Computational approaches for synthetic biology

- Design, optimization and control

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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

*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
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- Model-based design and optimization of synthetic circuits
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
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
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- 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 platform

- 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

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INRIA
Controlling gene expression at population level

![Graphs showing gene expression over time](image-url)
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

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Controlling gene expression at single cell level

![Graphs illustrating gene expression dynamics over time](image)
Control quality, noise, and model performances

(a) Time course of pSTL1-YFP over 800 minutes.
(b) Graph showing MSD (mean square displacement) values over 4 units of time.
(c) Graph showing SdV/Mean values over 80 minutes.
(d) Time course of pSTL1-YFP over 1000 minutes.
(e) Time course of pSTL1-YFP over 1000 minutes with a different scale for the y-axis.
(f) Time course of pSTL1-YFP with a color code indicating shock length.
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