Computational approaches for synthetic biology
-
Design, optimization and control

Gregory Batt

INRIA Paris-Rocquencourt

Outline

- Computational biology for synthetic biology

  How can computational sciences support and drive developments in SB?

- Computational biology at INRIA

  What are the various aspects of computational biology?

- Real-time control of gene expression

  A particular application of modeling and control in quantitative biology

Computational biology for synthetic biology

- Integrated design environment for design of synthetic circuits

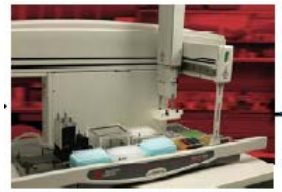
parts database

circuit editor

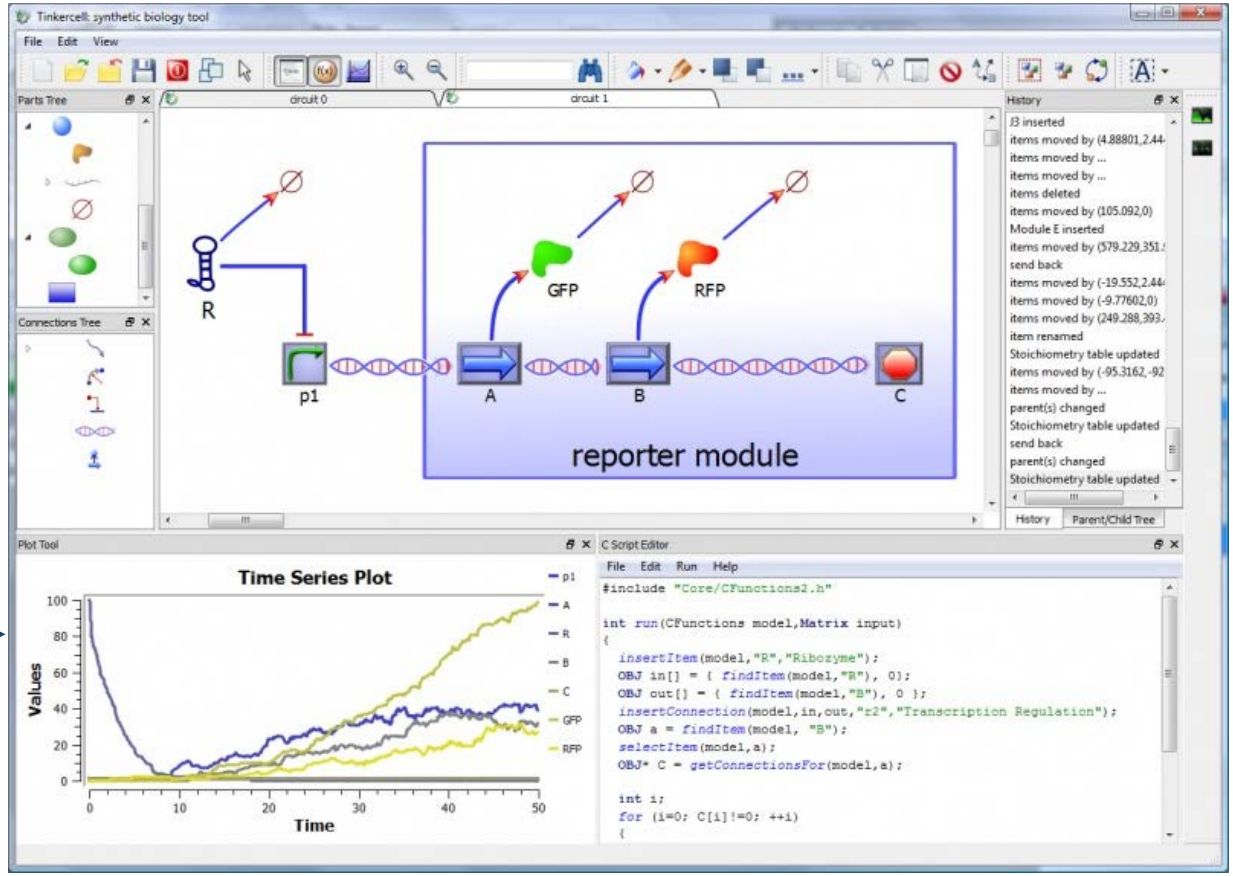
simulator / optimizer

build automation tools

version management tools



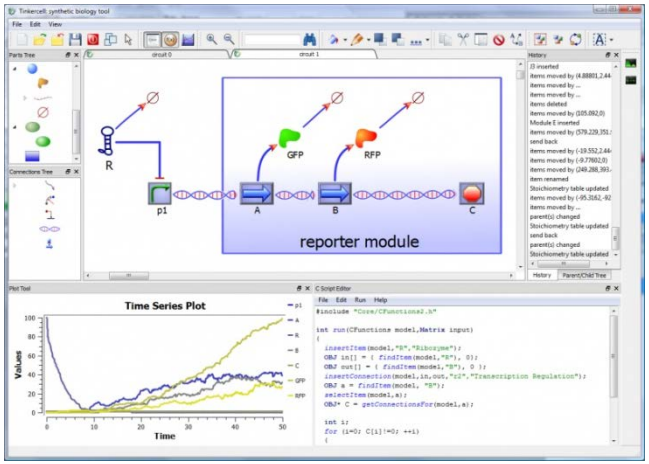
Physical Assembly



Chandran *et al*, 2009

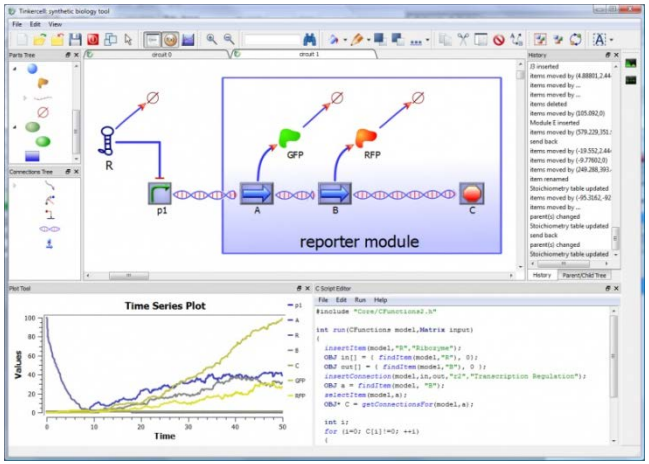
Computational biology for synthetic biology

- Integrated design environment
  - ambitious objectives
  - very recent attempts
  - relies on capability to standardize biology

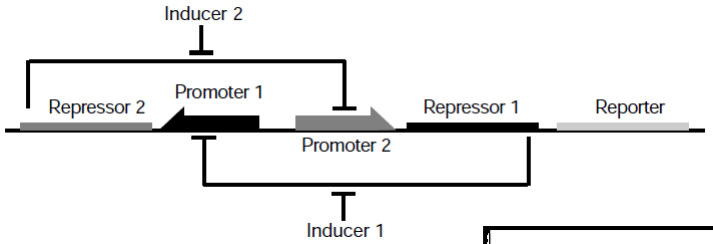


Computational biology for synthetic biology

- Integrated design environment
  - ambitious objectives
  - very recent attempts
  - relies on capability to standardize biology

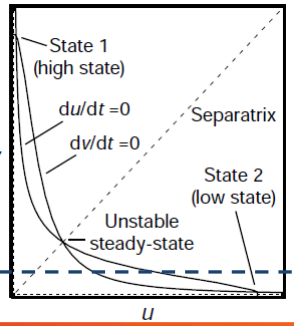


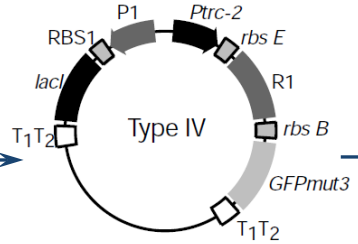
- Model-based design and optimization of synthetic circuits



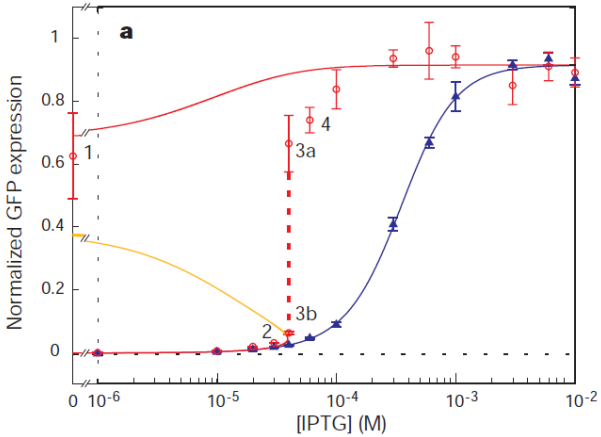
$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$



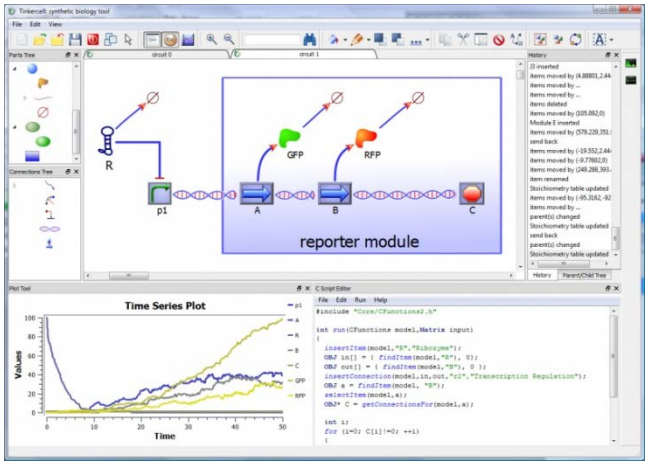


Gardner *et al*, 2000



Computational biology for synthetic biology

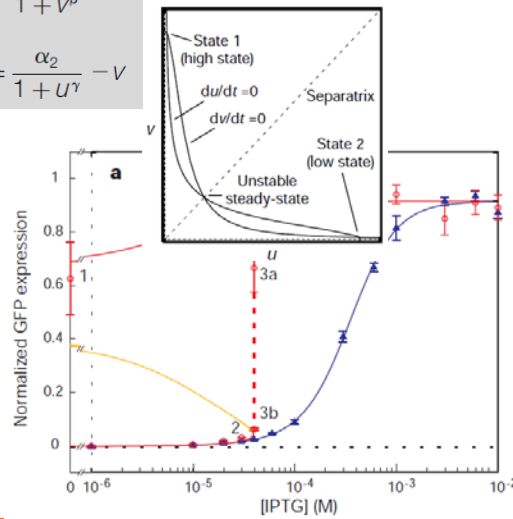
- Integrated design environment
  - ambitious objectives
  - very recent attempts
  - relies on capability to standardize biology



- Model-based design and optimization
  - gather (traditional) mathematical biology and (more recent) quantitative biology
  - main difference wrt systems biology: design problems
  - significant effort that has not yet reached expectations. But systems and synthetic bio communities nurtured by these rational approaches

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$



Computational biology at INRIA

- National institute dedicated to numerical sciences

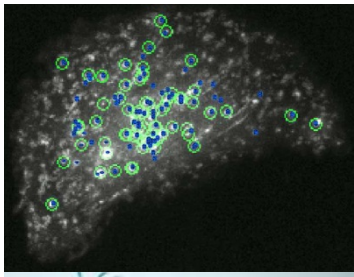
  8 research centers, 200 research groups, 3500 scientists (1400 permanents)

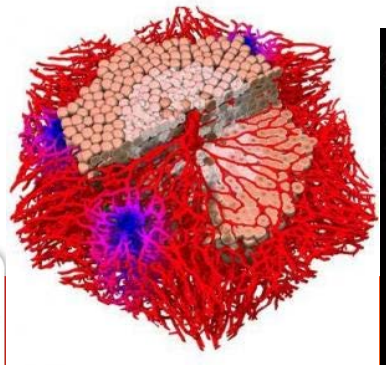
- Computational sciences for biology, medicine & environment

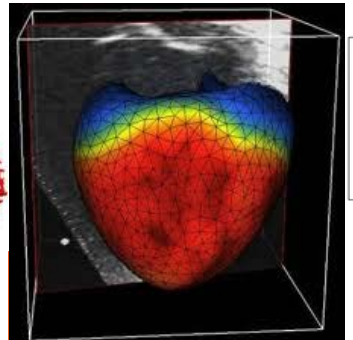
  One of the 5 major fields of research, 43 research groups

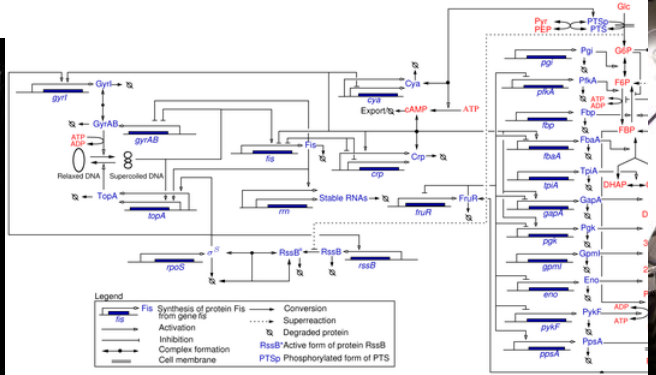
  Strong expertise in

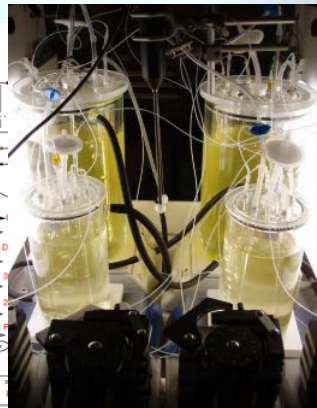
  - data analysis and modeling: Ibis, Serpico, Dyliss, Contraintes
  - spatial models (ABM, PDE): Bang, Reo, Macs, Carmen
  - multiscale simulation: Dracula, Numed, V.Plant, Amib, Morpheme
  - identification and control: Biocore, Sisyphe, Masiae
  - evolution and ecology: Beagle, Modemic







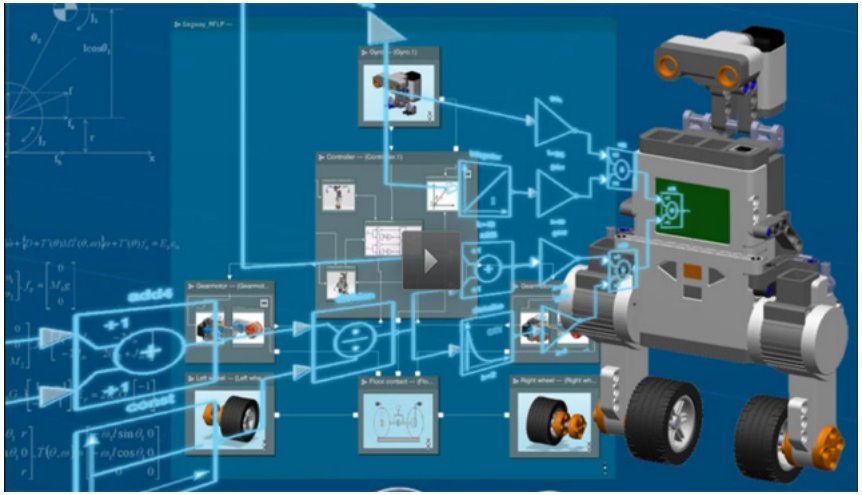




Computational biology in the Contraintes group

- Biointelligence: "Catia pour la biologie" [Oseo project]

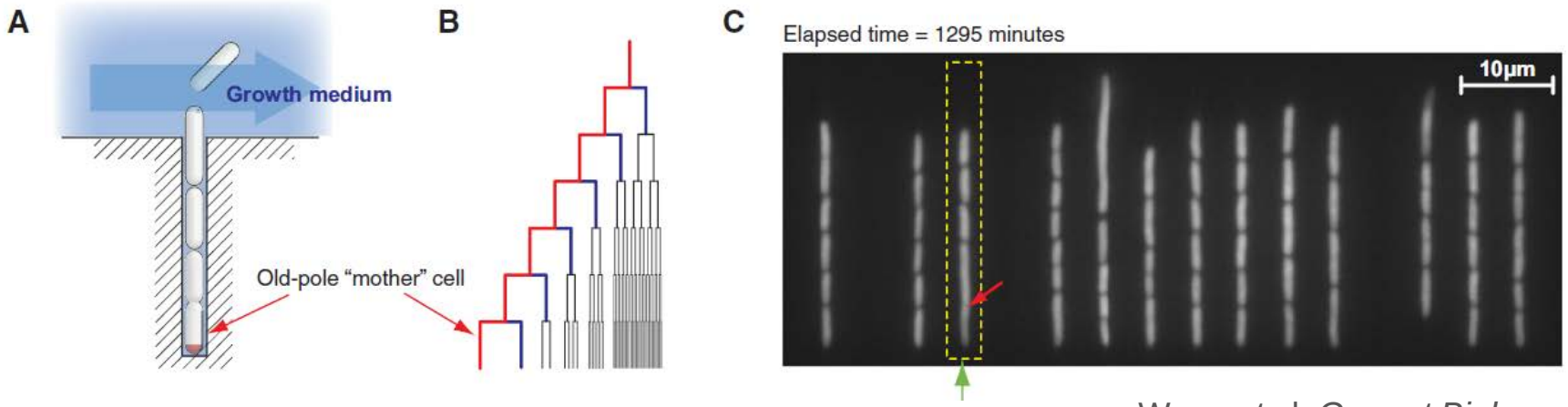
  devise a way of representing biological knowledge that is compatible with the product lifecycle management approach and to develop tools for systemic modelling and simulation of biological data



Integrate computational methods from Biocham into PLMBio platform

Computational biology in the Contraintes group

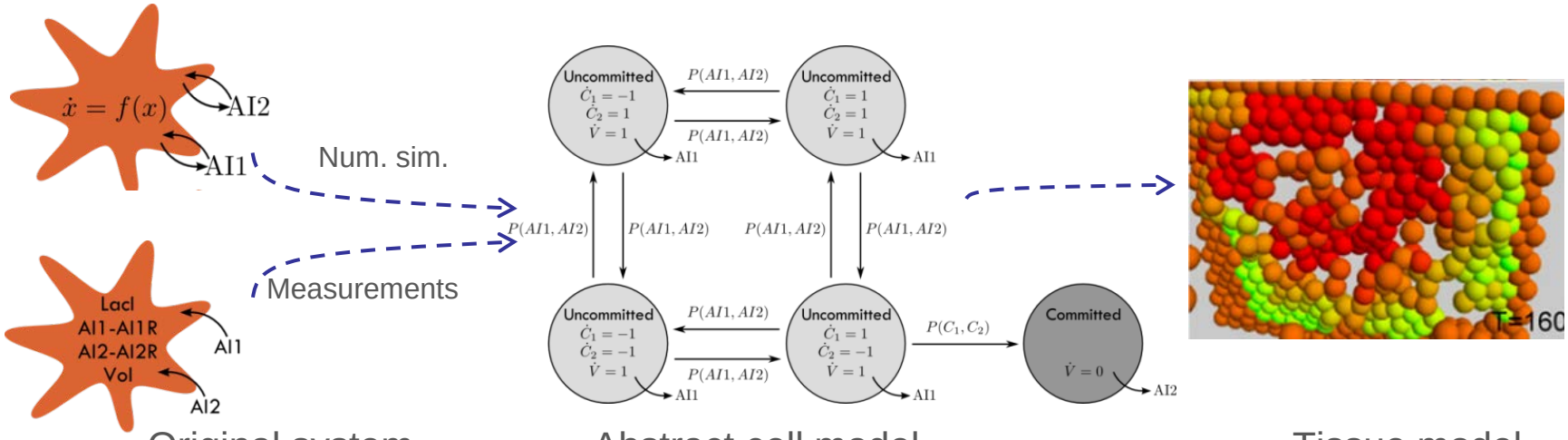
- Biointelligence: "Catia pour la biologie" [Oseo project]
- ColAge: natural and engineering solutions to the control of bacterial growth and aging [INRIA/INSERM Action d'envergure]



Wang *et al*, *Current Biology*, 2010

Computational biology in the Contraintes group

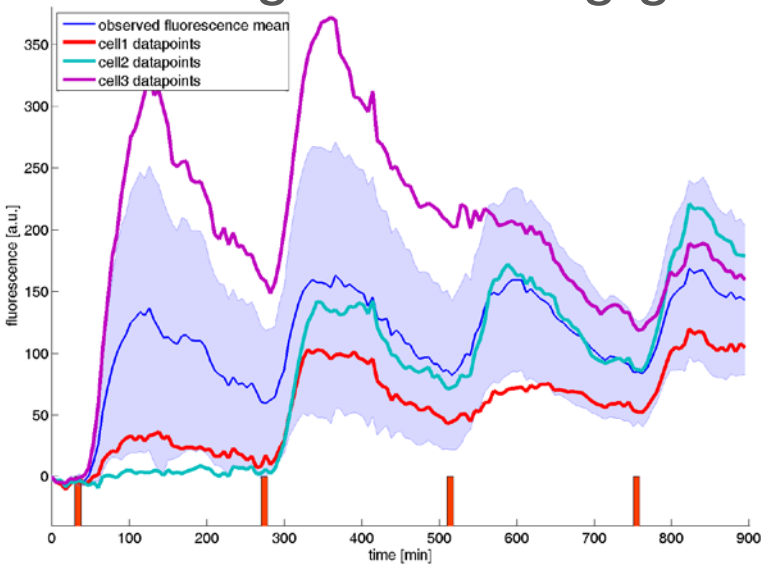
- Biointelligence: "Catia pour la biologie" [Oseo project]
- ColAge: natural and engineering solutions to the control of bacterial growth and aging [INRIA/INSERM Action d'envergure]
- Syne2arti: from synthetic networks to artificial tissues [ANR project]



Original system Abstract cell model Tissue model

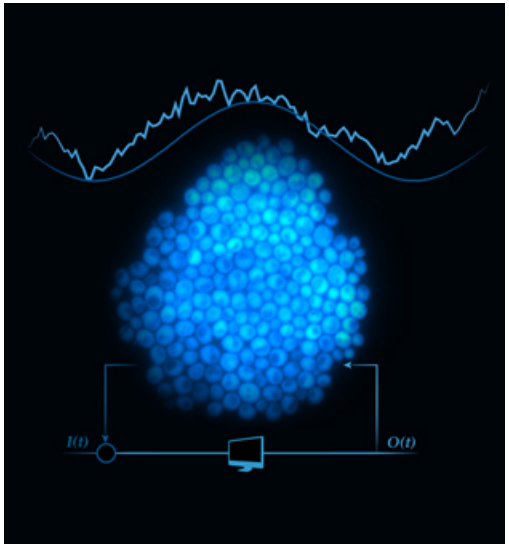
Computational biology in the Contraintes group

- Biointelligence: "Catia pour la biologie" [Oseo project]
- ColAge: natural and engineering solutions to the control of bacterial growth and aging [INRIA/INSERM Action d'envergure]
- Syne2arti: from synthetic networks to artificial tissues [ANR project]
- Iceberg: controlling gene expression [ANR Avenir project]



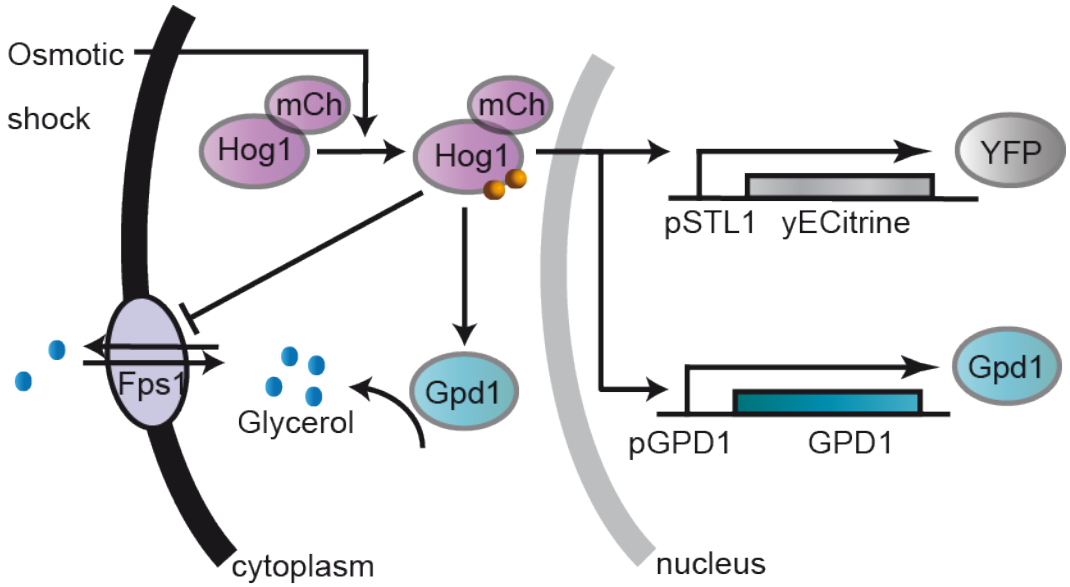
real-time control is needed

from population models to model populations…



Hijacking a natural cellular stress response

- Using natural osmostress response to trigger synthesis of fluorescent protein in yeast



The control plateform

- Control platform must allow for real-time observation, input computation and actuation on cell environment

  Integrates microfluidic, microscopy and software elements

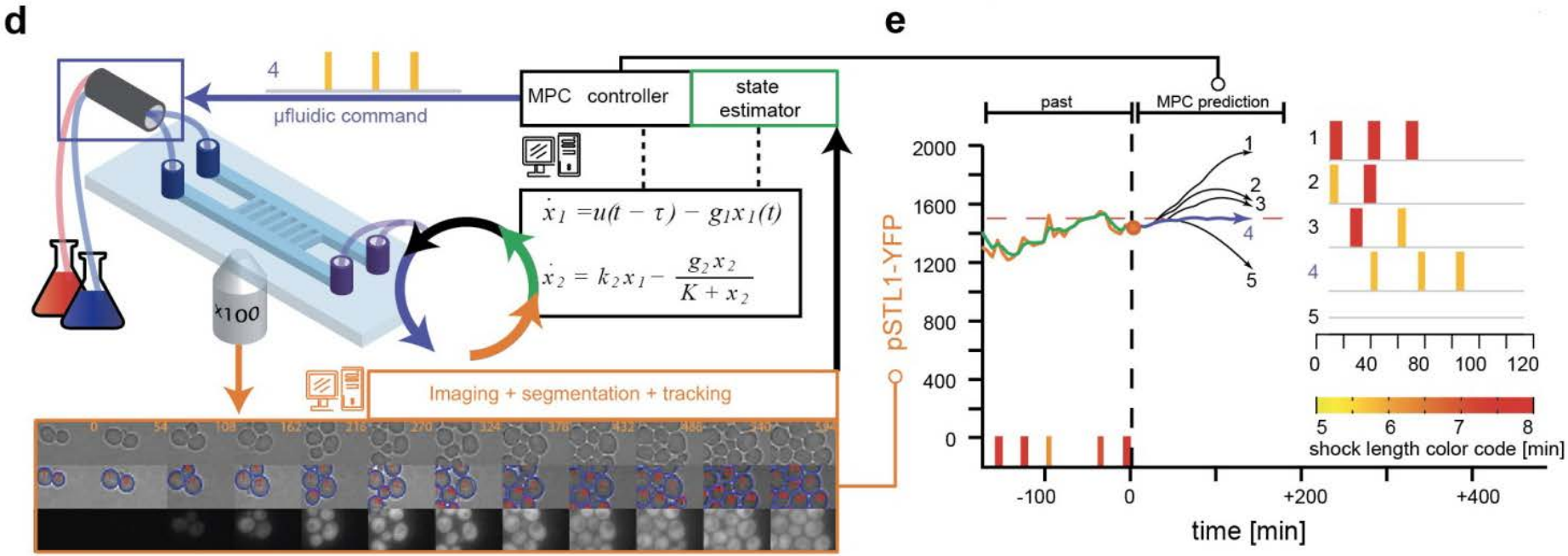
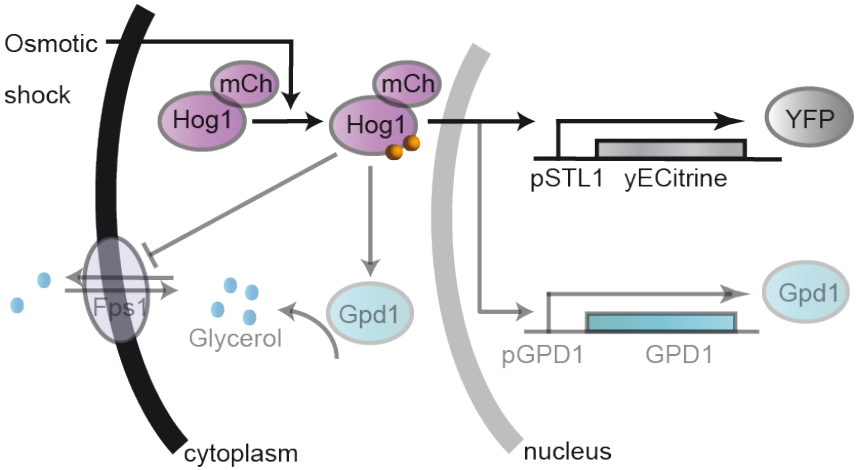


image analysis, state estimation, MPC using constrained global optimization for stress times and durations

Uhlendorf *et al*, *PNAS*, 2012

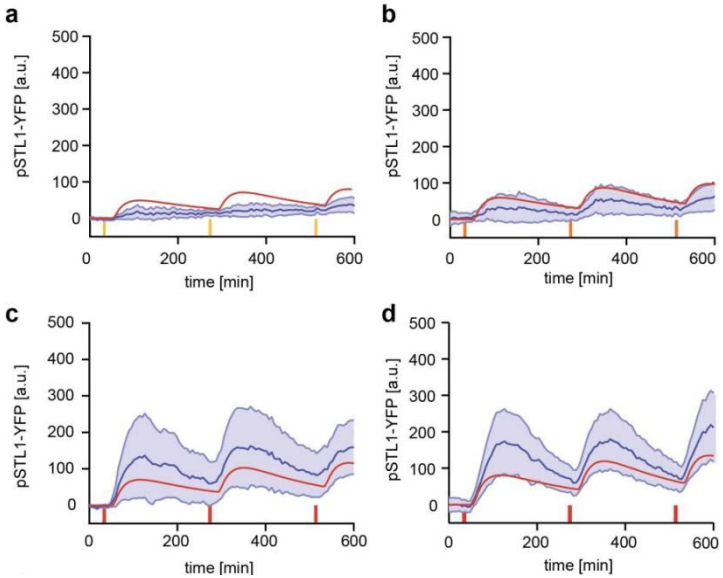
Modeling the system and calibration experiments

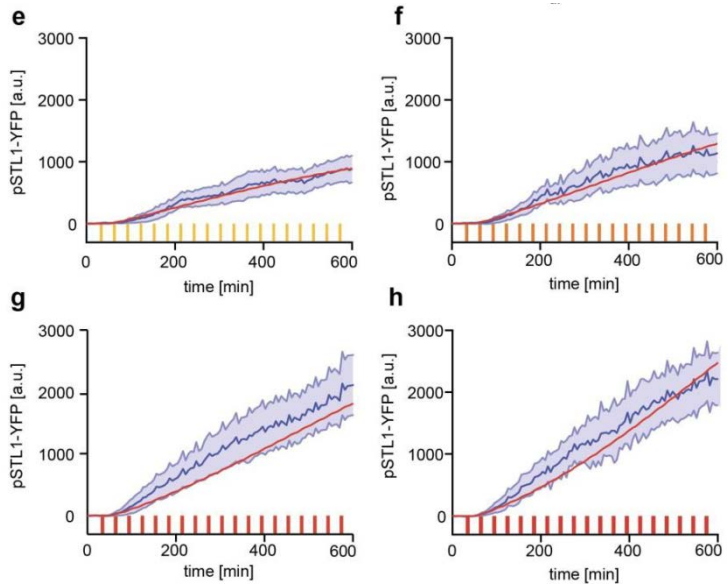


$$\dot{x}_1 = u(t-\tau) - g_1 x_1$$

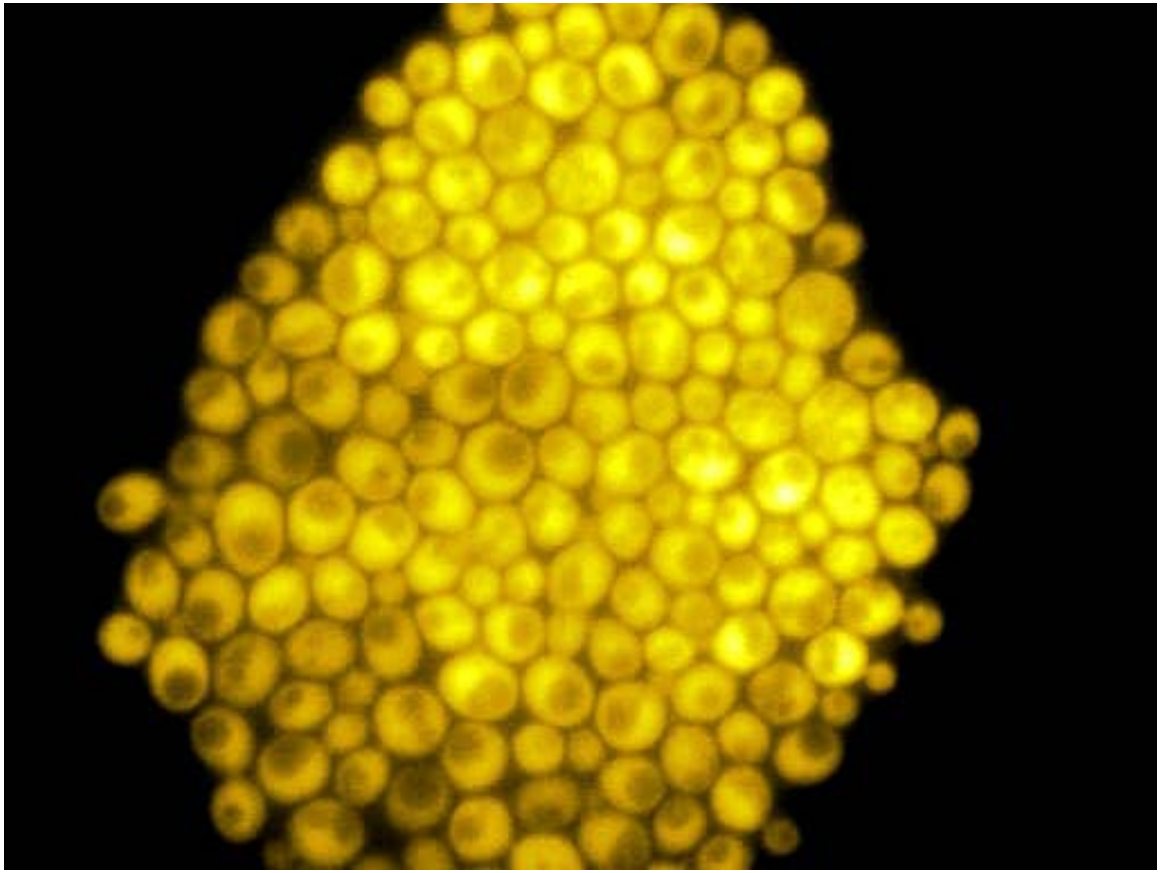
$$\dot{x}_2 = k_2 x_1 - g_2 \frac{x_2}{K + x_2}$$

x_1 recent osmotic stress felt by cell
x_2 protein fluorescence level
u osmolarity in imaging chamber





Controlling gene expression at population level



Joint work with Pascal Hersen (MSC lab)

Controlling gene expression at population level

SM 2 : Real time yeast population control to a sine wave target profile

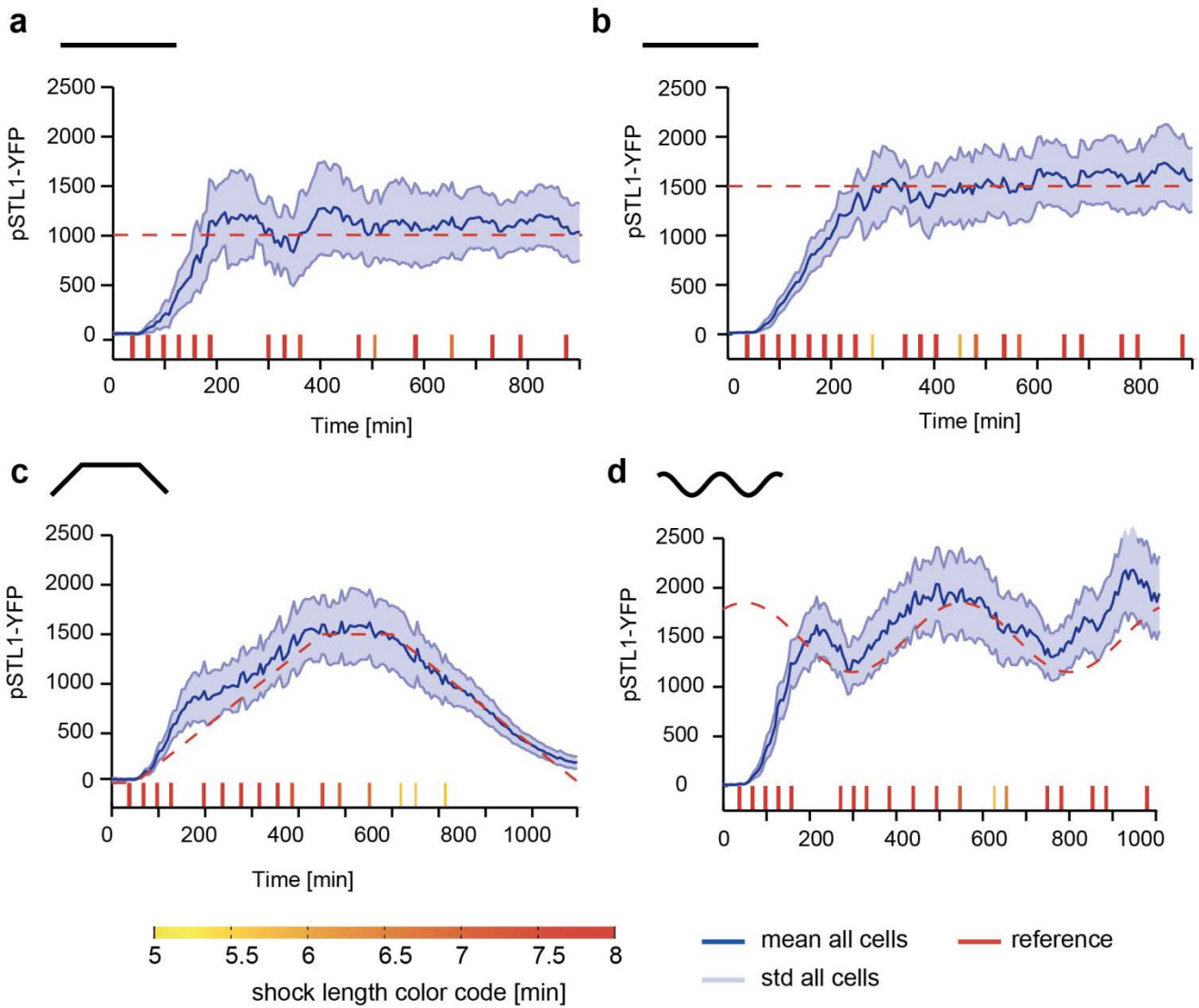
Long-term model predictive control of gene expression at the population and single-cell levels

J. Ulhendorf, A. Miermont, T. Delaveau, G. Charvin, F. Fages, S. Bottani, G. Batt* & P. Hersen*

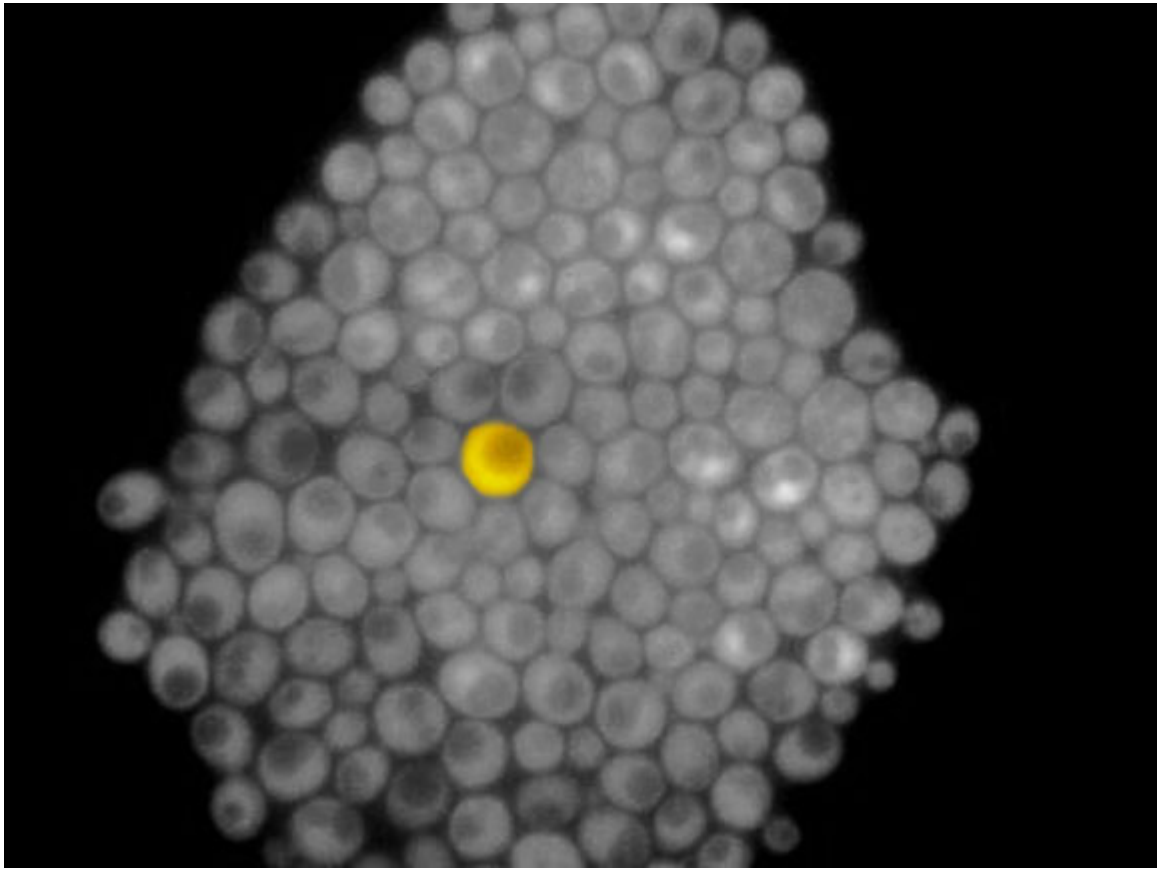
pascal.hersen@univ-paris-diderot.fr http://tinyurl.com/TeamHersen

gregory.batt@inria.f http://www-rocq.inria.fr/~batt/

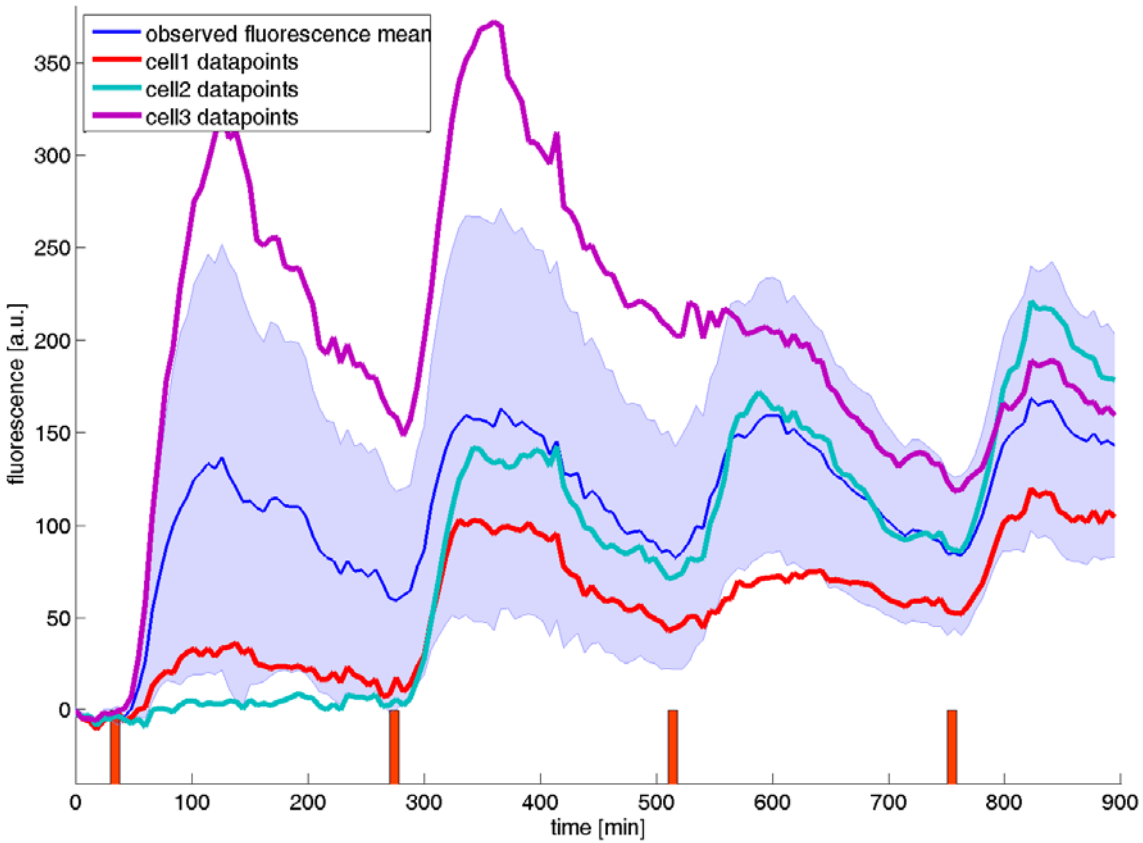
Controlling gene expression at population level



Controlling gene expression at single cell level



Controlling gene expression at single cell level



- Challenge for control: gene expression shows significant levels of stochasticity!

Controlling gene expression at single cell level

SM 6 : Real time yeast single cell control to a sine wave target profile

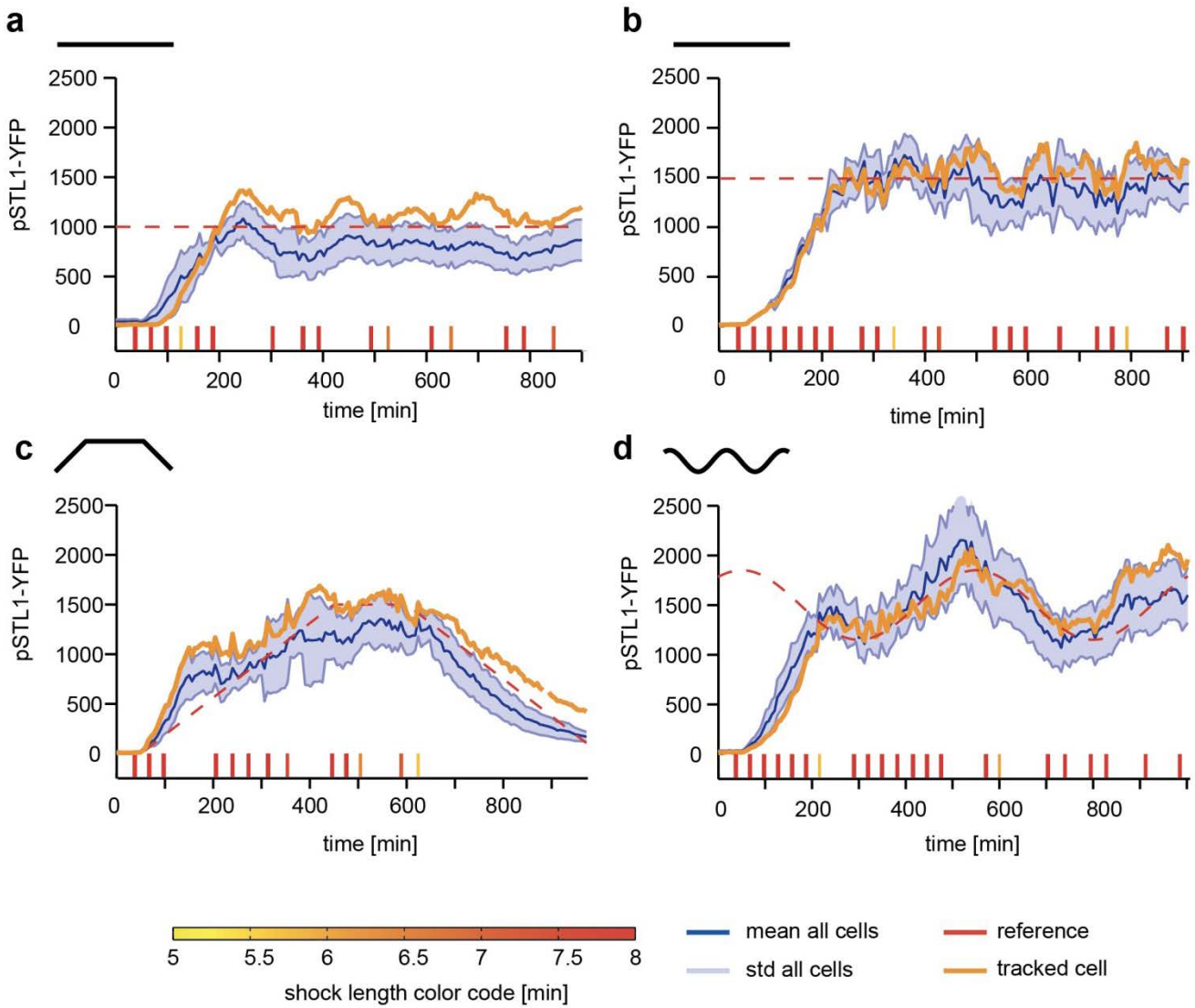
Long-term model predictive control of gene expression at the population and single-cell levels

J. Ulhendorf, A. Miermont, T. Delaveau, G. Charvin, F. Fages, S. Bottani, G. Batt* & P. Hersen*

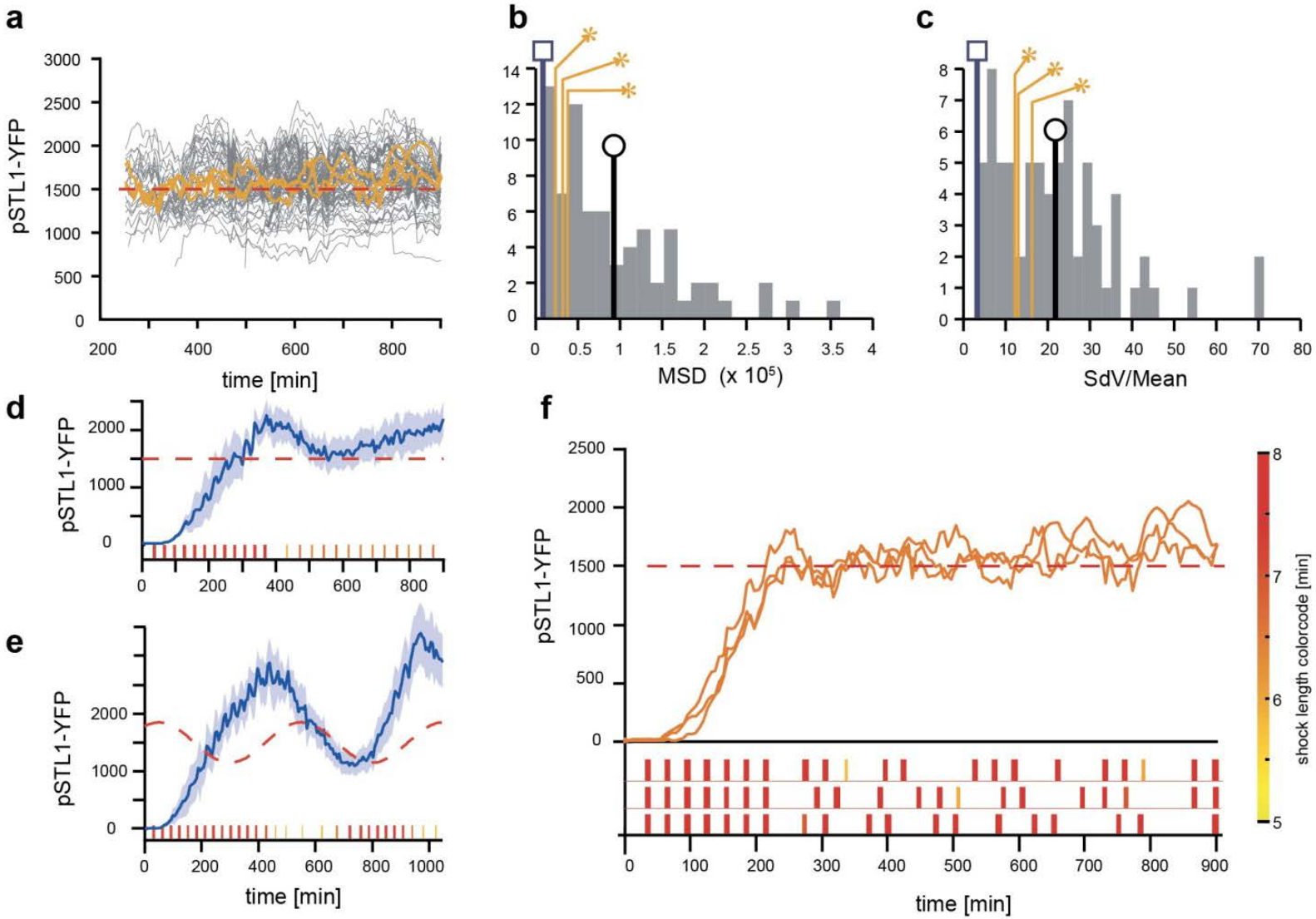
pascal.hersen@univ-paris-diderot.fr http://tinyurl.com/TeamHersen

gregory.batt@inria.f http://www-rocq.inria.fr/~batt/

Controlling gene expression at single cell level



Control quality, noise, and model performances



Conclusions

- Computational biology: numerical approaches for life sciences

  Broader than traditional bioinformatics; one of the main objectives of INRIA

- Computational sciences support design, analysis and optimization of engineered complex systems

  Should also play a large role for engineering biological systems

- On real-time control of gene expression
  - Will (hopefully) result in a platform useful for the biologists in practice
  - Raises several interesting scientific questions in quantitative biology

Acknowledgments

Thank you for your attention

Thanks to

- Pascal Hersen, Francois Fages, Dirk Drasdo, Ron Weiss
- Jannis Uhlendorf, Xavier Duportet, Francois Bertaux, Jean-Baptiste Lugagne, Artemis Llarmosi, Szymon Stoma
- Julianne Rieders, Aishah Prastowo, Joe Schaul, Hugues Asofa

… and also to INRIA and ANR (Syne2Arti and Iceberg) for support