Is it possible to understand a simple biological system in a quantitative manner?

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Understanding in a quantitative manner a living system is a holy grail goal of Systems Biology. In the past years we have seen the publication of whole cell models and the simulation of M. genitalium growth. Although this models are a tout de force in the filed they still are short of being successful in predicting in a quantitative manner the effect of perturbations in the system. This is for several reasons among which is the lack of quantitative knowledge for some reactions and the fact that we don't really know the function of many gene products. We have developed a whole cell model of M. pneumonia using all the quantitative data we have collected over the years and we see that despite having detailed numbers for concentrations of metabolites, RNA, proteins and half/lifes of proteins and RNA, we are far from predicting the effect of Kos and overexpressions. Thus we have decided to go step by step and model in detail different processes prior to their integration into a whole cell model. Here we described the first systematic analysis of the DNA-interactome in a minimal bacterium. We have determined by DNA affinity chromatography and intact chromatin isolation all potential DNA binding proteins. For all of them we have determined their DNA binding sequences by ChIP-seq or biochemical assays, as well as their functionality by overexpression, or in some cases knocking them out by transposon insertion. We found new DNA binding proteins with moonlighting properties like proteases and metabolic enzymes. Interestingly, more than 80%% of the proteins overexpressed we found no transcriptome or growth phenotype, indicative of the robustness of the system, despite its simplicity. Interestingly, we find that the main regulation in the cell happens at the level of metabolic control, suggesting a hidden non-TF factor layer of regulation in bacteria.