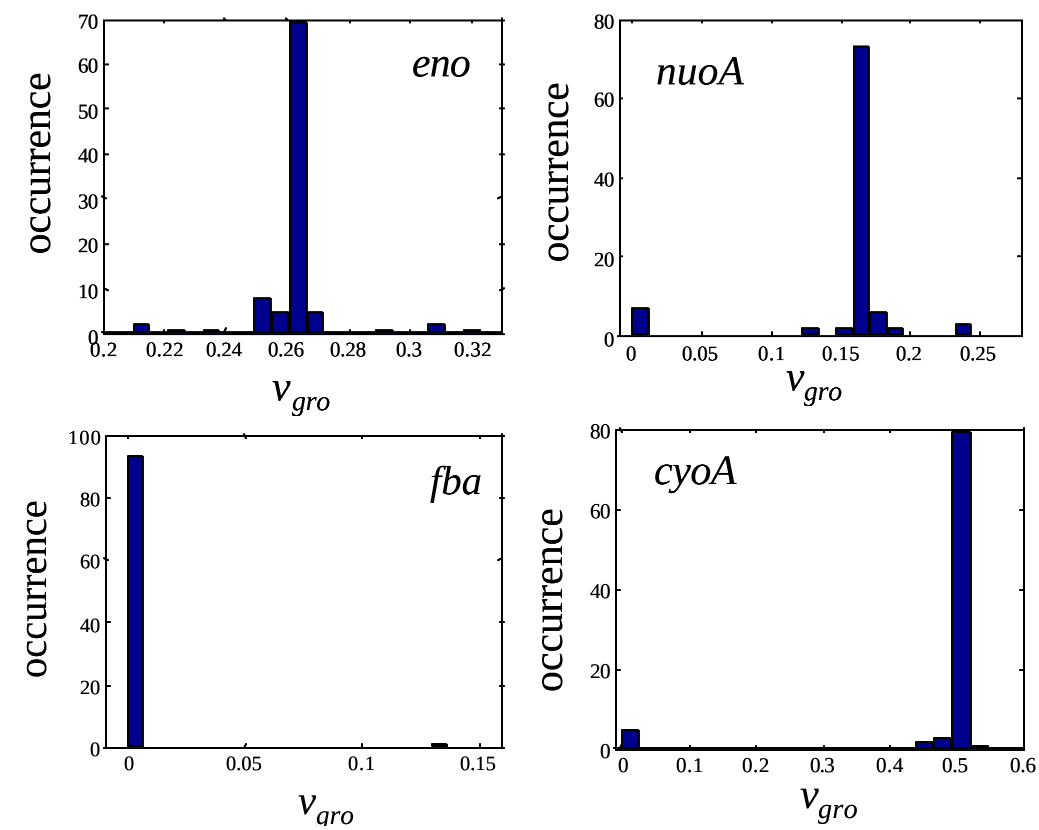
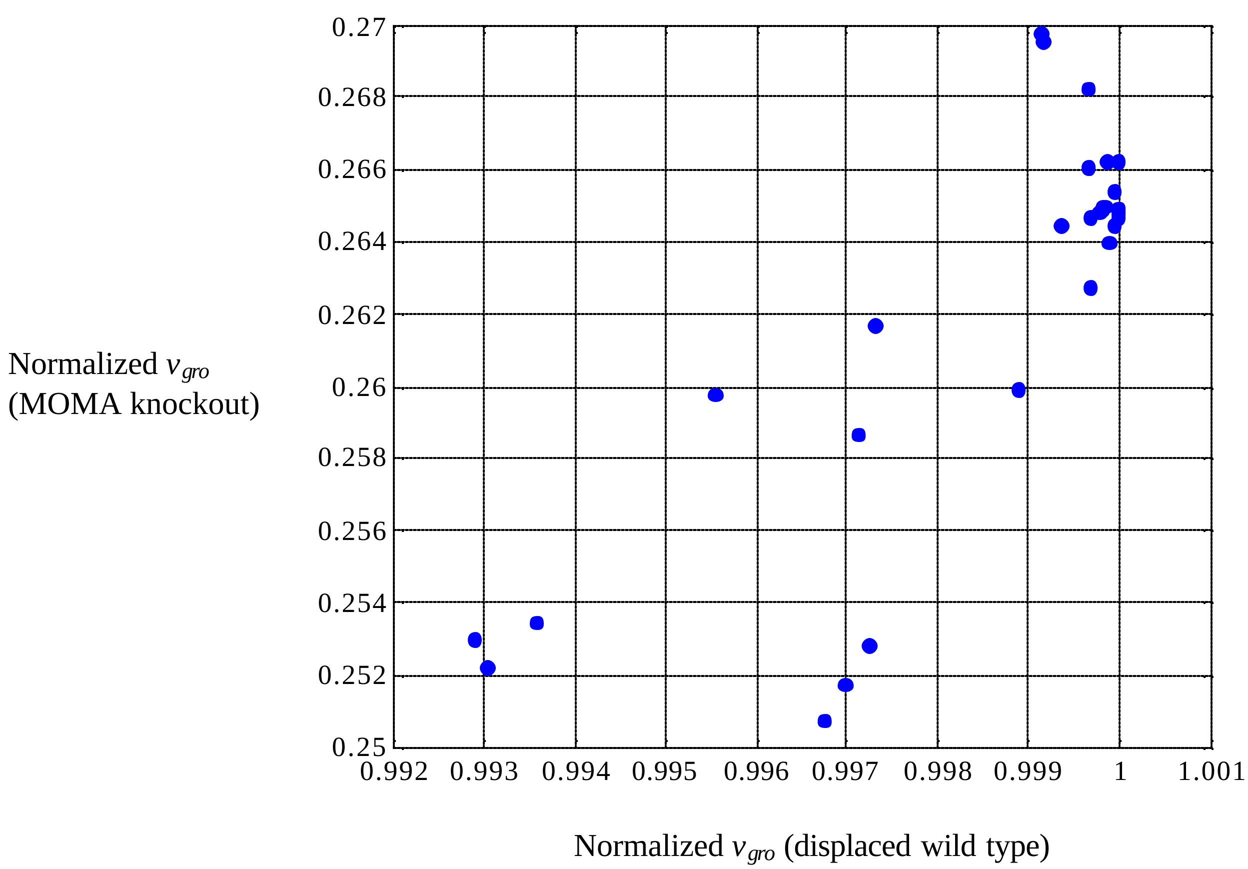
Robustness of MOMA with respect to displacements around the wild type

Here we address the question of how the flux coordinates and the biomass production rate of the knockout vary when the wild type point is displaced by a vector $d\mathbf{v}^{WT}$ from the optimal point $\mathbf{v}^{WT}$ found by the simplex algorithm in FBA. For mutant j, we calculated the MOMA projection of the point $\mathbf{v}^{WT} + d\mathbf{v}^{WT}$ onto F j for a set of possible displacements $d\mathbf{v}^{WT}$, and compared it to the projection $\mathbf{u}^j$ of $\mathbf{v}^{WT}$. The displacement can occur either along an edge parallel to the objective function, leaving it at the maximal value (point a' in Fig. 1C), or along an edge that decreases the objective function (point a'' in Fig. 1C). The sampling around $\mathbf{v}^{WT}$ was performed by limiting to 90% each of the fluxes and recalculating the optimum with simplex. We then identified those displaced points $\mathbf{v}^{WT} + d\mathbf{v}^{WT}$ which decrease the objective function by 5% or less of the original optimum. This is because we are only interested in small deviations from the optimum (or vanishing ones, i.e. alternative optima). The robustness of the MOMA solution was hence evaluated by analyzing the distribution of fluctuations in the growth rate for the projections obtained from all the displaced points that satisfy the above criteria. The following four pictures show the distribution of growth rate (normalized to the wild type one) for four different mutants calculated with MOMA. In each histogram we binned all the growth rates obtained with MOMA upon displacing the wild type point along a different direction in flux space. Therefore these histograms contain information about the sensitivity of MOMA to small displacements of the point being projected. It can be seen that in most cases the displacement is quite small.



While the wild type FBA prediction of the optimum always yields a single value for the maximal biomass production rate, it does not guarantee the uniqueness of the optimal point in the fluxes space. The presence of multiple optima, detectable by looking at the shadow prices of non-basic variables, can in principle affect the MOMA solution, and alter its prediction of the fluxes and of the growth rate (Fig. 1C).

The robustness analysis presented here can help detect such effects. In the following figure, we represent in a different way the same data shown in the above histogram for eno. The x axis here represents the growth rate of the displaced wild type point (normalized by the wild type growth). The y axes represents the growth rates for the corresponding MOMA projections. Here it can be seen that multiple optima do not affect significantly the outcome of MOMA, i.e. large differences in the MOMA solution arise only when the growth rate of the displaced point deviates significantly from 1.



In the following figure (for gene cyoA), however, the effect of multiple optima is detectable, as represented by the points in the lower right part of the figure. These points were obtained by projecting displaced points that have the same growth rate as the wild type; the corresponding MOMA results, on the other hand, differ significantly from the projection of the undisplaced wild type.