SYSTEMS BIOLOGY IN BIOTECH

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National Institute of Biology

- **Research departments**
  - Department of Biotechnology and Systems Biology
  - Department of Genetic Toxicology and Cancer Biology
  - Department of Organisms and Ecosystems Research
  - Marine Biology Station Piran
- **Management and administration**
  - Corporate Services
  - Technology Transfer Office

Department of Biotechnology and Systems Biology

Fields of research and applications:

- Microbiology
- GMO
- Systems biology
- Bacteriology and metrology

Basic and applicative research
Contract research for industry

Advanced molecular biology techniques

Quantitative real-time PCR, digital PCR, LAMP, NGS, barcoding…

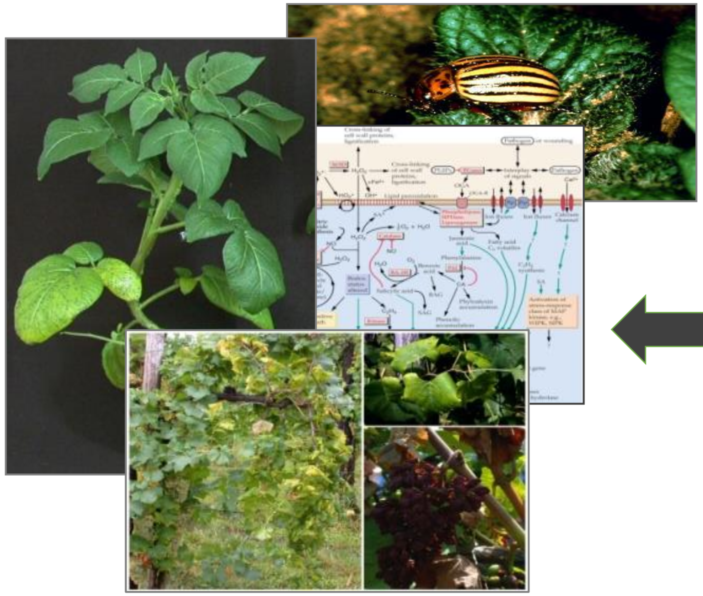
Statistical modeling and data integration

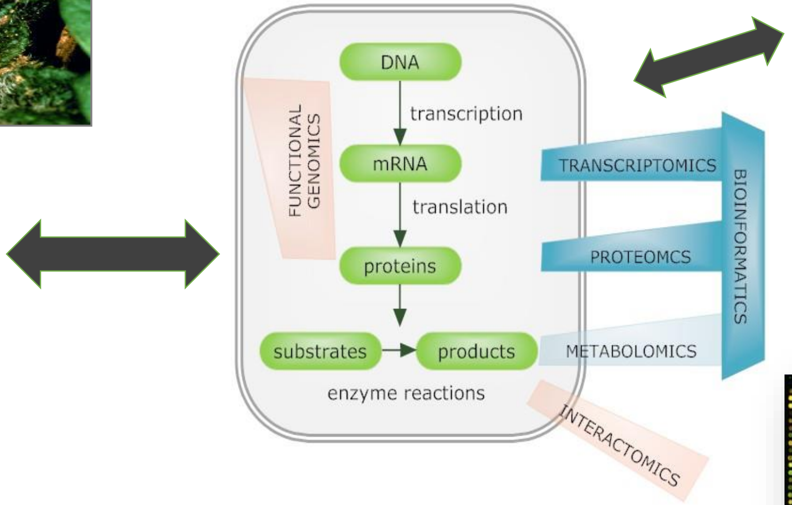
Workshops and trainings

Organization of proficiency tests

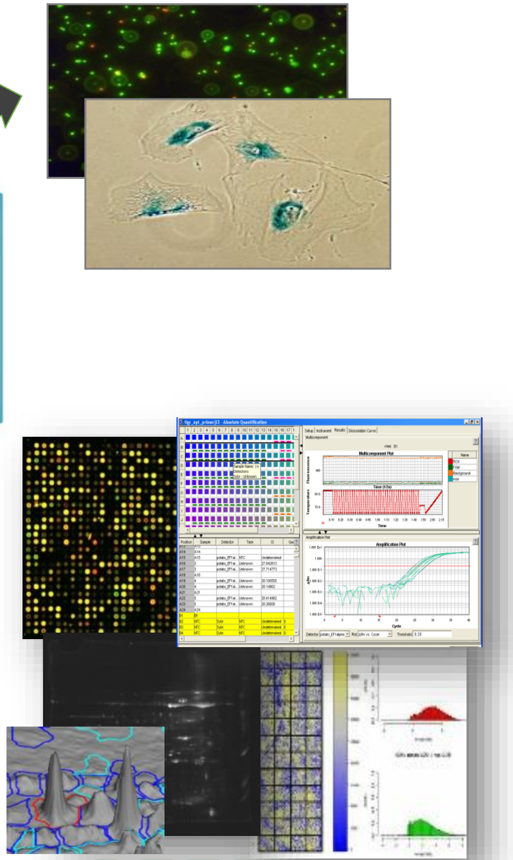
Omics approaches

Plant- pathogen/pest interactions

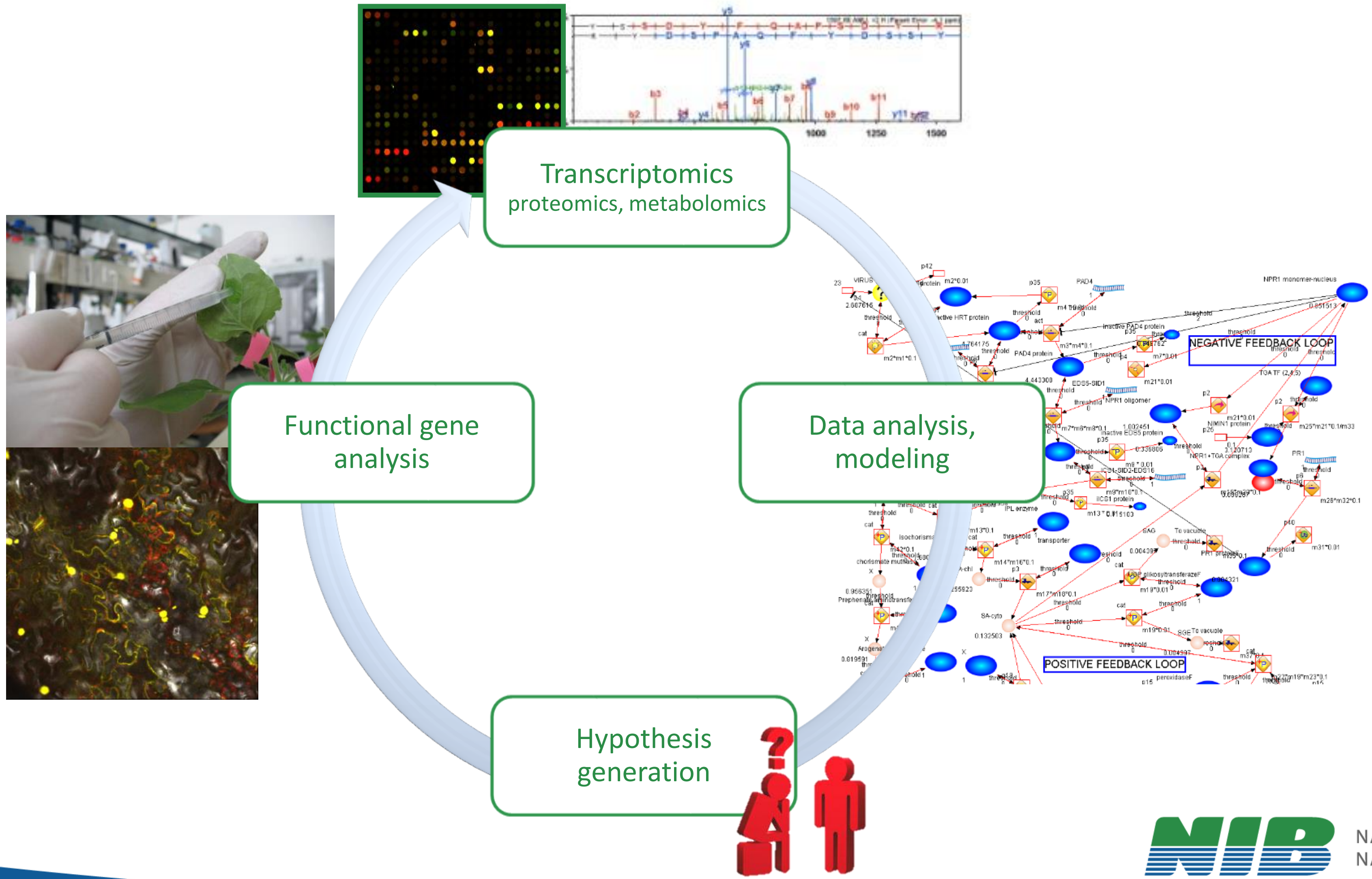




Projects with pharmaceutical industry:
Improved drug production
Development of cancer therapies

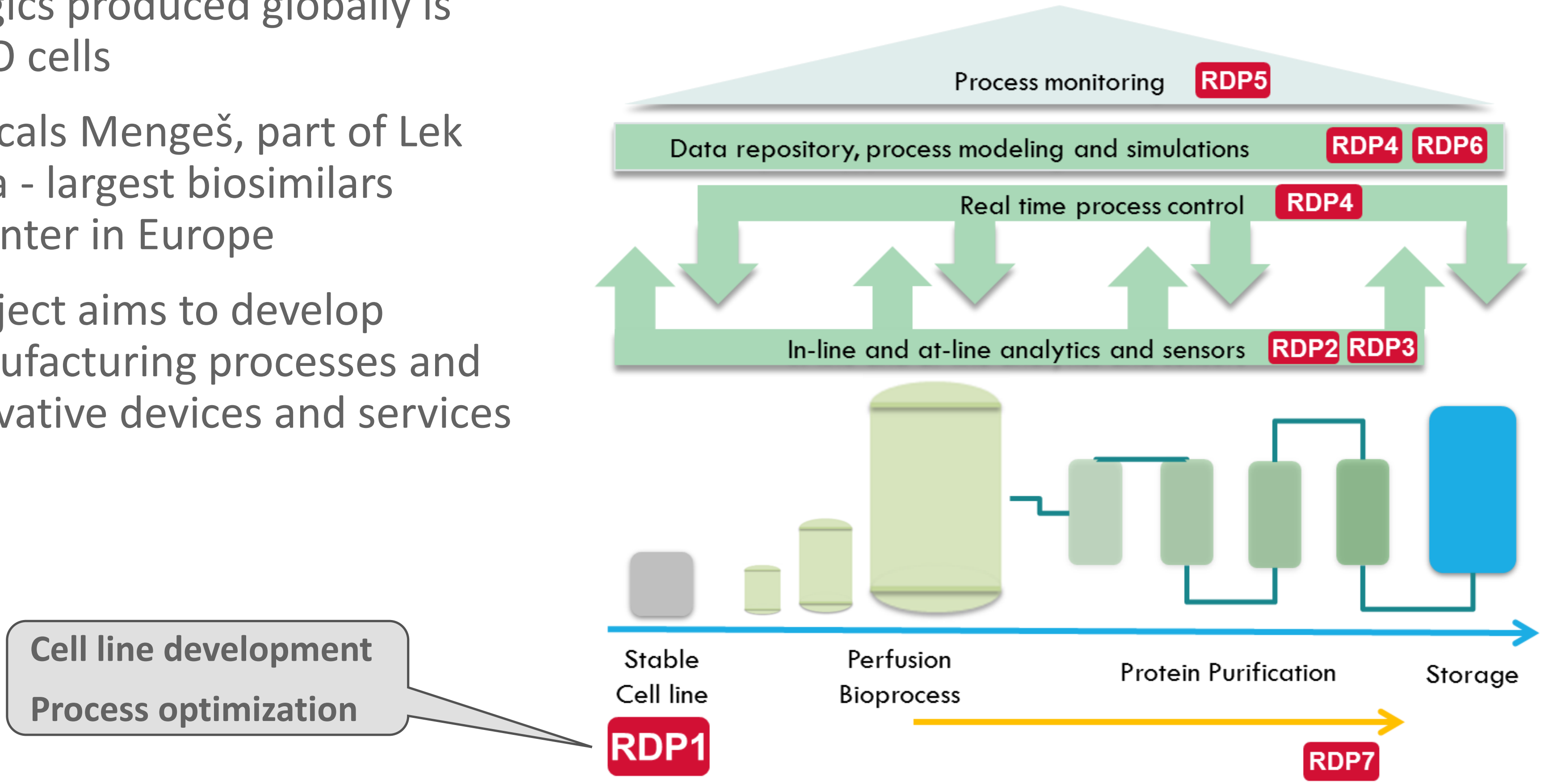


Systems biology circle



Use case 1: **Improving productivity of CHO cells**

- 70% of all biologics produced globally is produced in CHO cells
- BioPharmaceuticals Mengeš, part of Lek Sandoz, Slovenia - largest biosimilars development center in Europe
- Biopharm.si project aims to develop continuous manufacturing processes and supporting innovative devices and services



lek a Sandoz company

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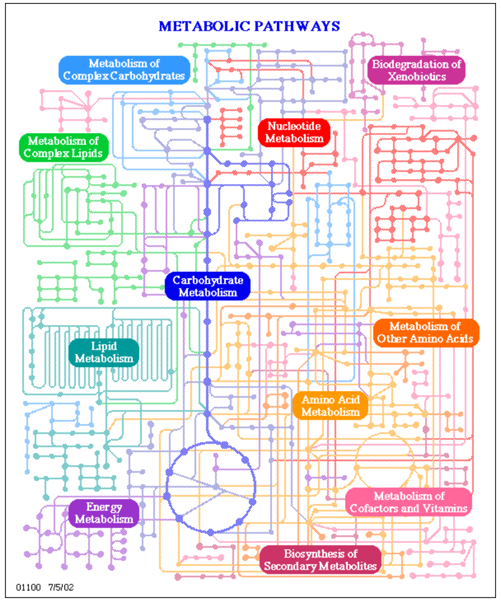
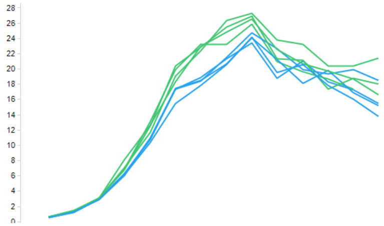
Systems biology approaches to increase the production

- Better designed parental cell lines
- Decrease cell line development time
- Monitor cell line well-being in the bioreactor

From Genomes & Genes



To the Phenotype



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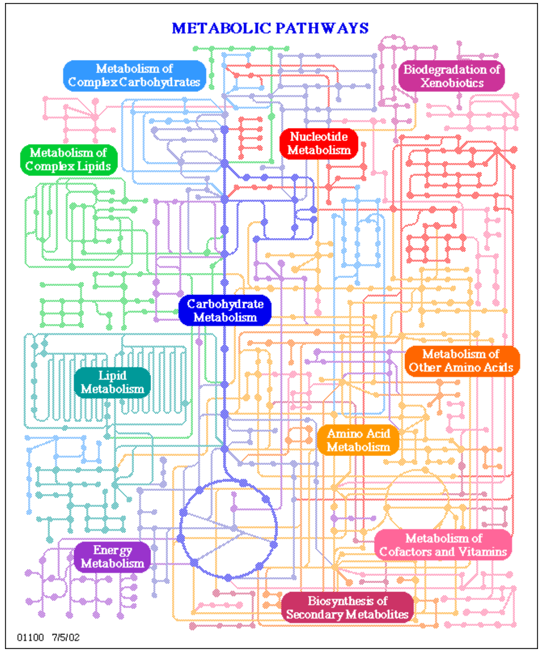
Better parental cell lines

Approach: Find the genes with higher expression in low producers → knock-out can lead to improved parental lines with increased potential for high productivity

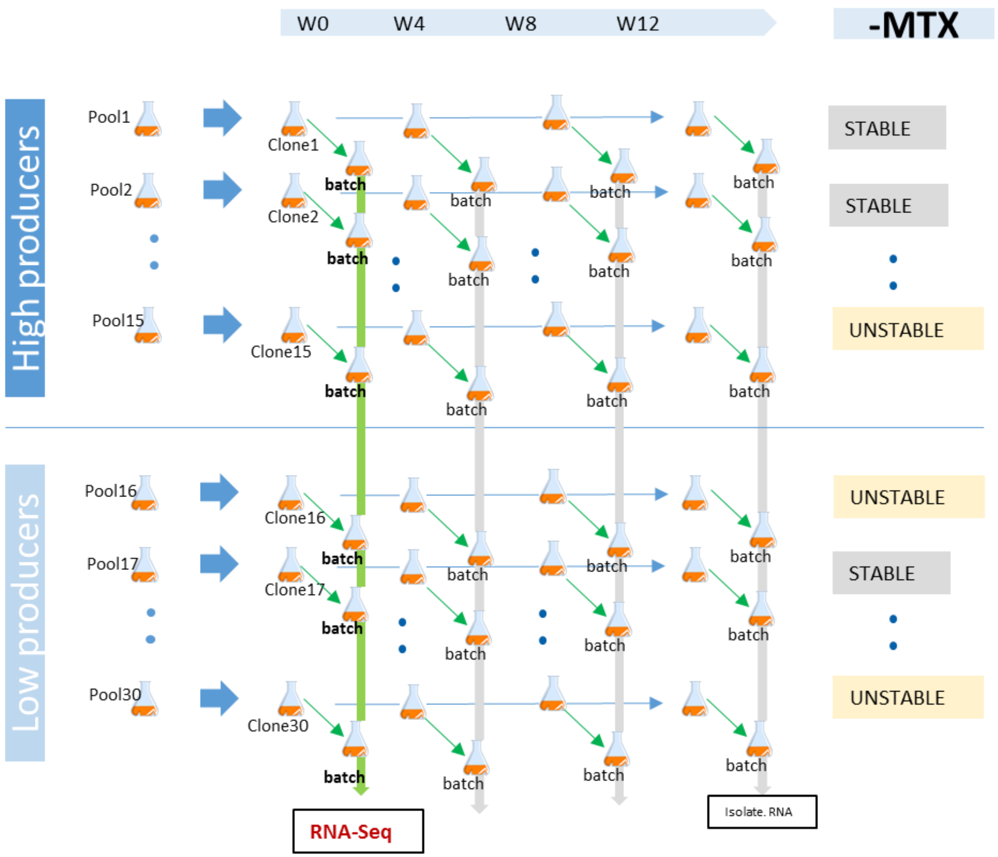
- Available transcriptomics dataset: 5 different parental lines, each from 2 – 5 different production clones, +/-MTX
- Statistical pipeline to identify genes with differential expression
  - no overlap between different cell lines
- Annotation of genes in background knowledge – involvement in relevant processes



Decrease the development time

- Checking the stability of cell lines takes 12 weeks: can we predict which cell line is stable already in first weeks?
- Using relevant transcriptomic datasets, we can find markers of stability tat we can use in the early stages of cell line development

Jamnikar et al., BMC Biotechnology 2015



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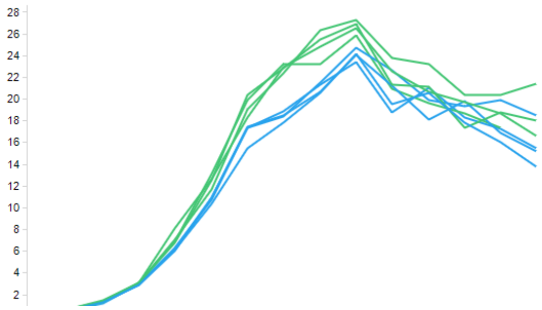
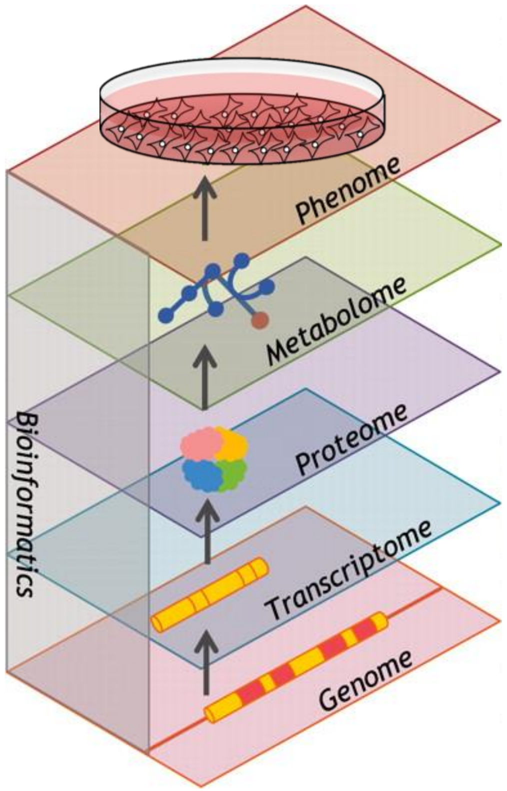
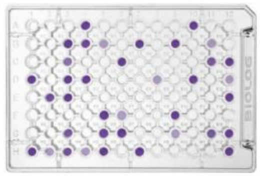
Monitoring the well-being of cells within bioreactor

- Important for the continuous bioprocess
- Metabolic or transcriptomic markers (implemented as at-line sensors)

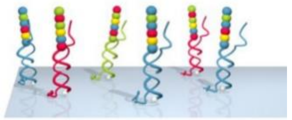




Metabolic phenotype (BioLog)



RNA markers (NanoString, qPCR)



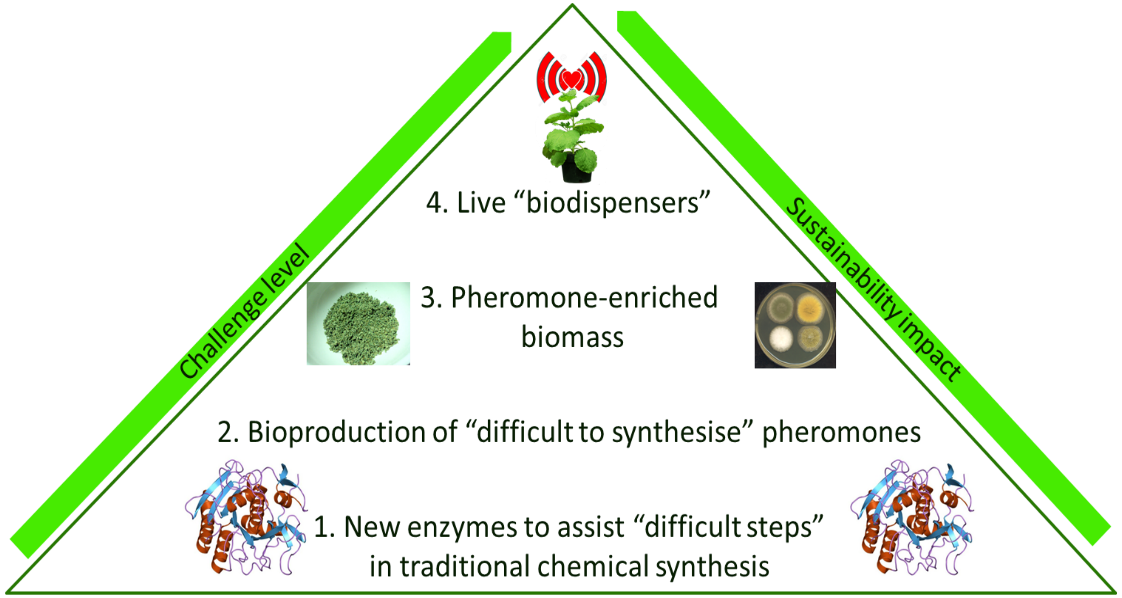
Use case 2: **Sustainable Bioproduction of Pheromones for Insect Pest Control in Agriculture**

SUSPHIRE project aims to provide sustainable, low-cost biomanufacturing (plant & fungal) platforms for insect pheromones

- Expand the use of sex pheromones to improve agricultural sustainability
- Environmentally-friendly production

SUSPHIRE
Sustainable Bioproduction of Pheromones for Insect Pest Control in Agriculture

ERA CoBioTech



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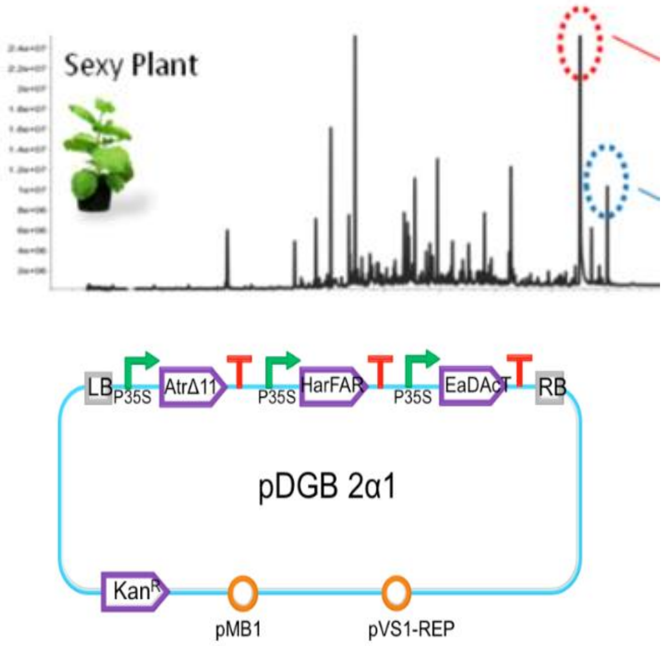
Earlham Institute

Aim 1: Demonstrate high yields of lepidopteran pheromones

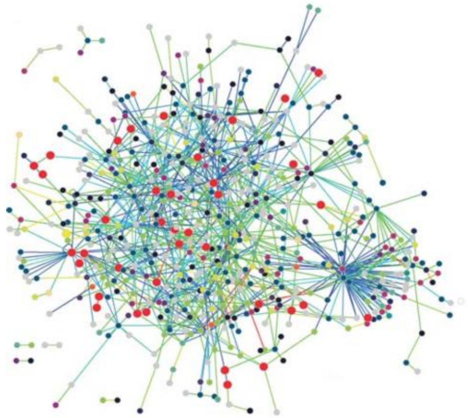
Sexy plants 1.0: expressing 3 lepidoptera pheromone biosynthesis genes



→ Use of systems biology tools to identify regulatory bottlenecks causing growth penalty

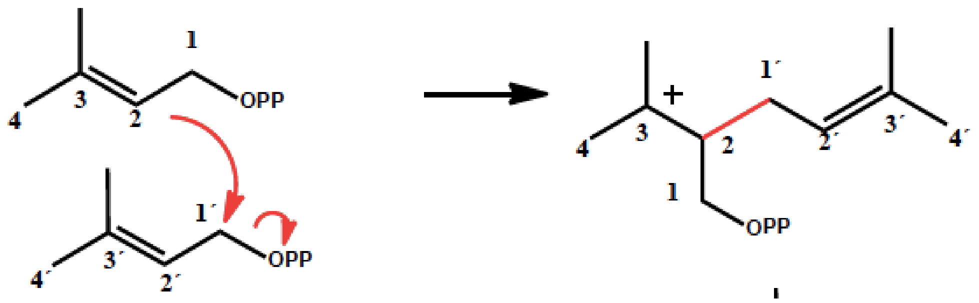
Aim 1: Demonstrate high yields of lepidopteran pheromones

- RNAseq analysis: 2 low producing, 2 high producing lines, wt
- The majority of gene expression changes are linked to pheromone production, but not to transgene insertion
- Stress response in high producing plants
- Further network analyses to identify regulatory bottlenecks



Aim 2: Discover & engineer mealybug pheromone biosynthesis pathways

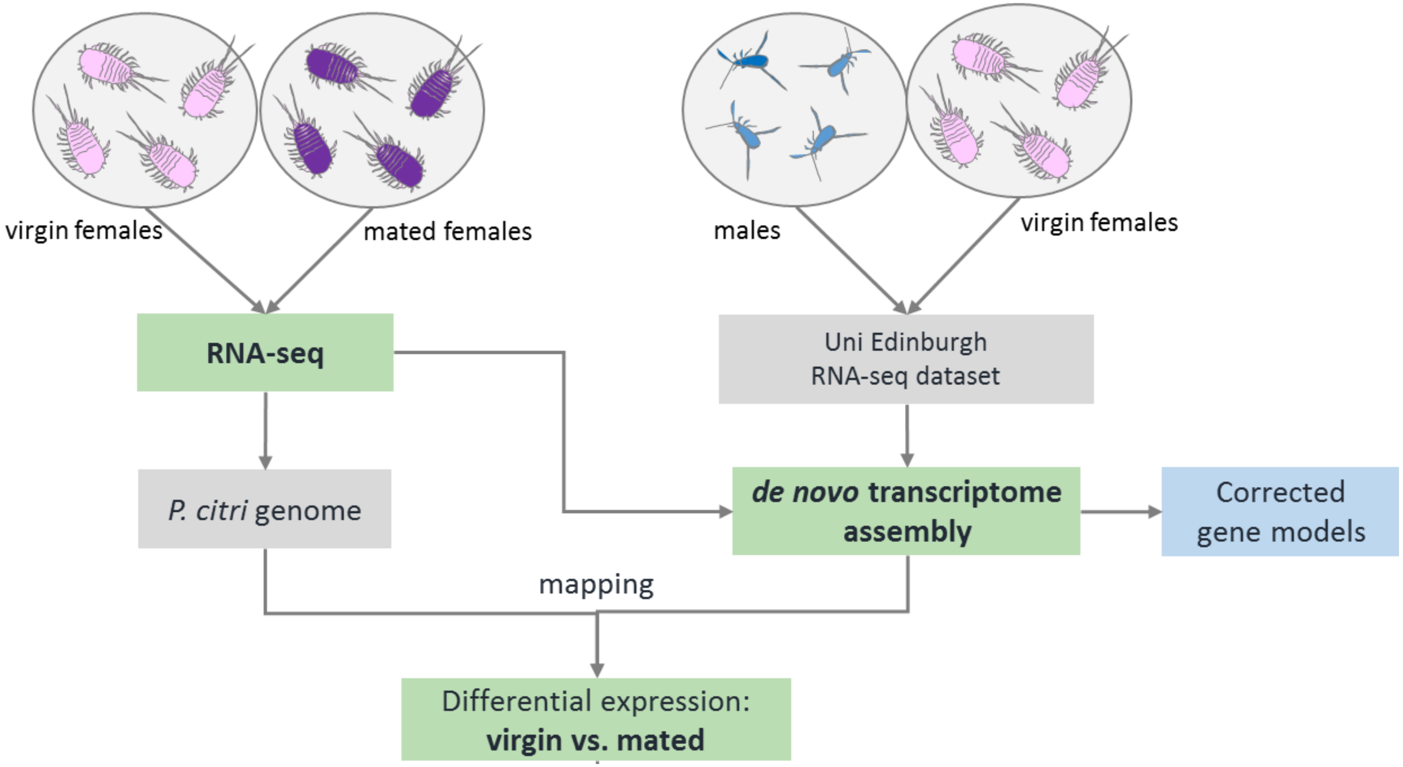
- Mealybugs – important plant pests
- Mealybug pheromones = irregular monoterpenoids (unusual NON-head-to-tail linkage of two isoprene units)
- Chemical synthesis difficult & biosynthesis unknown



ECONOMIC IMPORTANCE

Aim 2: Discover & engineer mealybug pheromone biosynthesis pathways

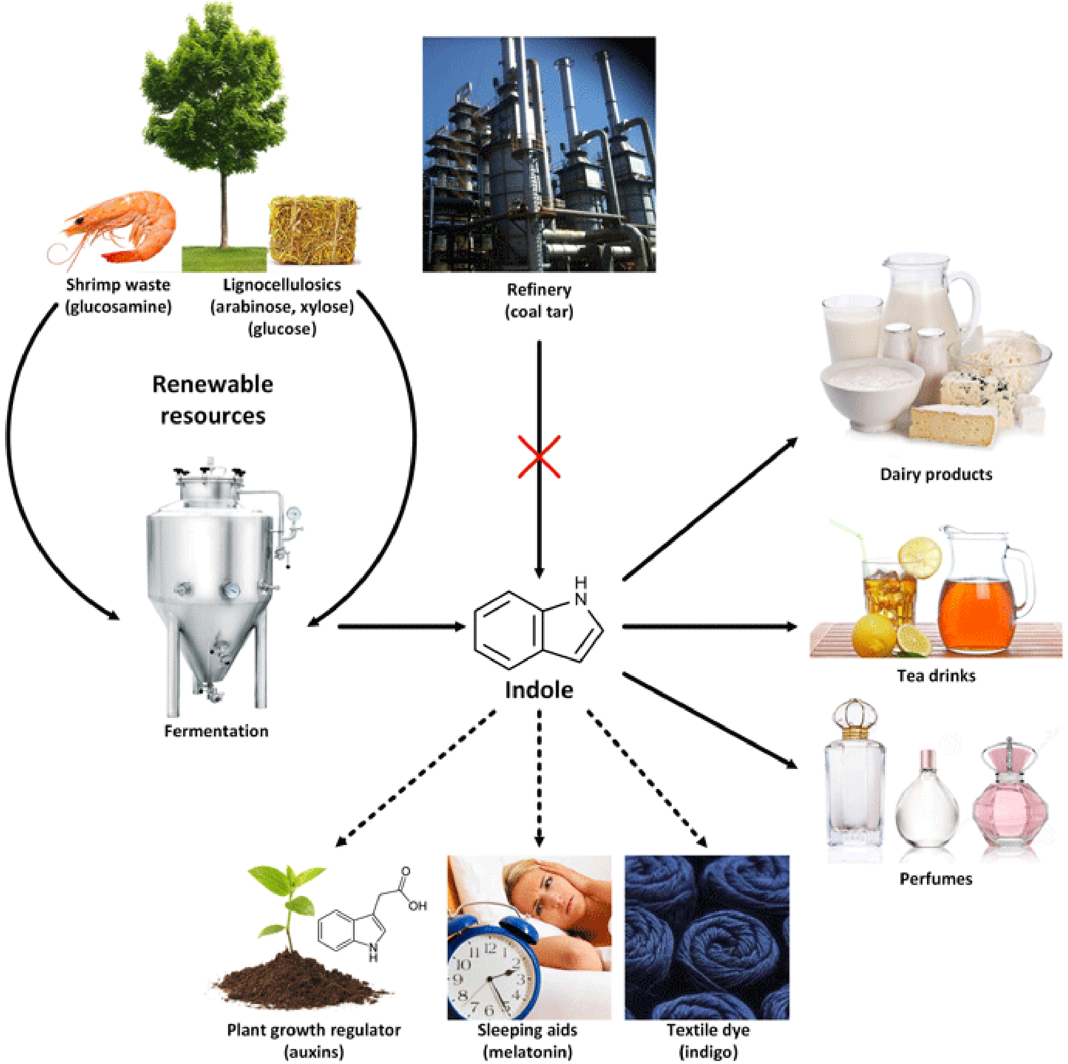
Identification of isoprenyl diphosphate synthase (IDS), first step in *Planococcus citri* pheromone biosynthesis) from transcriptome data



Use case 3: **Biotechnological production of indole**

InDIe

ERA CoBioTech



Establish sustainable production of indole

- *Corynebacterium glutamicum* (industrial amino acid producer)
- Identification of biosynthetic enzymes in bacteria in plants
- Pathway design and optimization
- Set up industrial scale production, using renewable resorces

AXXENCE

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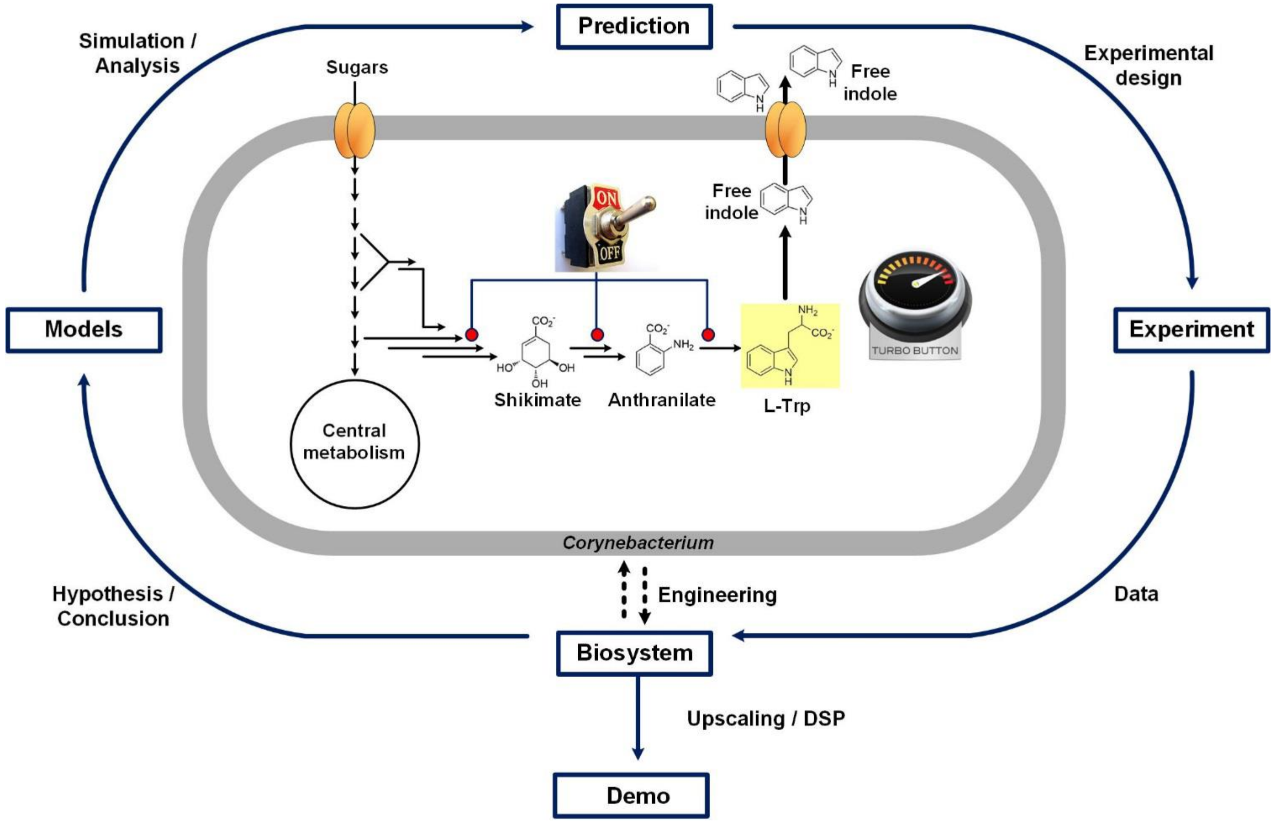
Identification of indole synthases in plants

Looking for INS motifs in proteomes of plant clades that produce indole derivatives using iGLOSS tool

→ Candidates for functional analysis identified

Optimization of designed production strains



Integration of transcriptomic and metabolomic data with the *C. glutamicum* metabolic model

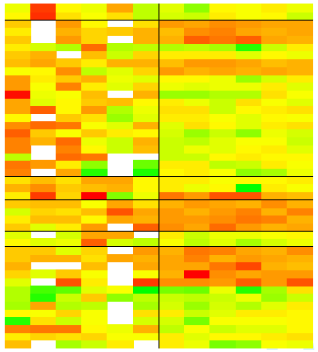
→ Identification for additional targets for optimization

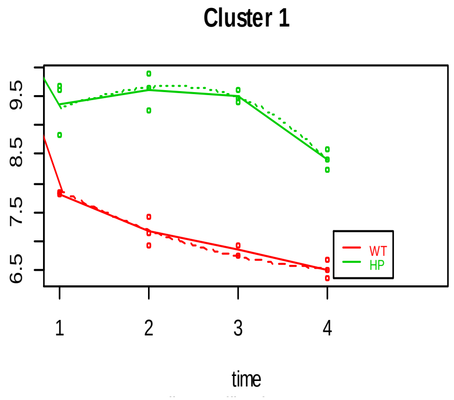
Use case 4: **Improving antibiotic production**

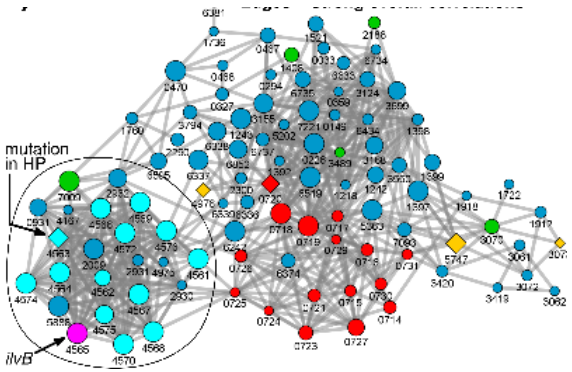
Improvement of *Saccharopolyspora erythraea production strain*

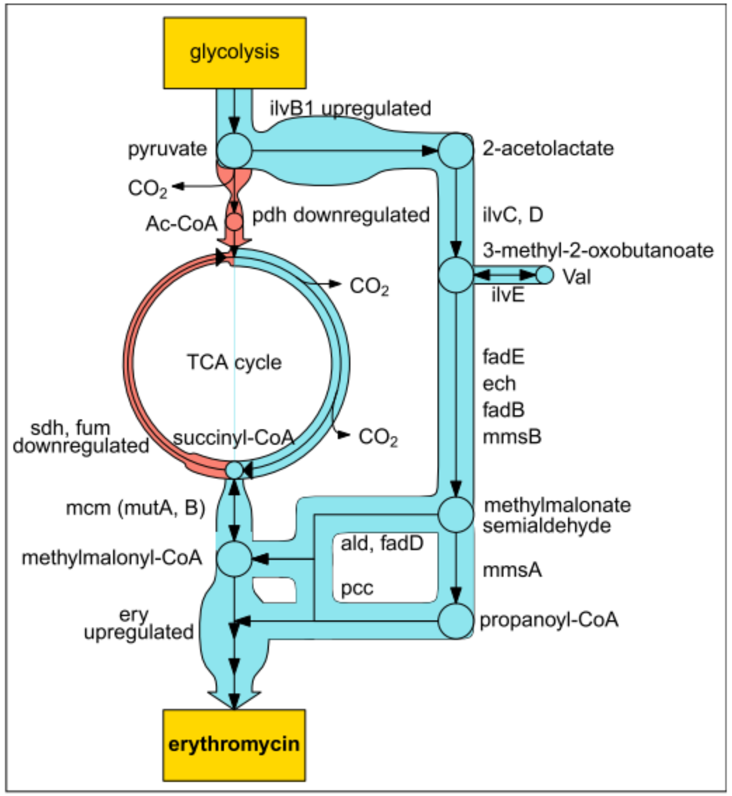
- Transcriptomics, proteomics in high-producing and wt strain
- Time-course statistical analysis
- Data integration, visalization & network analysis

→ Identification of key regulatory elements and targets for pathway reengineering









Karničar et al., Microbial Cell Factories, 2016

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