

# A model of homeostatic regulation: Copper flux control in *Enterococcus Hirae*

Elisabeth Pécou

Laboratoire J.-A. Dieudonné  
Université de Nice-Sophia Antipolis

Theoretical Approaches of the Genome, 2006

E. Pécou, A. Maass, D. Remenik, J. Briche, M. Gonzales, *Math. Biosciences* 203 (2006), 222-239

- 1 Biological Frame**
  - Copper
  - *E.Hirae* copper homeostasis system
- 2 Mathematical Frame**
  - Motivations
  - General setting
- 3 The Model**
  - Metabolic pathway
  - Genetic regulation
  - Global picture
- 4 Conclusion**

# Outline

## 1 Biological Frame

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# Copper homeostasis

## Problem

- Copper is an essential micronutrient both for eucaryotes and procaryotes. It mediates electron transport by cycling between  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  in biological redox reactions.
- Copper is toxic (It products hydroxyl radicals).
- Living systems have developped molecular mechanisms for the safe management of copper.

## Comments

The avidity with which  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  bind to biomolecules makes it difficult to measure experimentaly the inside concentration of copper.

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## Comments

In humans, **Wilson disease** is caused by a genetic fault which induces the accumulation of copper inside the liver.

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## Comments

Copper is used in agriculture against bacterial and fungal diseases on crops (ex: grapes).

# Copper homeostasis

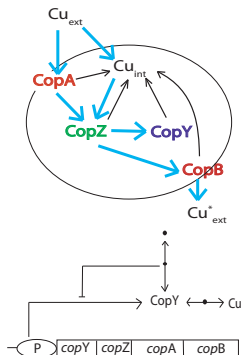
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## Comments

The copper homeostasis system in *E. Hirae* is the best understood procaryotic mechanism for copper management (*Marc Solioz and co-workers*).

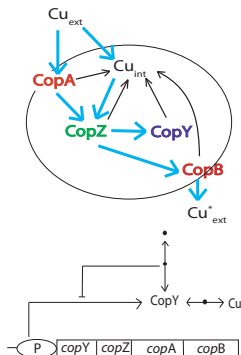
# A microbial model system



## Description

- 1 Homeostasis is controlled at the genetic level.
- 2 *E. Hirae* can grow in a wide range of ambiental copper concentration: from copper limiting conditions to 8mM.

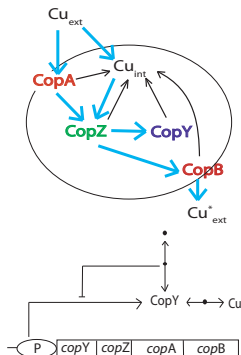
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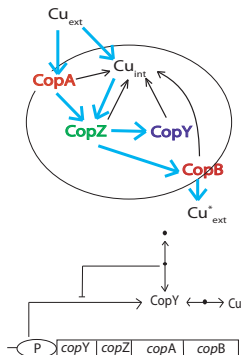


## Description

4 proteins are involved:

- two membrane ATPases **CopA** and **CopB**, in charge of copper uptake and extrusion respectively.
- one chaperone, **CopZ**, for intracellular copper routing.
- one copper-responsive genetic repressor **CopY**.

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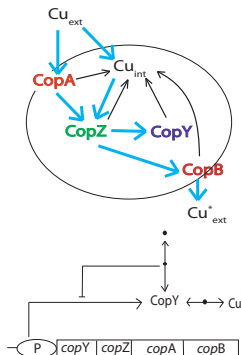


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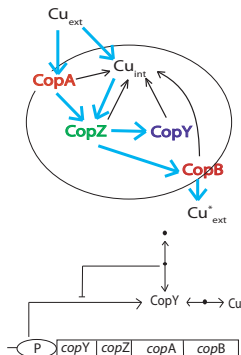


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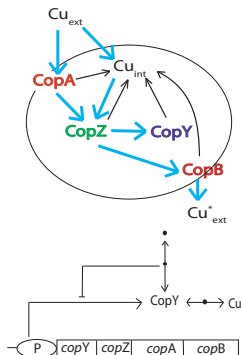
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# Motivations for a mathematical model

- Test the coherence of the biological description: have a global, quantitative picture of the system.
- Identify the minimal structure which ensures homeostasis (lowest number of variables, parameters, hypotheses).
- Propose an analysis and simulation tool for further biological investigation.

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# General Setting for the mathematical model

## Formalism

- 1 We use the differential equation formalism.
- 2 We mainly use polynomial equations, simply based on mass action law of chemical reactions.
- 3 In order to focus on the *cop*-operon system, we do not take into account the metabolic activity of internal copper independent of *cop*-operon.

## Comments

To deal with stochastic effect possibly involved by the sparse number of genes, we assume that the system is a **population** of cells and the variables account for a mean behavior.

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## Comments

Law of Mass Action: given  $\alpha A + \beta B \longrightarrow P + Q$ , the rate of the reaction is:

$$\frac{dP}{dt} = k \cdot A^\alpha \cdot B^\beta.$$

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## Comments

This is possible when mechanisms can be described as a set of simple chemical reactions. When the biological information is missing, other types of function might be used.

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## Comments

For this purpose, we introduce a variable  $Cu_{int}$  which represents all copper contained in the cells, and not bound to a Cop protein and we suppose that this variable is not affected by any reaction which does not involve a Cop protein.

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# Copper uptake

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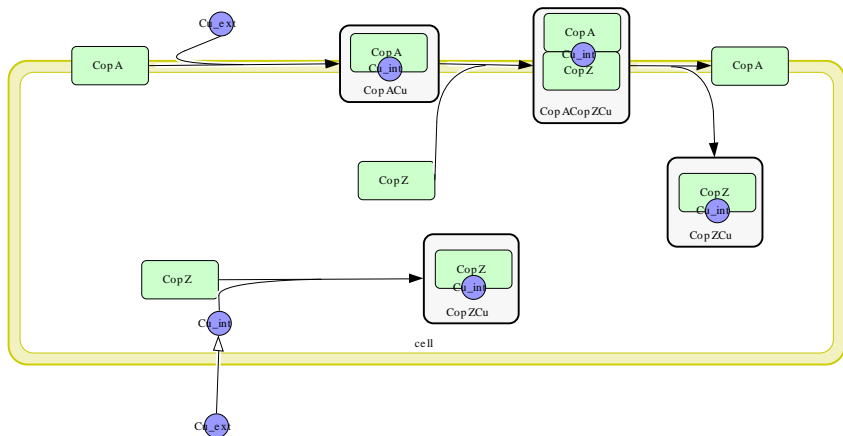
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Metabolic pathway

# Representation with CellDesigner™

(<http://celldesigner.org>)



# Copper transfer to CopY

## description

- 1 CopY naturally forms a homodimer CopY<sub>2</sub>.
- 2 The complex CopZCu transfers copper to CopY, presumably by direct protein-protein interaction.



- 3 Without available copper, CopY<sub>2</sub> binds to the promoter region of the *cop*-operon. It is thought that CopZCu can again transfer copper to the complex OCopY<sub>2</sub>, with consequence the release of (CopYCu<sub>2</sub>)<sub>2</sub> from the promotor site.

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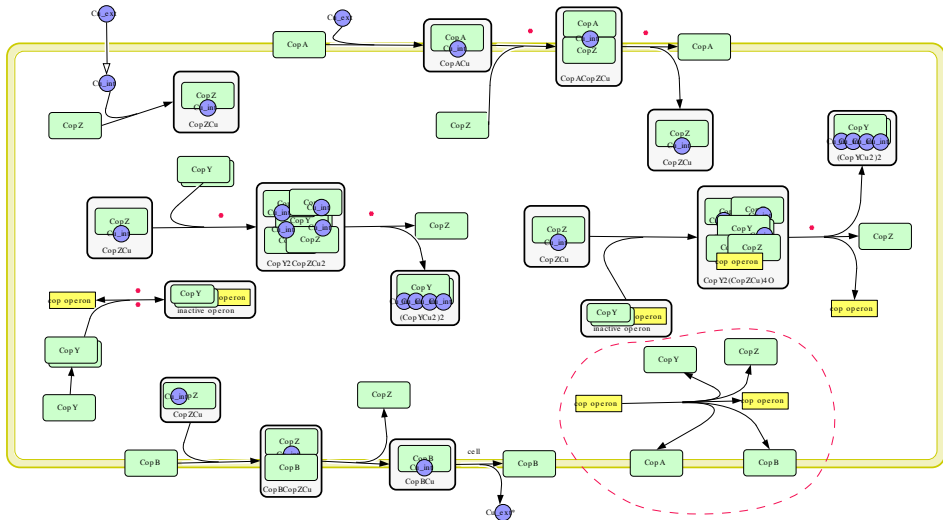
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# Mathematical homeostasis

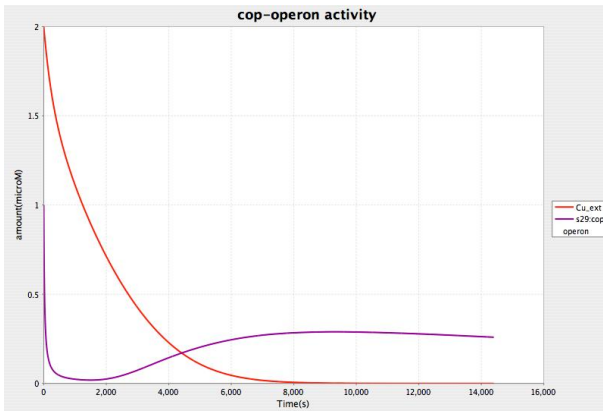
## Definition

A parameter-dependent system  $S(p)$  is **homeostatic** with respect to a variable  $x$  if there exist  $x_0$  *independent* of  $p$ , such that  $x(t) \rightarrow x_0$  when  $t \rightarrow +\infty$ .

## Theorem

The *E. hirae* is homeostatic with respect to internal copper. The asymptotic value of internal copper is 0, whatever are the parameters.

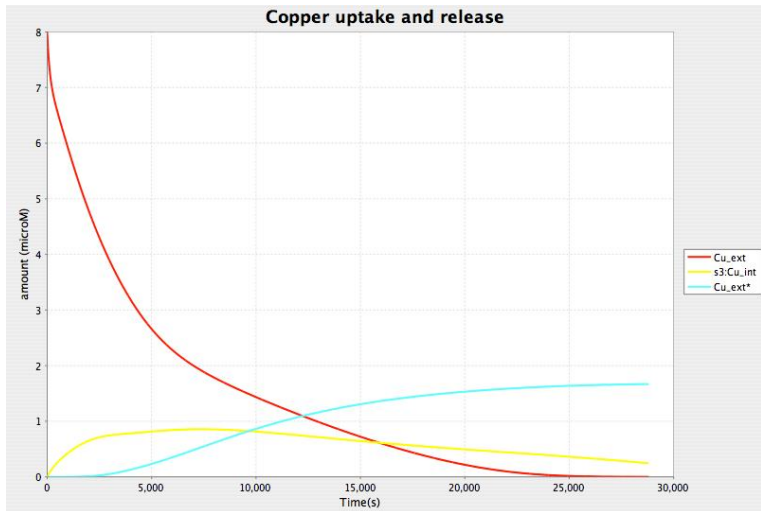
# Genetic activity



**Figure:** Operon activity as external copper is loaded

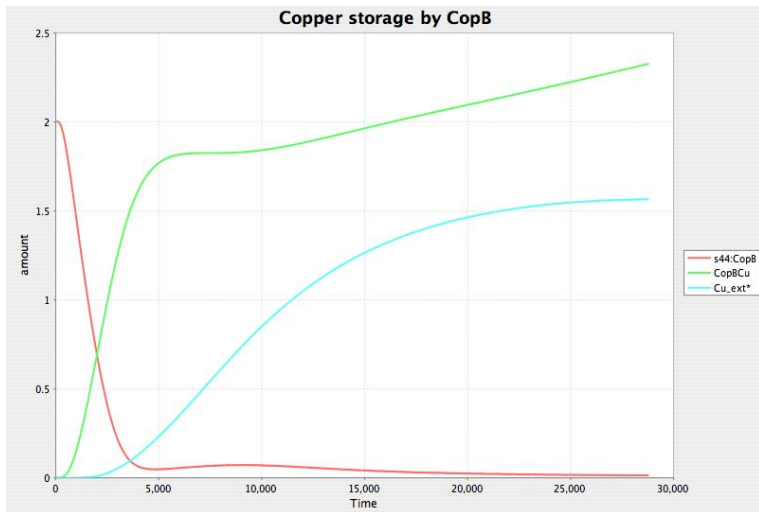
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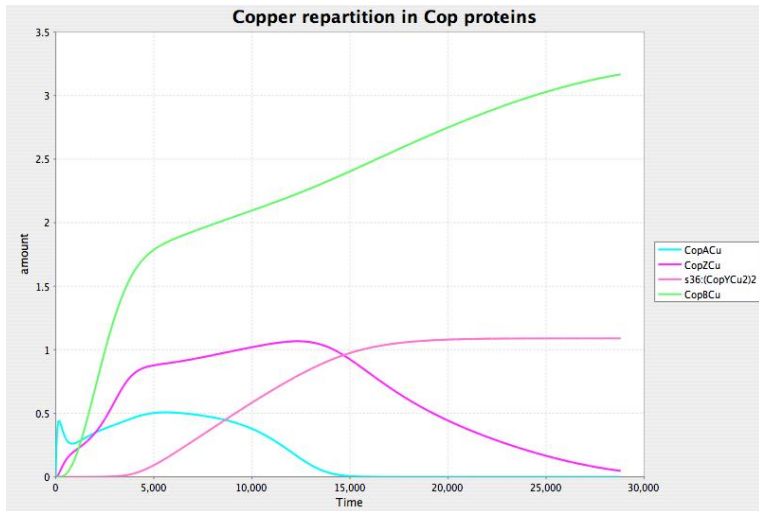
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# Copper storage by CopB



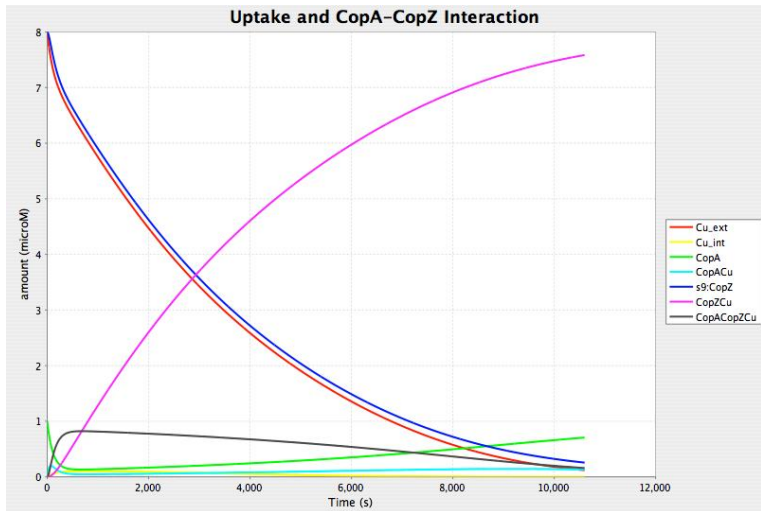
Global picture

# Copper Repartition



Global picture

# Dynamics



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# Conclusion

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- 1 Fix a range for unknown parameter values;
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