# TOWARDS BIOTECHNOLOGY 2.0: SYNTHETIC BIOLOGY OF BIOACTIVE MOLECULES

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We explore the possibilities of synthetic biology in *Streptomyces* bacteria, targetting their most important ability: producing a large variety of secondary metabolites, diverse in both chemical structure and bioactivity. The biosynthesis gene clusters are modular, thus an ideal system to apply synthetic biology and engineer new and diverse bioactive molecules (1, 2). As a first step towards re-engineering antibiotic biosynthesis, we studied the regulatory circuitry controlling antibiotic production in *Streptomyces coelicolor* A3(2), using experimentation and computational modelling. In this species, antibiotic production is regulated by γ-butyrolactones. We could show that the two major players of the butyrolactone signalling system, γ-butyrolactone synthase and the γ-butyrolactone receptor, exert a concerted regulation (3) set up to create a bistable switch. We also show how antibiotic biosynthesis is additionally regulated at the translational level by small non-coding RNAs. Now that we have a detailed understanding of the circuitry regulating antibiotic biosynthesis, we can start to re-engineer bacterial genomes to awaken cryptic antibiotic clusters, 20–50 of which are typically found in each newly sequenced genome (4). For this purpose, we are exploiting computational constraint-based modelling of bacterial metabolism to automatically identify suitable overproduction hosts and pinpoint biosynthetic bottlenecks that will be target for further cellular engineering (Figure) (5). We have also developed a high-throughput, *in vivo* reporter system to aid in creating a library of orthogonal promoters.

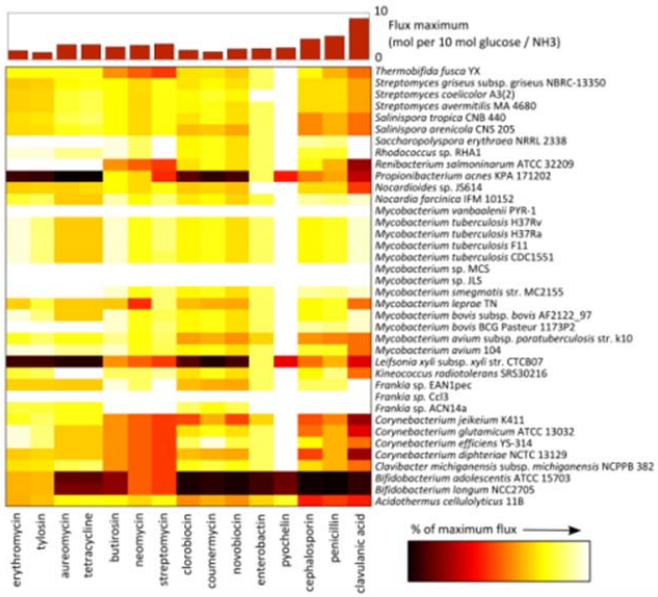


**Figure Theoretical maximum fluxes of secondary metabolite production (based on ref. 5)**

## References.

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