

# An integrative genome-scale *E. coli* model for Systems and Synthetic biology

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UC Davis Genome Center**



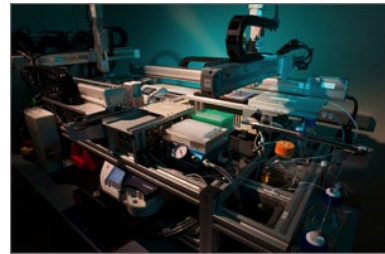
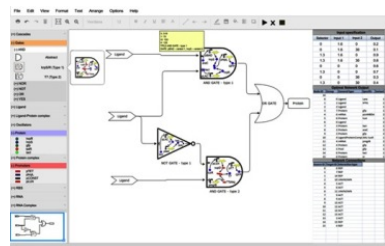
**University of California, Davis**



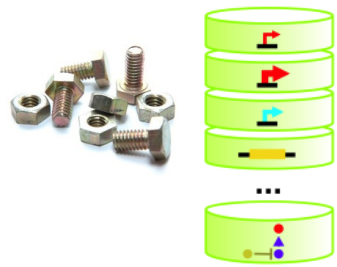
ENGINEERING

SCIENCE

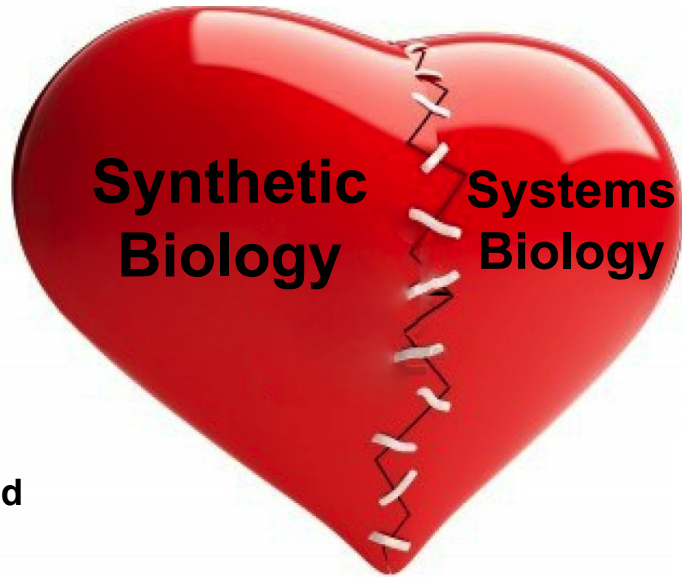
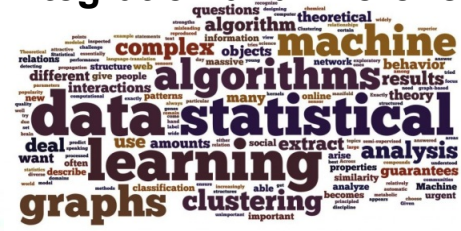
## Circuit design automation



## Part construction and Characterization



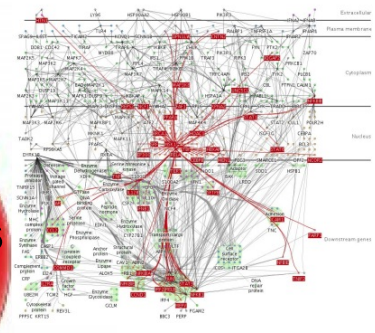
## Machine Learning Algorithms Integration and Inference



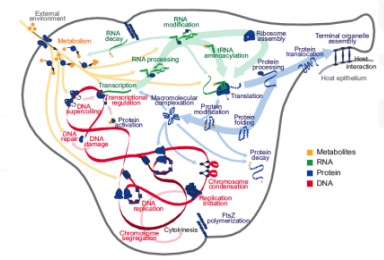
Synthetic Biology

Systems Biology

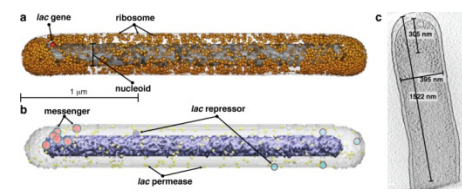
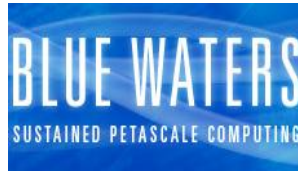
## Biological Networks



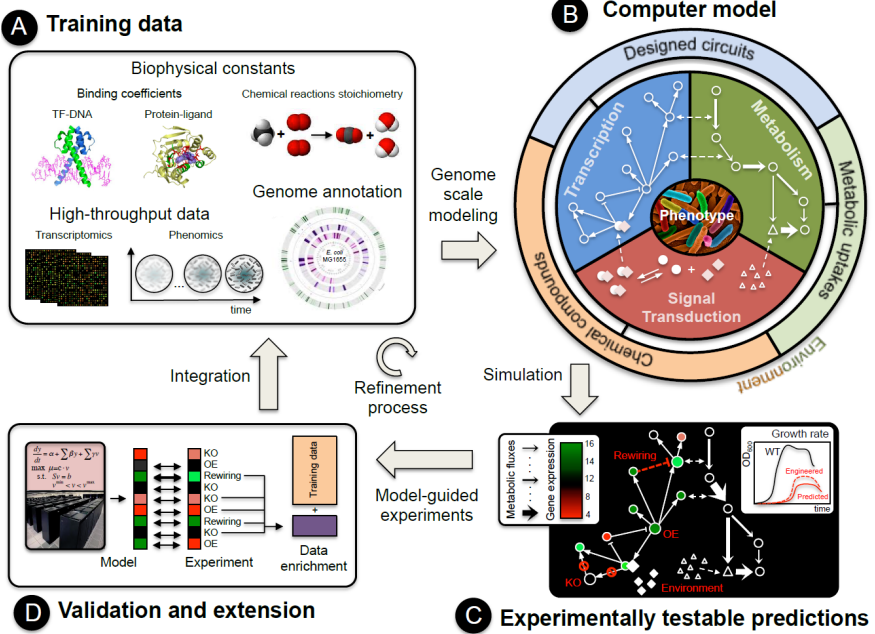
## Whole cell modeling



## Multi-scale simulation



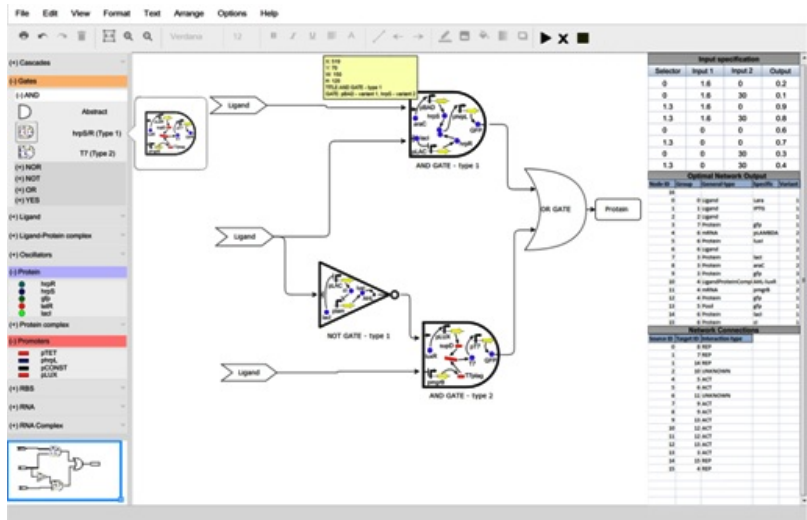
# Relevant projects in our lab



## Multi-scale modeling and HPC simulation



## Automated CAD tools for Synthetic Biology

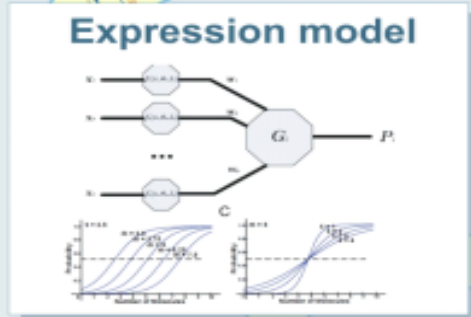
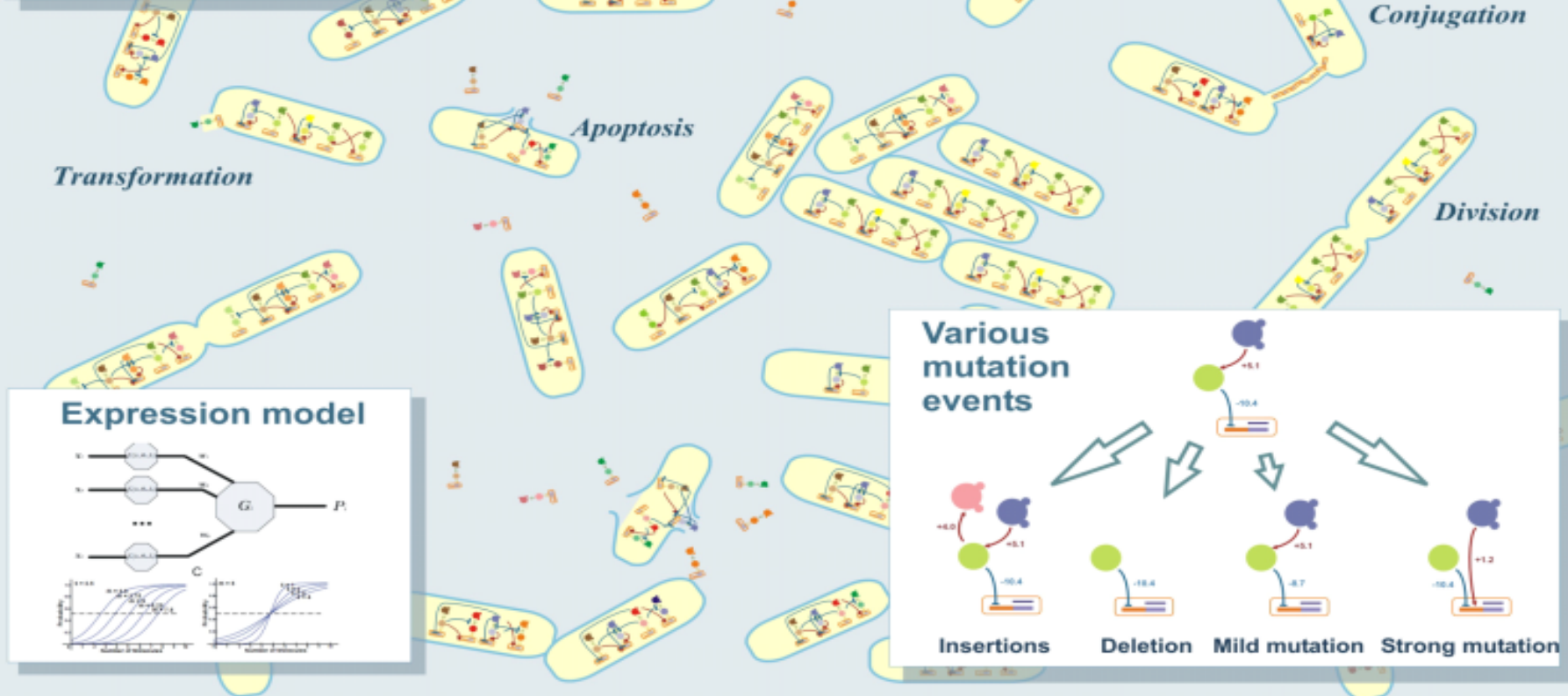
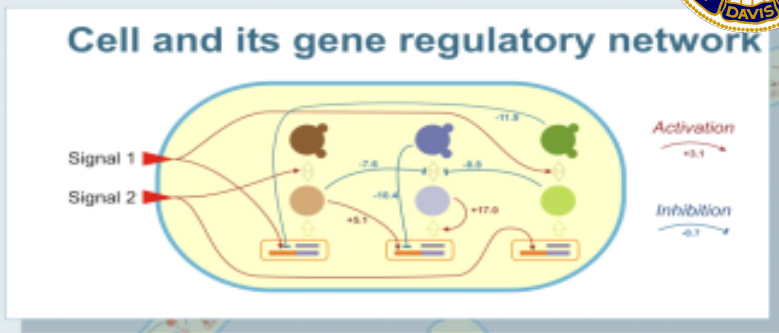
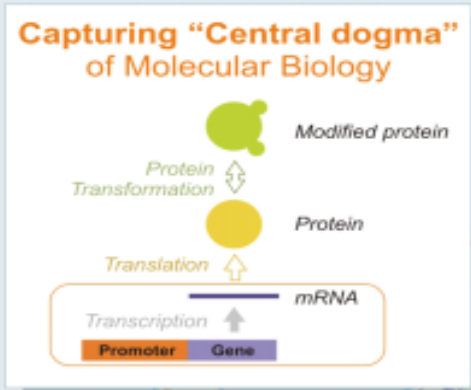


## Decision support tools for agriculture and medicine





# EVE: Evolution in Variable Environments





## Challenges:

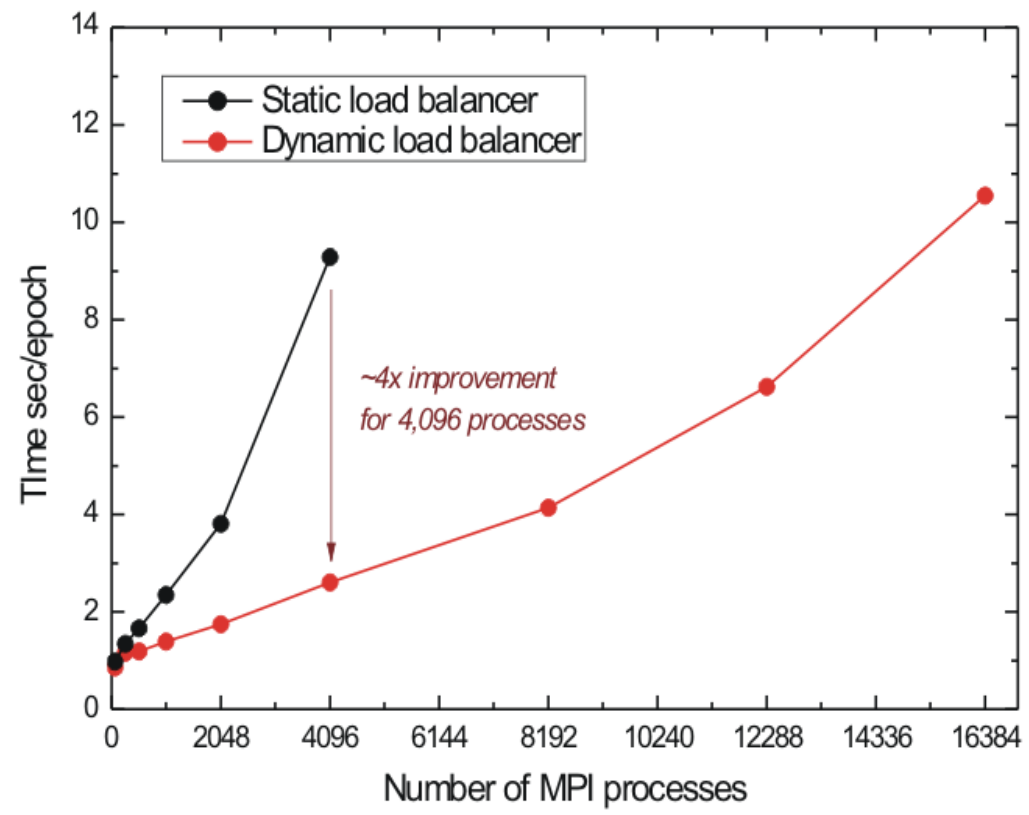
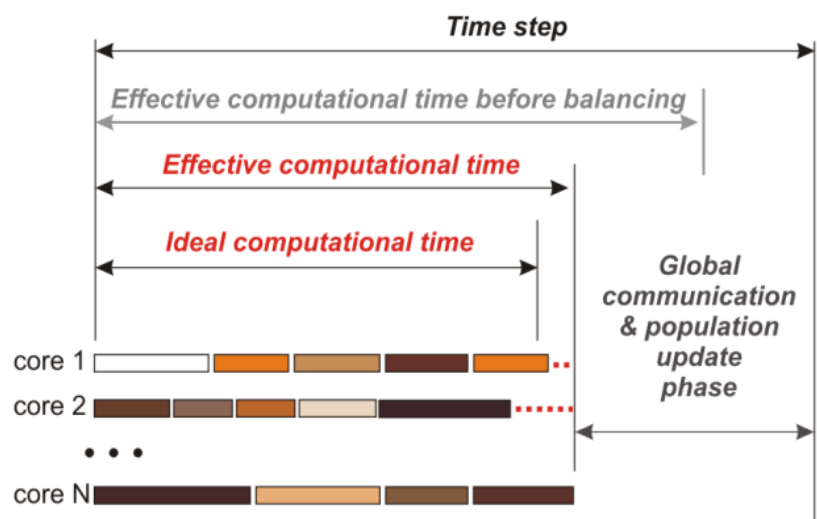
- Balancing **biological realism** and **computational feasibility**
- Different **spatial and temporal scales** across various phenomena (genes, proteins, networks, cells, populations)
- Modeling evolution, inherently **hard to predict**, leads to different cell sizes, growth rates, etc., which translates to **load imbalance**
- **Size does matter**: a bacterial colony may have **billions of cells** and small population size leads to biases (clonal interference, genetic drift)
- **Storage, fast access and visualization** of the ***evolutionary fossil record*** from replicate simulations.



## Accomplishments:

- EVE microbial evolution simulator scaling up to **8,000 MPI processes** and **128,000 cells**.
  - To compare: our previous work (run on a Blue Gene machine) scaled up to **200 organisms** and had a less complex underlying model
    - I.Tagkopoulos, Y.Liu, S. Tavazoie, "Predictive Behavior Within Microbial Genetic Networks", *Science*, 320:1313-7, 2008
- Tackling growth and evolution: **static and adaptive load balancing** for both fixed and non-fixed population sizes
  - V. Mozhayskiy, I.Tagkopoulos, "In silico Evolution of Multi-scale Microbial Systems in the Presence of Mobile Genetic Elements and Horizontal Gene Transfer", *ISBRA2011, Lecture Notes in Bioinformatics*, LNBI 6674, pp.262-273, Springer, 2011
  - V. Mozhayskiy, R. Miller, KL. Ma, I.Tagkopoulos, "A Scalable Multi-scale Framework for Parallel Simulation and Visualization of Microbial Evolution", *TeraGrid2011*; Salt Lake City, Utah, 2011 (**Best of Science** and **Best of Show awards**)
- Other extensions: HDF5 storage, AMPI

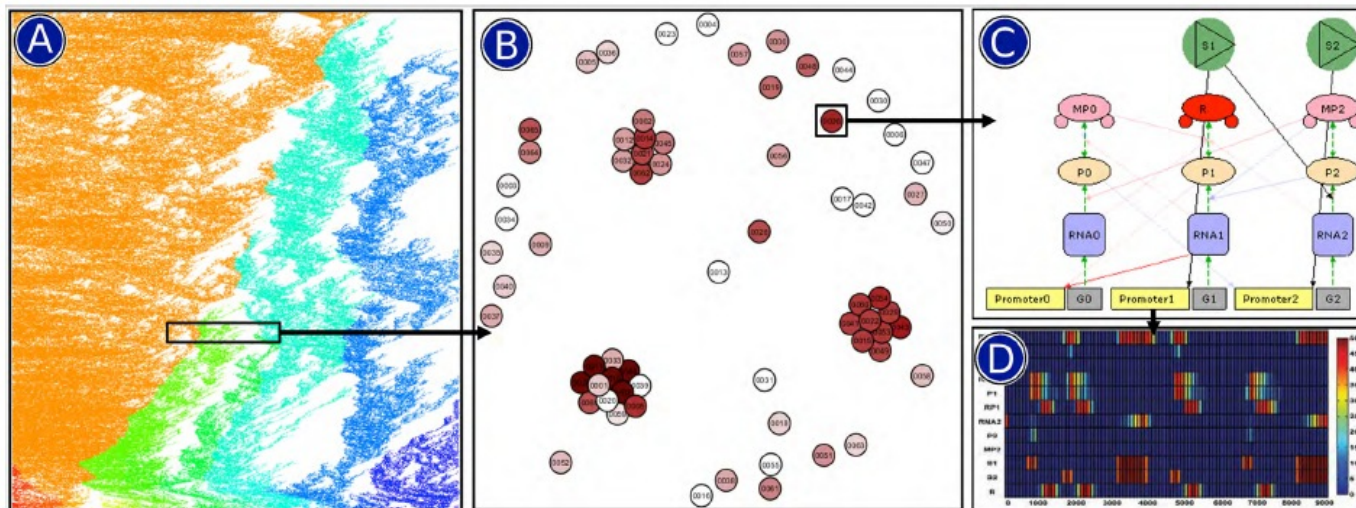
# Load Balancing in simulations of cell populations





# Visualization

- **Visualization** and **information flow analysis tools** to cluster cells based on phenotype, view hierarchical organization, mutations and evolutionary trajectory.
  - R. Miller, V.Mozhayskiy, I.Tagkopoulos, KL. Ma, "EVEVis: A Multi-Scale Visualization System for Dense Evolutionary Data", *1st IEEE Symposium on Biological Data Visualization*, pp. 143-150, Rhode Island, 2011
  - A. Pavlogiannis, V. Mozhayskiy, I. Tagkopoulos, "A flood-based information flow analysis and network minimization method for bacterial systems", 14:137 DOI: 10.1186/1471-2105-14-137, *BMC Bioinformatics*, 2013

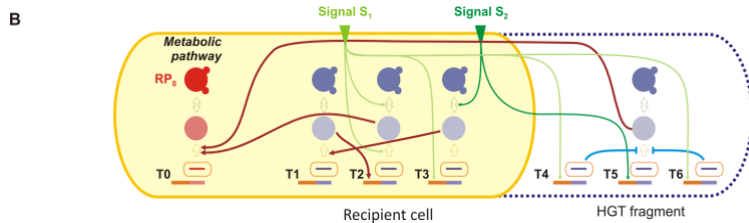
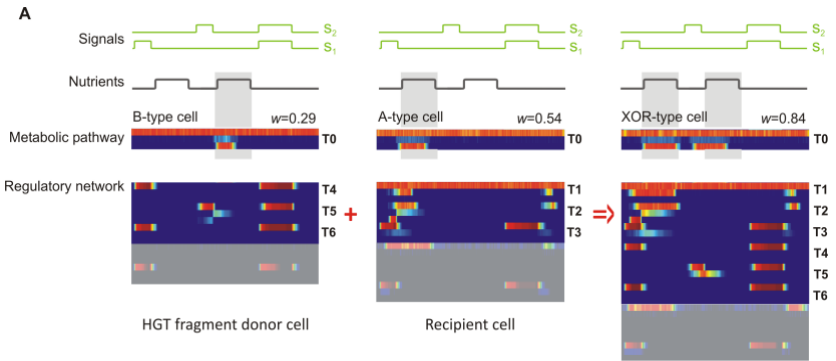
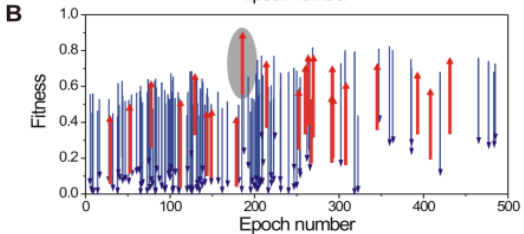
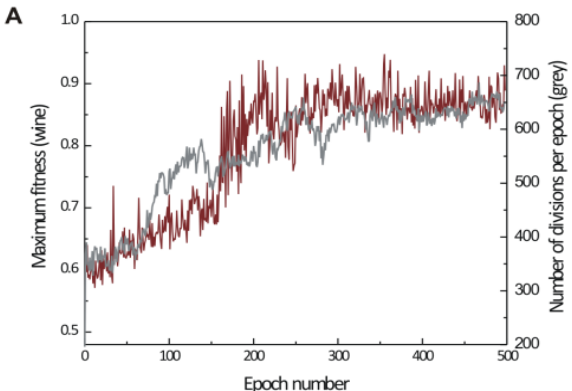




# Large-scale simulations to explore evolutionary hypotheses

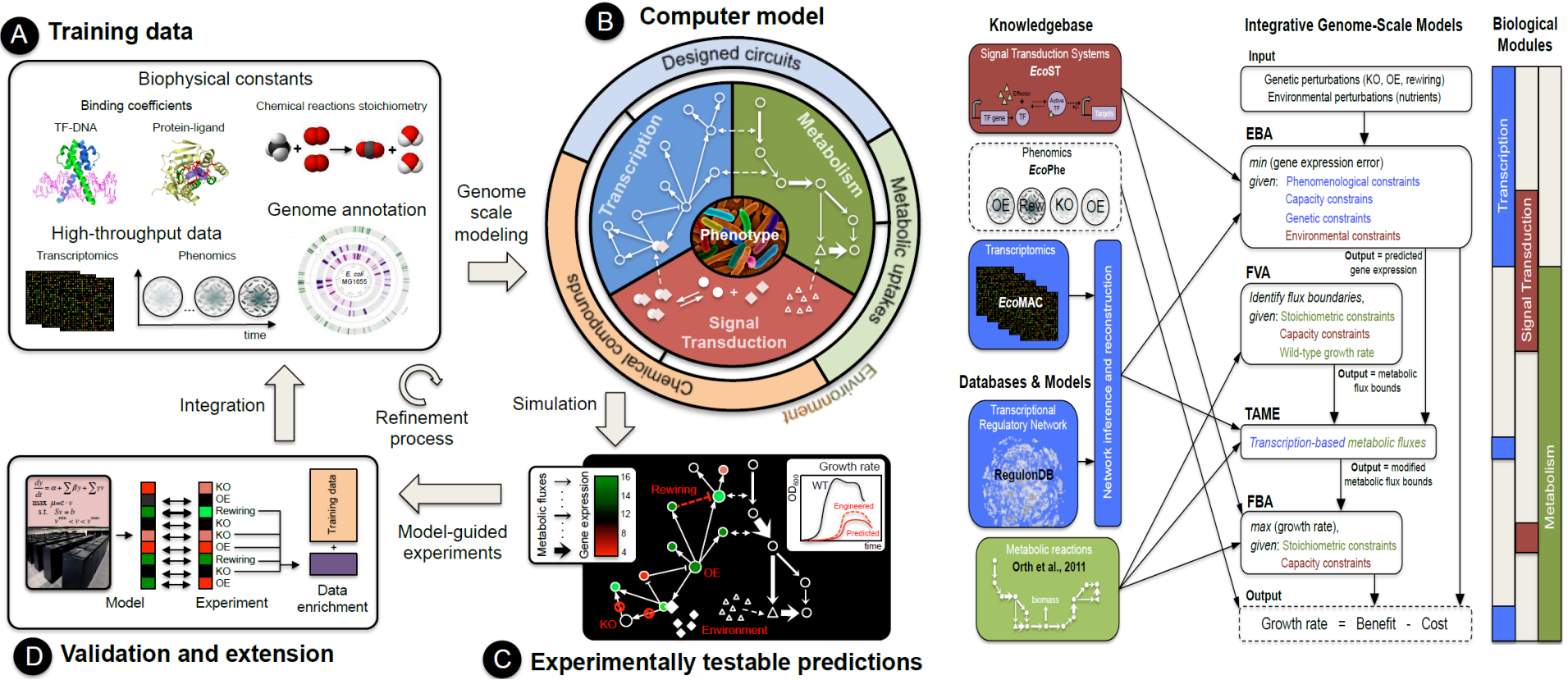
- Used to investigate **Horizontal Gene Transfer** and **evolutionary hypotheses**

- V.Mozhayskiy, I.Tagkopoulos, "Horizontal gene transfer dynamics and distribution of fitness effects during microbial In silico Evolution", 13:S13, *BMC Bioinformatics*, 2012
- V.Mozhayskiy, I.Tagkopoulos, "Guided evolution of in silico microbial populations in complex environments accelerates evolutionary rates through a step-wise adaptation", 13:S10, *BMC Bioinformatics*, 2012
- V. Mozhayskiy, I. Tagkopoulos, "Microbial evolution *in vivo* and *in silico*: methods and applications", 5(2):262-77, *Integrative Biology*, 2013



# The road ahead

## A data-driven probabilistic graphical model for microbial evolution (*E. coli* as a proof-of-concept case)

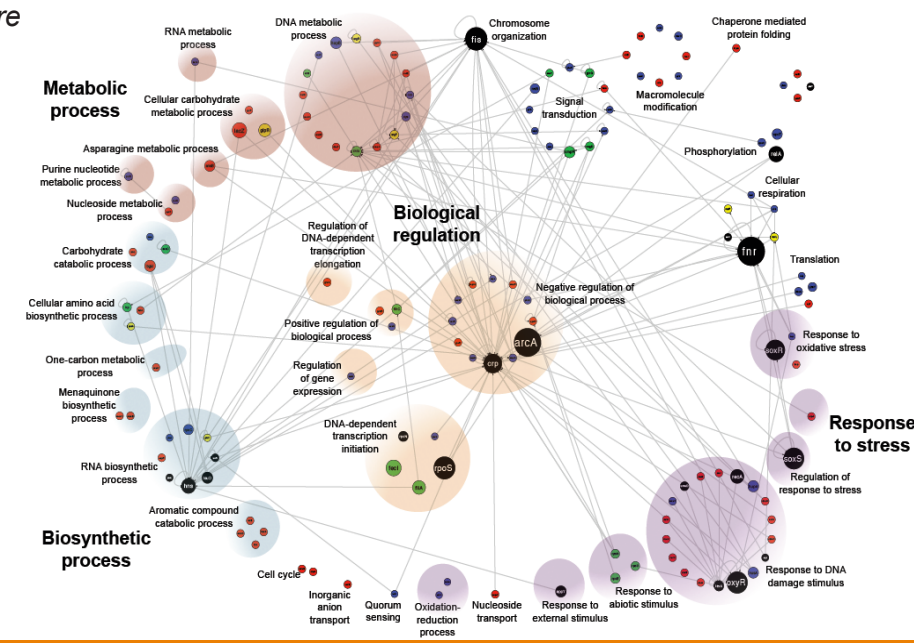
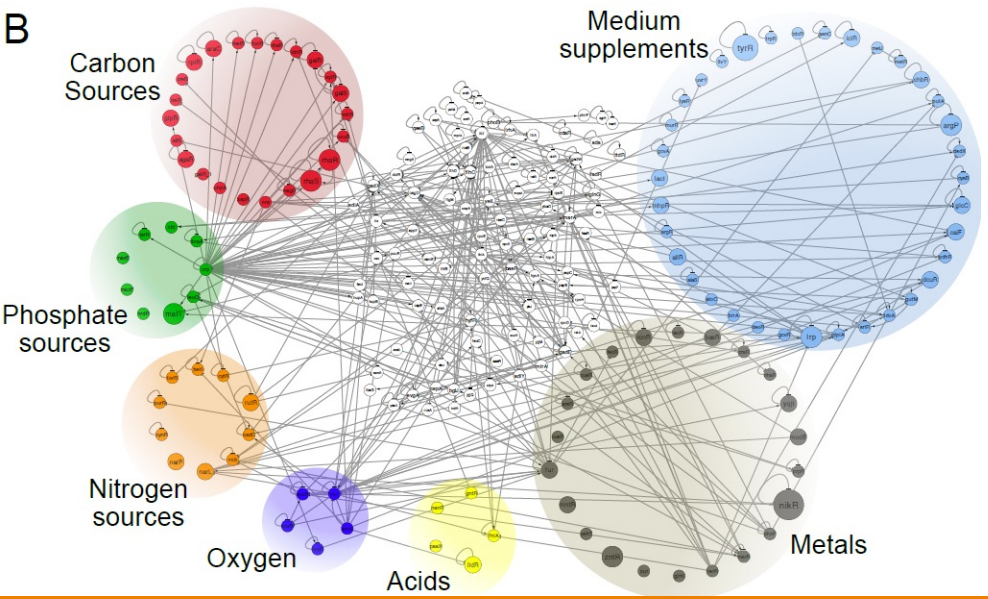
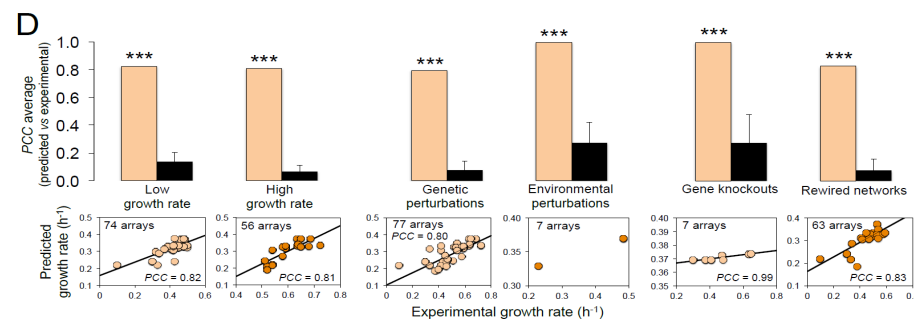
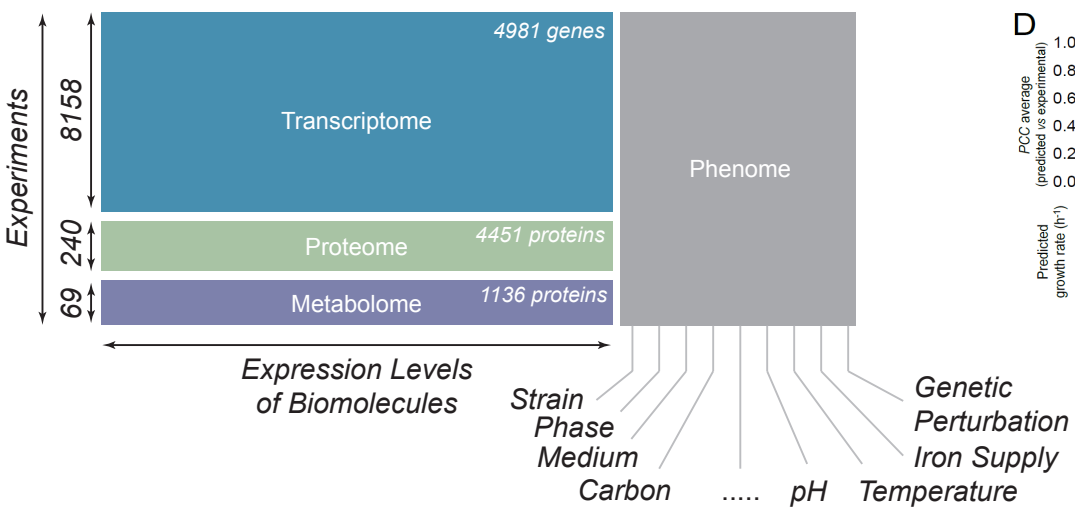


J. Carrera, R. Estrela, J. Luo, N. Rai, A. Tsoukalas, I. Tagkopoulos, "An integrative, multi-layer, genome-scale model reveals the phenotypic landscape of Escherichia coli", accepted, *Nature/EMBO Molecular Systems Biology*, 2014



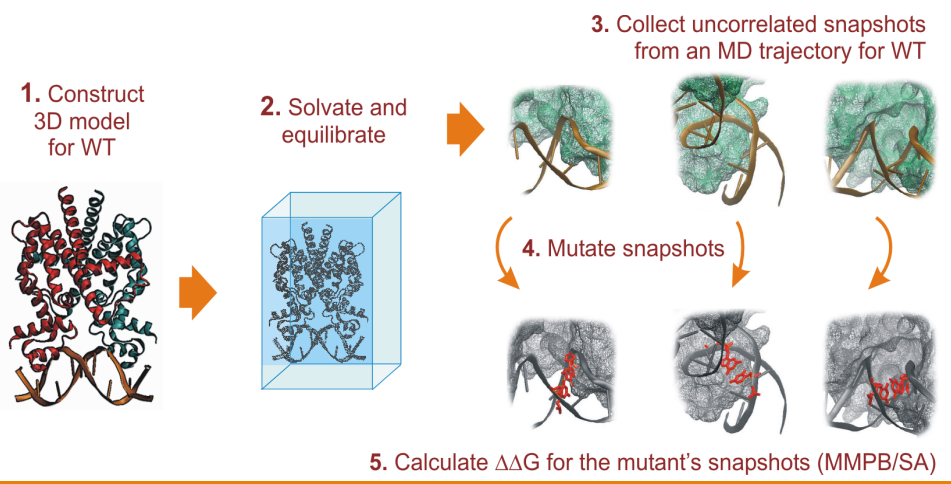
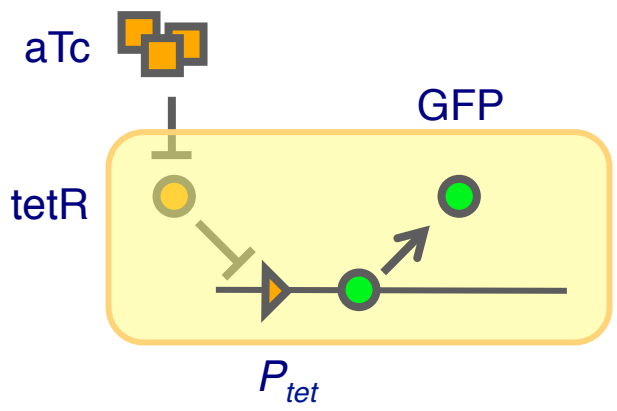
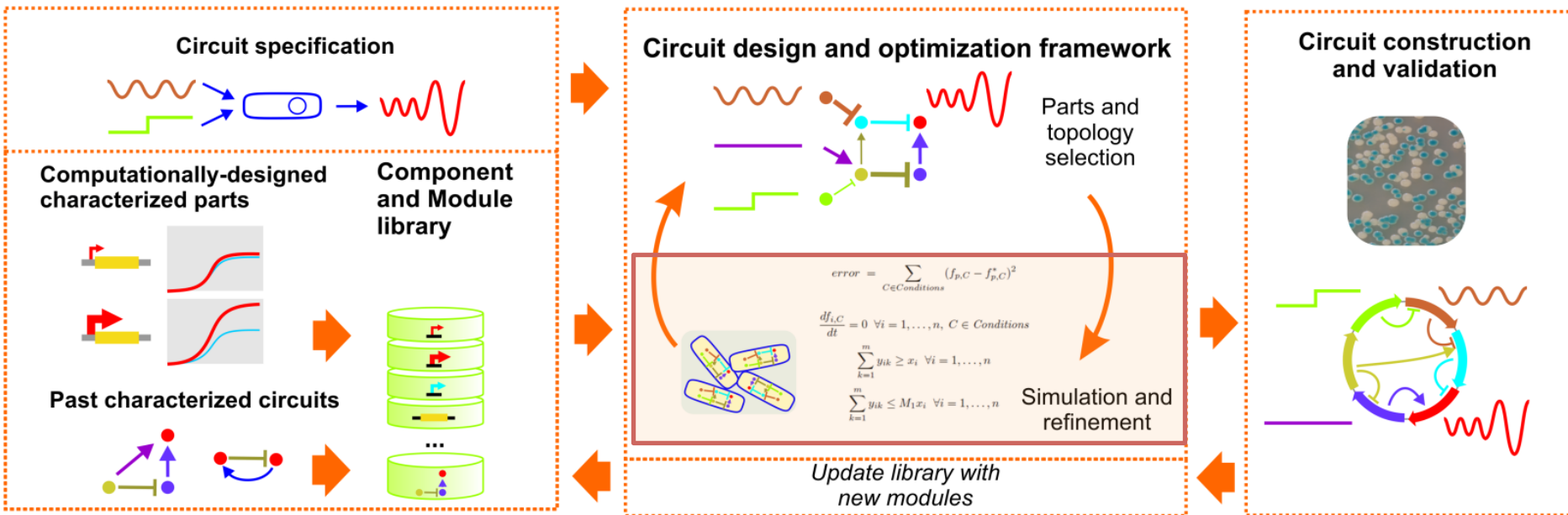
# An integrative genome-scale model for *E. coli*

### *E. coli* Multi-OMICS Dataset



# Genome-scale models in Synthetic Biology

## SBROME: Synthetic Biology Reusable Optimization Methodology





# Acknowledgements



## Lab members:

### Postdocs

- Violeta Zorraquino
- Navneet Rai
- Nasos Tsoukalas
- Dina Zhabinskaya
- Javier Carrera (now with Markus Covert, Stanford)
- **Vadim Mozhayskiy** (now with Life Technologies)

## Funding

## Links

<http://tagkopouloslab.ucdavis.edu>

### Graduate students

- **Linh Huynh**
- **Minseung Kim**
- Runyu Shi
- Matt Meisner
- Beatriz Pereira



BLUE WATERS PROJECT



- Dragosits, V. Mozhayskiy, S. Quinones-Soto, I. Tagkopoulos, “**Evolutionary potential, cross-stress dependencies, and the genetic basis of acquired stress resistance in of *E. coli***”, doi:10.1038/msb.2012.76, 9:643, *Molecular Systems Biology*, 2013
- J. Carrera, R. Estrela, J. Luo, N. Rai, A. Tsoukalas, I. Tagkopoulos, ” **An integrative genome-scale model reveals the phenotypic landscape of *Escherichia coli*.**, accepted, *Molecular Systems Biology*, 2014.