

# Comparative analysis for noise propagation in a coarse-grained model linking metabolism to cellular growth

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Biomatematica – Parte III

## Motivation - Metabolic noise

- The term **metabolism** denotes the set of biochemical reactions responsible for maintaining the living state of cells and organisms

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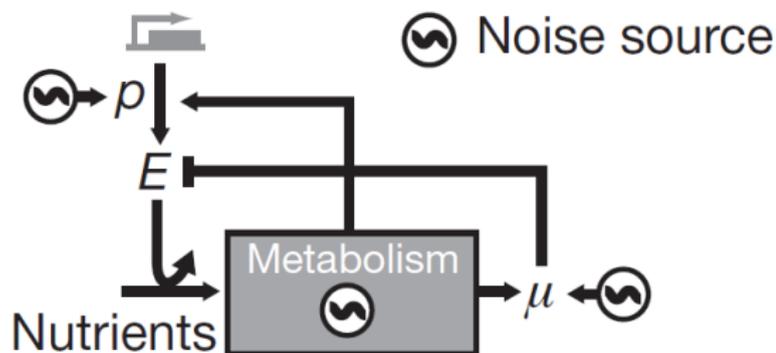
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- Most literature so far neglects the **propagation of molecular stochasticity** from the enzymatic to the metabolic level (because of their averaging over the great deal of reactions involved in metabolic networks)

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- Most literature so far neglects the **propagation of molecular stochasticity** from the enzymatic to the metabolic level (because of their averaging over the great deal of reactions involved in metabolic networks)
- Instead, recent single-cell investigations have highlighted how **fluctuations in gene expression and enzymes may affect**, in terms of metabolic noise, resource allocation, fluxes, as well as the **rate of cellular growth**

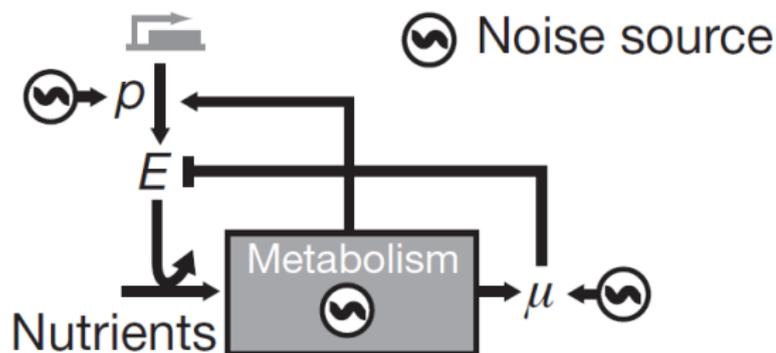
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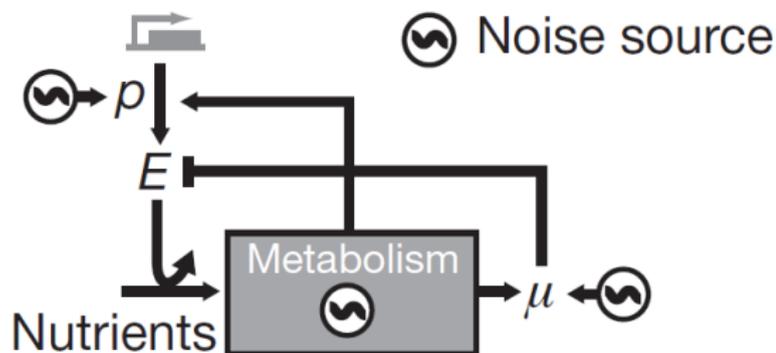
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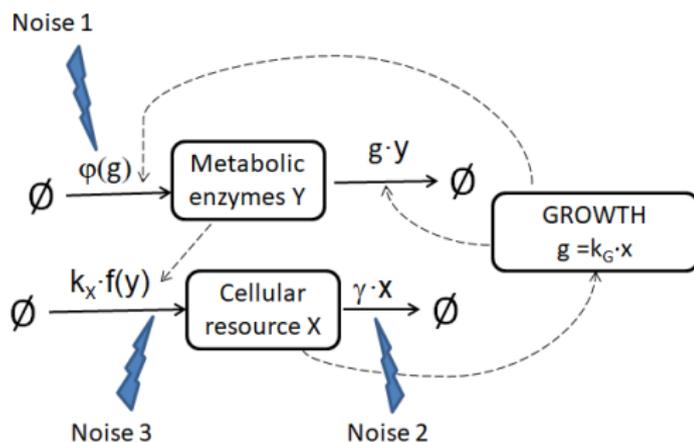
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- In [Borri et al, CDC2018] we proposed a model detailing 1 such noise source providing similar results
- Here we substantially extended the model to include different noise sources and (possibly) suggest new experiments

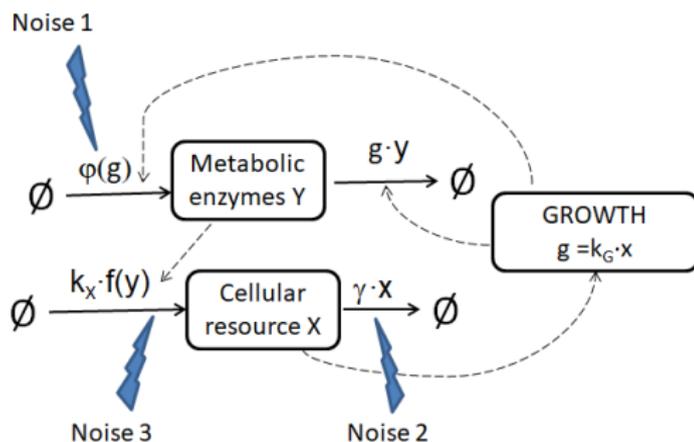
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- Different noise sources are modeled in different ways. When dealt with in a discrete fashion, a [Stochastic Hybrid System \(SHS\)](#) is exploited: between any two discrete resets, the remaining dynamics evolves according to an Ordinary Differential Equation (ODE)

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- SHS models, entailing both continuous and discrete events, are usually preferred to purely discrete Chemical Master Equations (CMEs) because of their lower complexity, in particular when the **bursty production is dominant with respect to the other reactions**, e.g. because of a large average burst size

## Methods

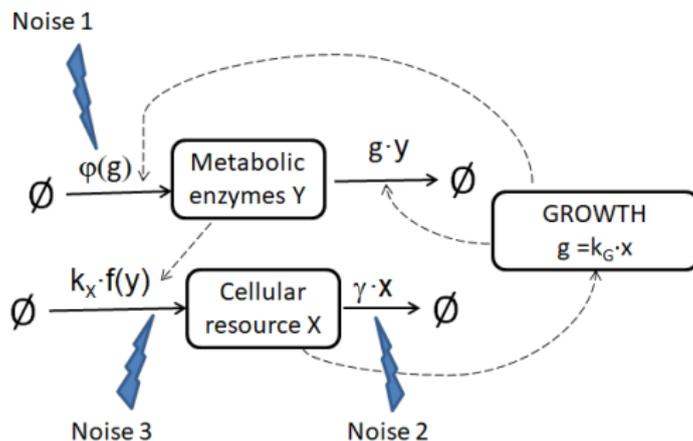
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- Model nonlinearities are linearized in order to have analytical expressions
- Approximated analytical results are validated by Monte Carlo random paths simulations, carried out by properly implementing the  $\tau$ -leap version of the Gillespie algorithm

## Model setting

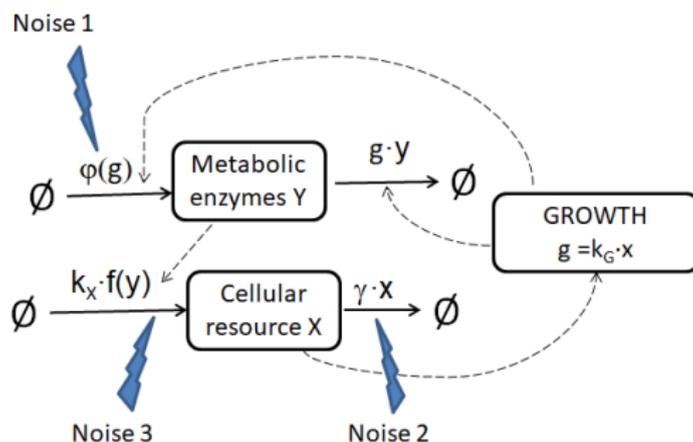


- $x$  and  $y$  are the **copy numbers** of the molecular players  $X$  and  $Y$
- $X$  stands for a **cellular resource** whose accumulation linearly modulates the **growth rate**:

$$g(\mathbf{x}) = k_G \mathbf{x}.$$

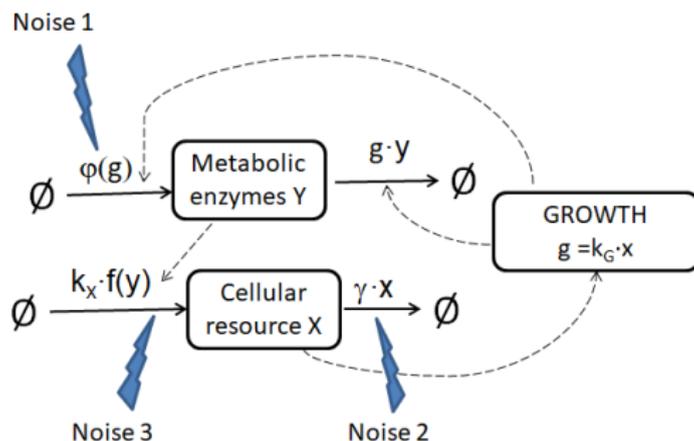
- $Y$  represents the accumulation of a set of metabolic **enzymes**.

## Model setting



- $X$  exerts an **incoherent feedforward control** on  $Y$  by means of the growth rate  $g(x)$ , which tunes both enzymatic production (via a nonlinear increasing **saturating function**  $\varphi(g)$ ) and degradation, in a linear fashion.

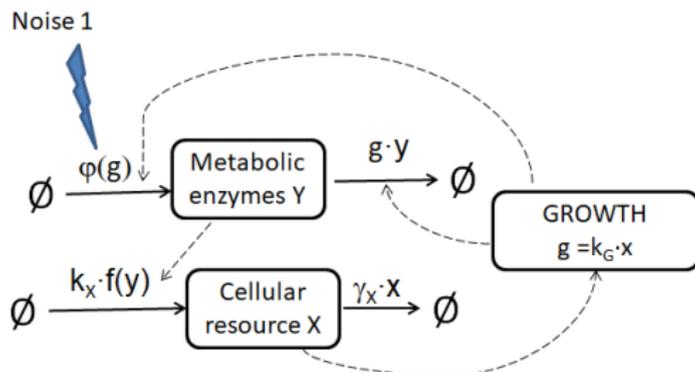
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- On the other hand,  $Y$  is supposed to **control in feedback** the resource  $X$  production rate, according to a nonlinear increasing **saturating function**  $f(y)$ .



## Noise source 1: related to the production of the metabolic enzyme $Y$



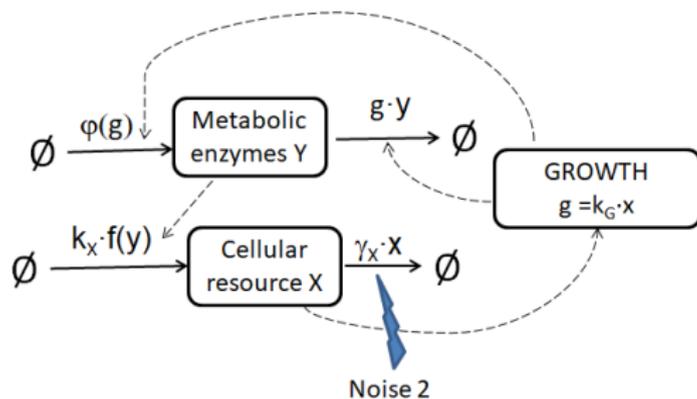
- $\mathbf{y} \mapsto \mathbf{y} + \mathbf{j}$ ,  $j = 1, 2, \dots$  with a propensity

$$a_j(\mathbf{x}) = \varphi_g(\mathbf{x}) \mathbb{P}(\eta = j), \quad \varphi_g(\mathbf{x}) = \varphi(g(\mathbf{x})) = \varphi(k_G \mathbf{x})$$

- Between any 2 bursts events, the system evolves continuously according to an ODE

$$\begin{cases} \dot{\mathbf{x}} &= k_X f(\mathbf{y}) - \gamma_X \mathbf{x} \\ \dot{\mathbf{y}} &= -k_G \mathbf{x} \mathbf{y} \end{cases}$$

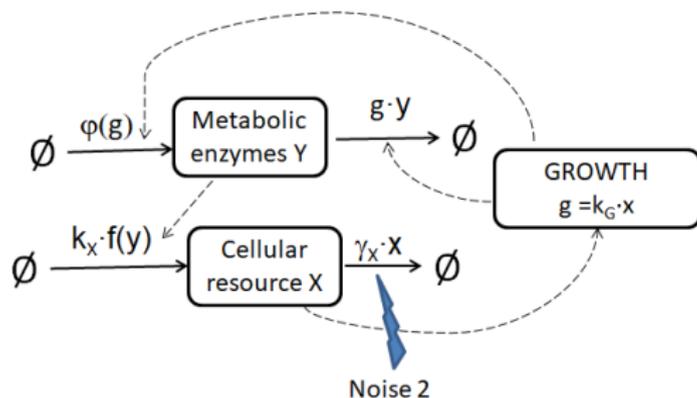
## Noise source 2: related to the clearance of $X$



- $X$  clearance rate is modeled by an Ornstein-Uhlenbeck process

$$d\gamma_{\mathbf{x},t} = \theta(\bar{\gamma}_X - \gamma_{\mathbf{x},t})dt + \sigma dW_t$$

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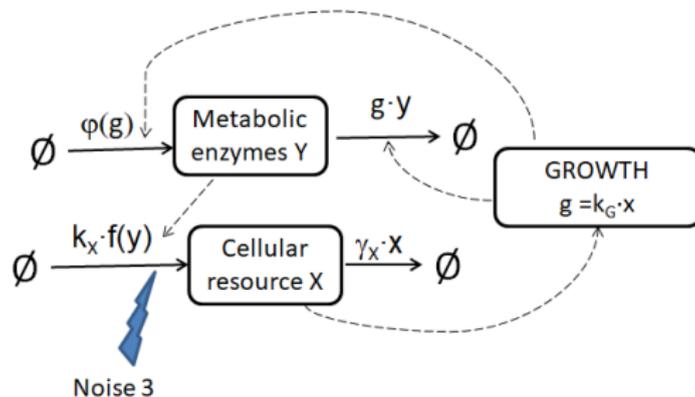
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$$\begin{cases} d\mathbf{x}_t &= k_X f(\mathbf{y}_t)dt - \gamma_{X,t} \mathbf{x}_t dt \\ d\gamma_{X,t} &= \theta(\bar{\gamma}_X - \gamma_{X,t})dt + \sigma dW_t \\ d\mathbf{y}_t &= -k_G \mathbf{x}_t \mathbf{y}_t dt + \bar{\eta} \varphi_g(\mathbf{x}_t) dt \end{cases}$$

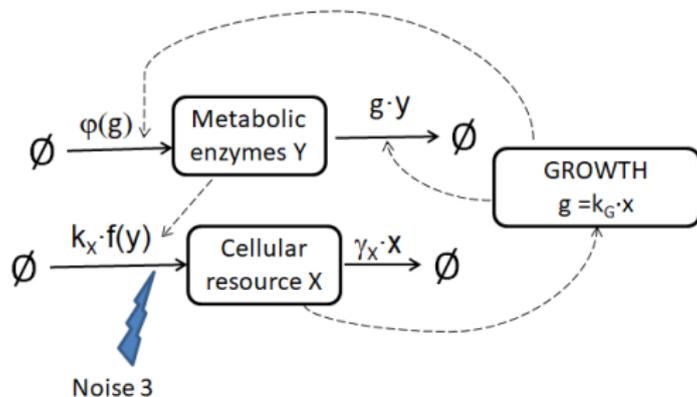
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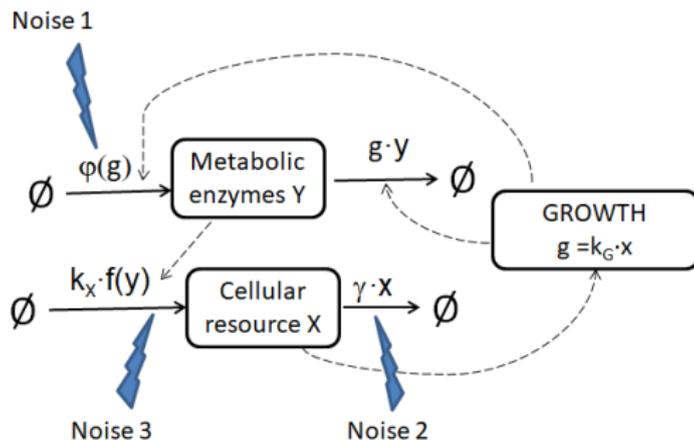
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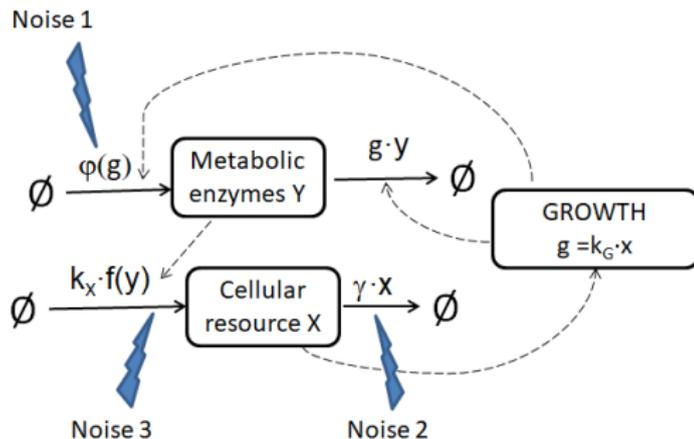
## Main Goal

- Question: do noise fluctuations in the enzyme production propagate to cellular growth, or vice versa?



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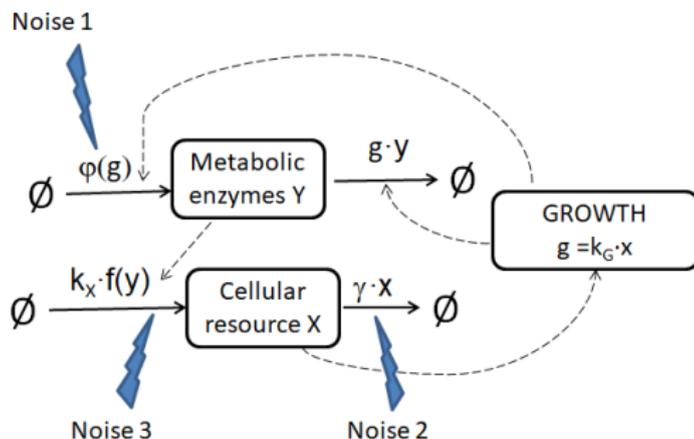


- Idea: exploit stationary second-order moments to compute the **cross-correlation** function between  $\mathbf{y}(t)$  and  $g(t) = g(\mathbf{x}(t))$ :

$$\rho_{yg}(\tau) = \frac{\langle \mathbf{y}(t)g(t + \tau) \rangle - \bar{\mathbf{y}}g(\bar{\mathbf{x}})}{\sigma_Y \sigma_g},$$

where the lag  $\tau \in \mathbb{R}$  describes a **delay related to noise propagation**

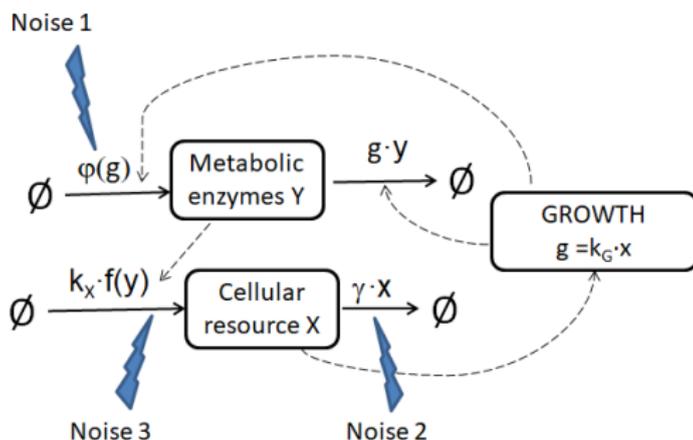
## Model setting



- Nonlinear functions  $f(\cdot)$  and  $\varphi(\cdot)$  set as [Michaelis-Menten](#) functions:

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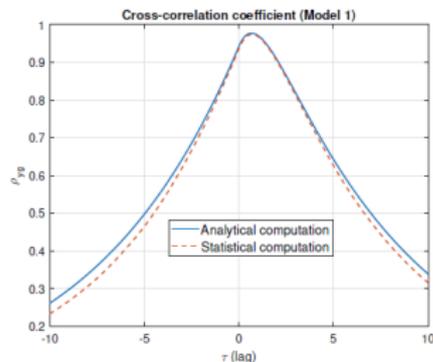
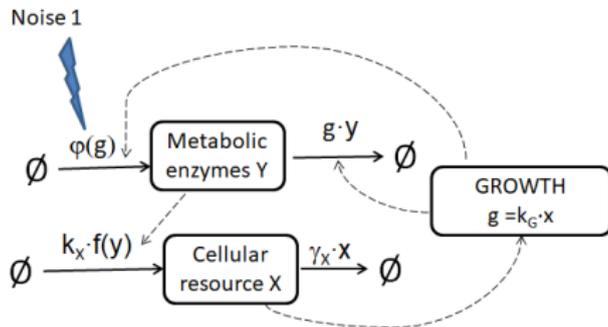
$$f(\mathbf{y}) = \frac{\mathbf{y}}{\mathbf{y} + \theta_F}, \quad \varphi(g) = k_\phi \frac{g}{g + \theta_\phi}.$$

- **Geometric probability distribution** for the bursty  $Y$  production:

$$\mathbb{P}(\eta = j) = (1 - \lambda)^j \lambda, \quad \lambda \in (0, 1], \quad j = 0, 1, \dots$$

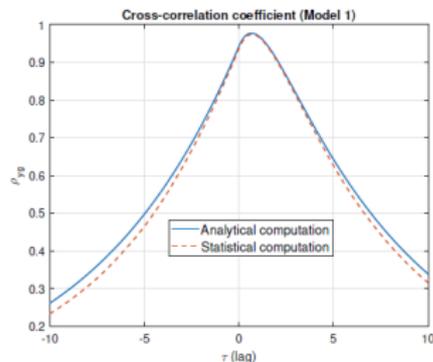
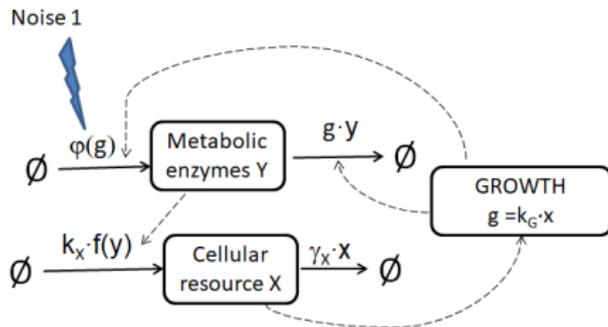
providing an average burst size  $\bar{\eta} = (1 - \lambda)/\lambda$ .

## Main results: Noise source 1



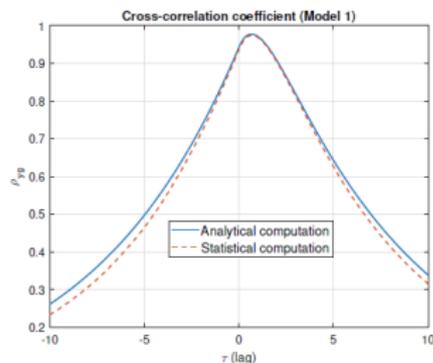
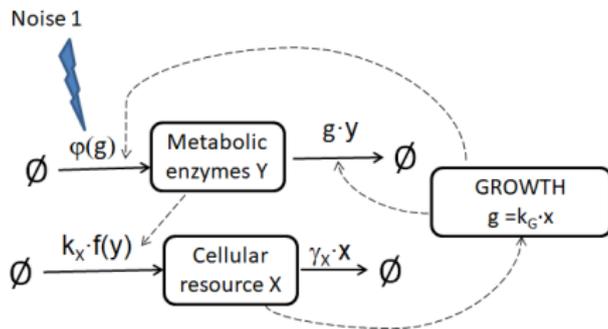
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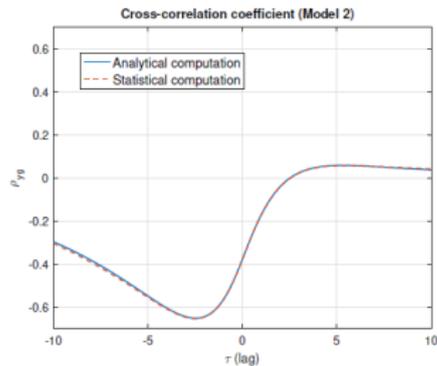
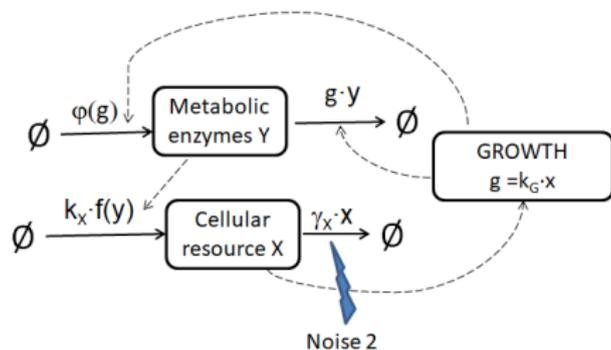
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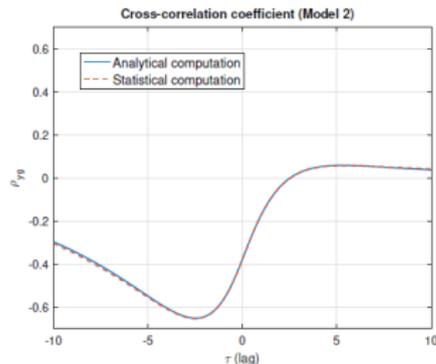
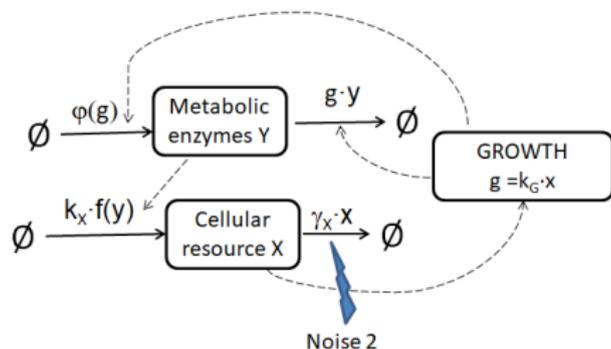
- The approximate analytical computations are validated by numerical simulations since there is a very good overlapping of the two curves
- A positive cross-correlation function with an apparent positive delay
- This fact is coherent with the analogous experimental results [**Kiviet et al (2014), Nature**], where it was highlighted that current enzyme expression correlates better with growth some time later. In other words, growth fluctuations arise because of the noise in the enzyme expression, and not vice versa

## Main results: Noise source 2



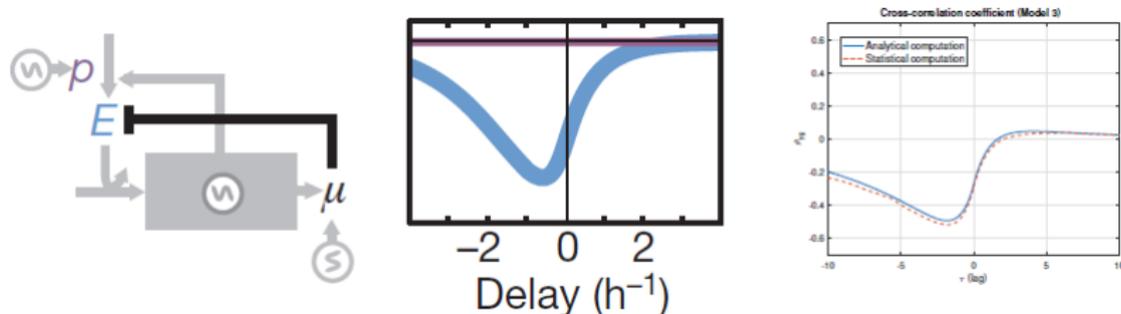
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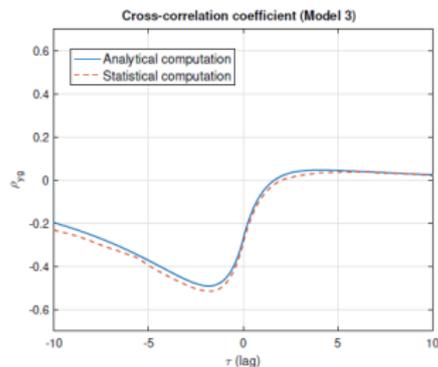
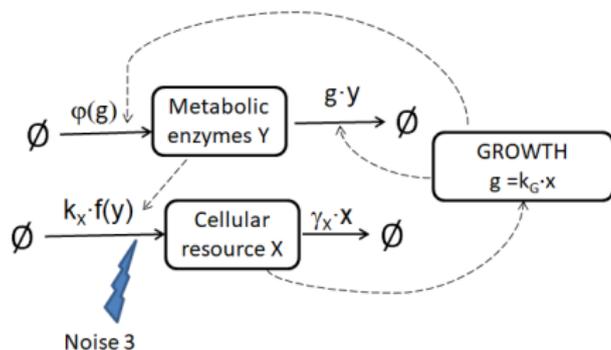
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- Same qualitative behavior with the experimental framework of **[Kiviet et al (2014), Nature]**, where noise source involved dilution of the cellular resource

## Main results: Noise source 3



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- Noise source 3 seems to impact very similarly to Noise source 2

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- Analytical computations are carried out according to linear approximations of nonlinearities. Results are validated by an exhaustive campaign of Monte Carlo simulations, and are in good matching with experiments [**Kiviet et al (2014), Nature**]
- Results (achieved by means of cross-correlation functions) show that fluctuations may propagate from metabolism to growth and vice versa: growth noise may affect gene expression