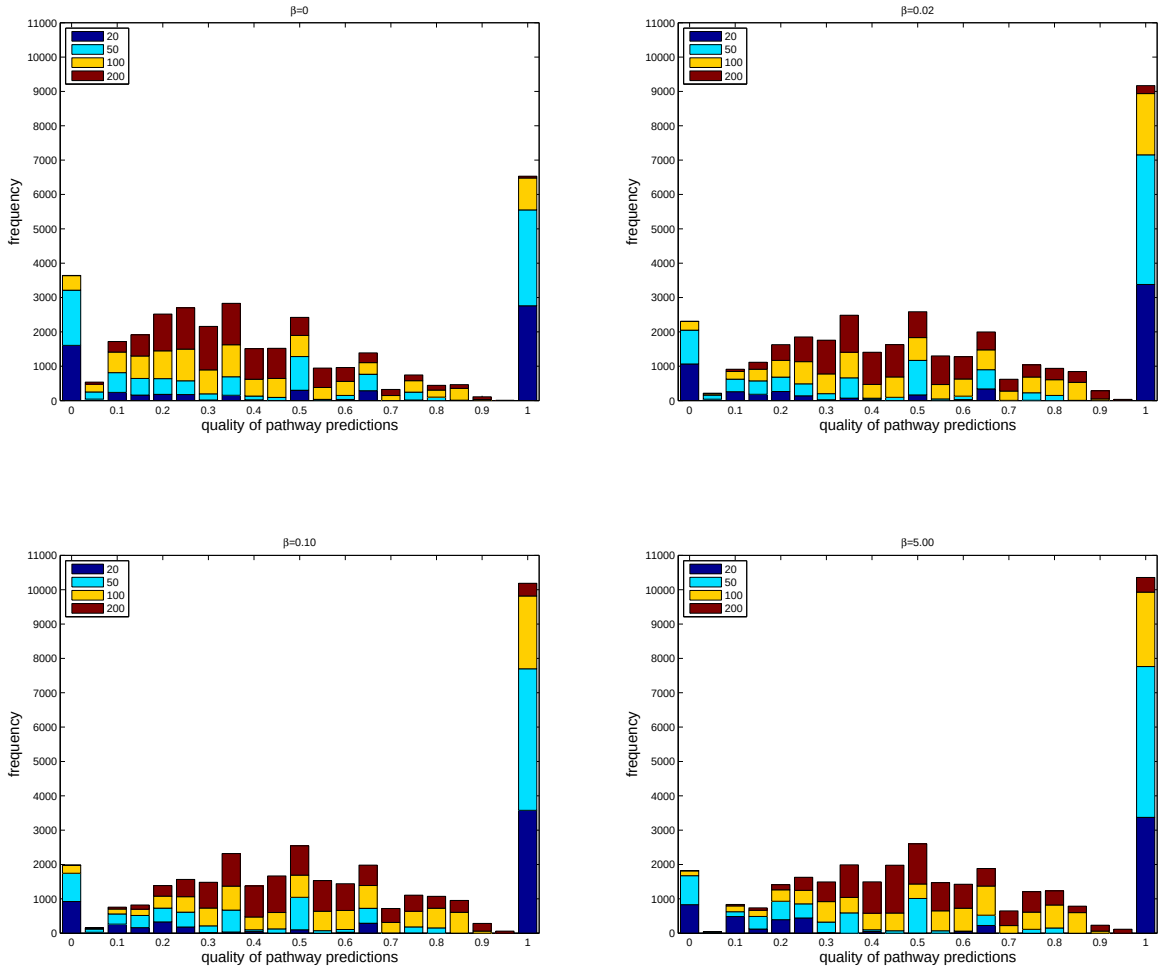

Figure 1: Histogram of the quality of predicted extensions for different values of β. The quality is measured by the fraction of correctly predicted reactions in a calculated extension. The bars are stacked indicating the contributions of pathway predictions obtained for different numbers of removed reactions.

predictions is getting better with increasing β. But while the quality is increasing, the diversity (simply measured by the average number of different reactions found in all extensions) is decreasing from 145.4 for $\beta = 0$ to 16.3 for $\beta = 5.0$. Thus, the choice of the parameter β reflects the trade-off between quality and diversity, while the quality is not strictly increasing with increasing β.

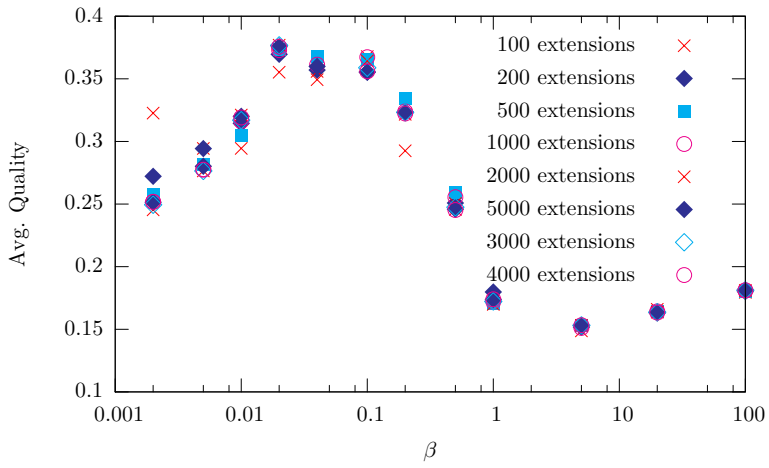

Figure 2: Quality of extensions for one *E. coli* draft network with different β and different number of extensions. The maximum for the quality is around the chosen $\beta = 0.04$ used for our thorough studies.

Since our algorithm to find extensions is of a stochastic nature, it is important to know whether the results are critically influenced by the numbers of extensions that were calculated. For this, we have taken one particular draft network of *E. coli* and created 5000 extensions for different values of β. We have analyzed how the quality and the diversity for this particular example depends on the value β and on the numbers of extensions included in our analysis. The dependence of the quality is shown in Fig. 2. It can be seen that a maximal quality is reached for values close to the value of $\beta = 0.04$ which was chosen for the analyses in the main text. The dependence of the diversity on the number of included results is depicted in Fig. 3. Expectedly, the diversity within the solution increases with larger ensembles. However, for very large ensembles the increase becomes very slow. Fluctuations in the average prediction qualities are only observed for the smallest ensemble sizes of 100 and 200 extensions. This indicates that for ensemble sizes of 10000, which were used for the Chlamydomonas network, statistical effects should be negligible.

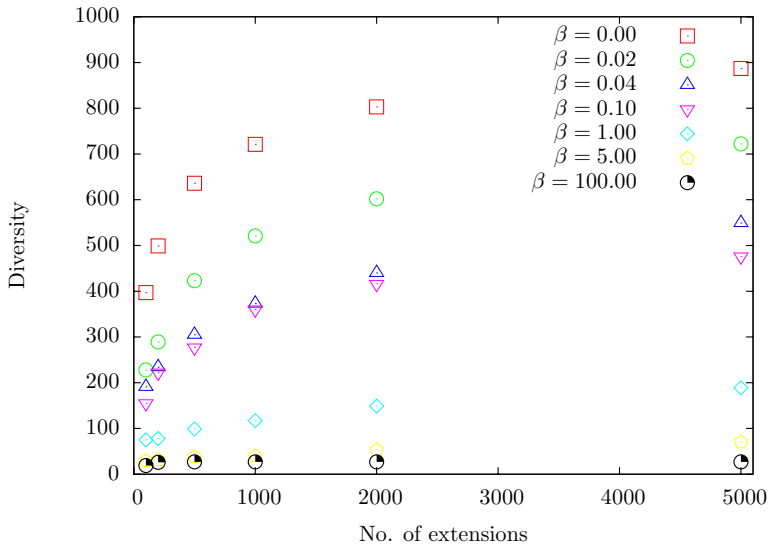

Figure 3: Effect of the ensemble size on the diversity of the extensions