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Construction of a probabilistic boolean model of iron homeostasis in yeast : a tool to decipher the molecular basis of pathogenesis

ABSTRACT

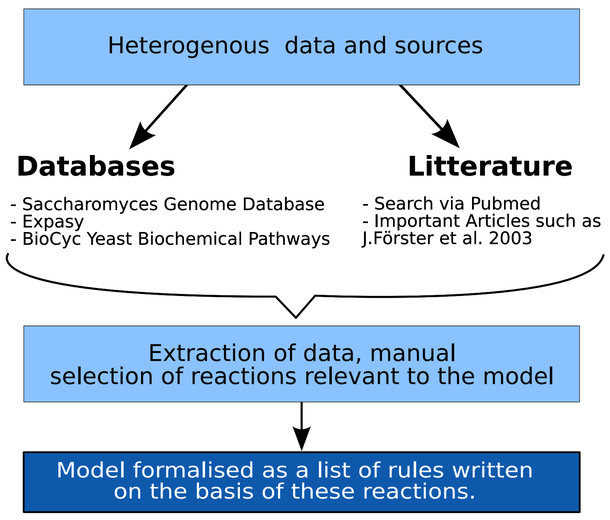
Iron homeostasis is tightly regulated at every levels in organisms. Its deregulation leads to a wide range of diseases[2] such as Friedreich Ataxia (FA), a human recessive genetic disease due to a deficiency in frataxin : a mitochondrial protein involved in iron homeostasis but whose precise function is still unknown. Appropriate iron supply is critical for cell survival but the consequences of its deregulation are still poorly understood. We focus on a simple eukaryote unicellular system, the yeast *Saccharomyces cerevisiae*, which has an homolog (YFH1) of the frataxin gene and a mutant available. To this day, no formal model of iron homeostasis is available yet. Therefore we constructed a probabilistic Boolean model of iron regulation in yeast taking into account diverse and heterogeneous data.

1 Choosing a type of model

We want the model to include:
- different types of elements: genes, proteins, metabolites, ions, cofactors
- different levels of regulation: genes, metabolism and biochemical components
- several cellular compartments
- different levels of knownledge: from well-known metabolic reactions to still questionnable ones such as iron-sulfur clusters synthesis

Thus, the model includes a large amount of qualitative data leading us to choose a boolean formalism. This model is probabilistic and asynchrone (see Simulation program).

2 Model building



Exemple : Fe2::extracellular =[Fet4p::cytoplasm]=> Fe2::cytoplasm

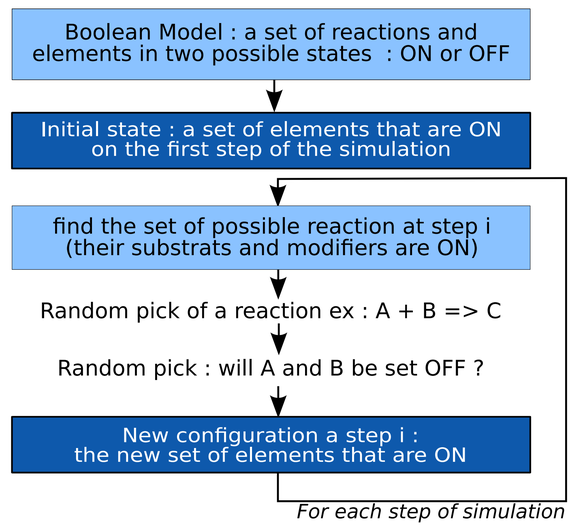
3 Model Overview

- 469 Elements: 176 genes, 199 proteins and protein complexes, 76 others chemical components and metabolites, 18 unlimited elements (always ON)
- 786 Reactions:
  - 155 Genes transcription/traduction
  - 30 Transcription/Traduction under some condition
  - 80 Translocation of elements between compartments
  - 36 Protein complexes synthesis/Cofactor binging
  - 14 Transcription factor change of compartment
  - 34 Active transport of element
  - 16 Sulfur metabolism
  - 22 Heme/FeS/PLP Synthesis
  - 2 Glutathion synthesis
  - 52 ATP synthesis
  - 17 Oxidative stress
  - 298 Elements degradation
- 5 Compartments: extracellular space, cytosol, nucleus, mitochondrion (as one space), vacuol.

$=>$ 2^{469} possible states $=>$ standard boolean model analysis tools unusable. This model was validated by a biologist specialist of iron homeostasis in yeast and by coherence with experimental phenotypes.

4 Simulation Program

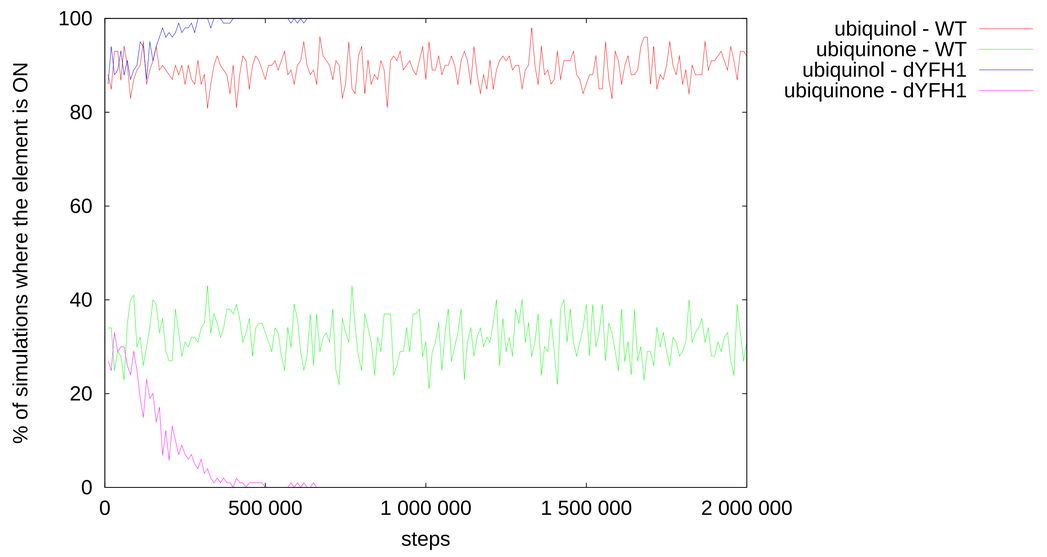
The simulation program uses an algorithm by Calzone et al [1].



Time needed to perform one simulation of 5 millions steps : 1 hour.
Size of the output file : 84 Mo (using a condensed format specially designed for this purpose).

5 Results : An Exemple

For one initial state, the model is currently simulated 100 times. Then, for each element, we compute the percentage of simulation where this element is present for each step. Here, we compare the evolution of the presence of ubiquinol and ubiquinone in the standard model (where all element is present at step 0) to the model without the gene YFH1.



Evolution of the presence of ubiquinol and ubiquinone with and without YFH1.
Note that the only traitement for FA is a quinone: coherence with observations in patients.

6 Perspectives

- Mutations *in silico*: finding mutations with similar effects.
- Initial state modifications
- Definition of the set of conserved reactions between yeast and human
- Construction of a version of the model appropriate to human iron homeostasis

References

[1] L. Calzone, F. Fages, and S. Soliman. Biocham: an environment for modeling biological systems and formalizing experimental knowledge. *Bioinformatics*, 22:1805–1807, July 2006.
[2] E. L. MacKenzie, K. Iwasaki, and Y. Tsuji. Intracellular iron transport and storage: from molecular mechanisms to health implications. *Antioxidants & Redox Signaling*, 10:997–1030, June 2008. PMID: 18327971.

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