Rule-based Modeling in Systems Biology

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- Better than simulation: model-checking, temporal logic constraints
  - Formalizing experimental observations with temporal logic formulae
  - Query language for all possible behaviors in CTL
  - Continuous satisfaction degree in [0,1] of LTL(R) properties
  - Parameter inference, robustness, sensitivity analyses w.r.t. LTL(R) spec

Conclusion

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- Synthetic Biology
  - Program the living with programming tools
  - Computational design and optimization tools

References

- I will put the slides on my web page (papers available)
  http://contraintes.inria.fr/~fages/BioTeaching
- Biocham 3.1 http://contraintes.inria.fr/Biocham
- S. Gay, S. Soliman, F. Fages A graphical method for reducing and relating models. *ECCB 10, Bioinformatics 2010.*
- F. Fages and S. Soliman. From reaction models to influence graphs and back: a theorem *Formal Methods in Systems Biology*, Springer-Verlag, Lecture Notes in Bioinformatics, LNBI 5054. June 2008

- F. Fages and S. Soliman. Abstract Interpretation and Types for Systems Biology. *Theoretical Computer Science* 403, pp.52-70, 2008

- A. Rizk, G. Batt, F. Fages, S. Soliman. A computational method for robustness analysis. *ISMB 09, Bioinformatics 2009.*
- A. Rizk, G. Batt, F. Fages, S. Soliman.On a continuous satisfaction degree and for temporal logic formulae applications to systems biology. CMSB 08, Springer Verlag LNCS 2008.

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" EraSysBio C5Sys (follow up of FP6 Tempo) on cancer chronotherapies, coord. *Francis Lévi*, INSERM; *Jean Clairambault* INRIA; &

Coupled models of cell and circadian cycles, p53/mdm2, cytotoxic drugs.

" INRIA/INRA project Regate coord. *F. Clément* INRIA; *E. Reiter, D. Heitzler*

Models of GPCR Angiotensine and FSH signaling.

" ANR project Calamar, coord. *C. Chaouiya, D. Thieffry* Univ. Marseille, *L. Calzone* Curie Institute

Modularity and Compositionality in regulatory networks.