Population-level control of heterologous protein production in bacteria

A. Vignoni[1,2]; G.-B. Stan[2]; D.A. Oyarzún[2]; J. Picó[1]

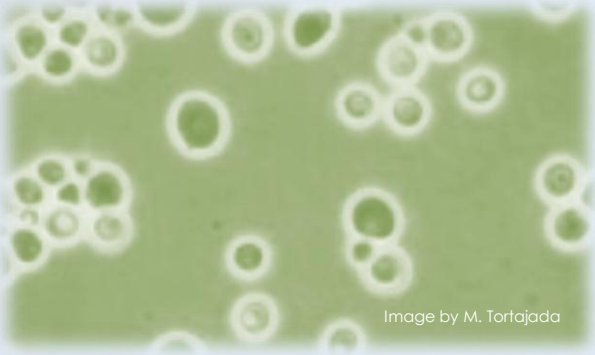
[1]Institut d'Automàtica I Informática Industrial, Universitat Politècnica de València, Spain

[2]Centre for Synthetic Biology and Innovation, Imperial College London, UK

Applied Synthetic Biology in Europe Programme

Barcelona, February 7th 2012

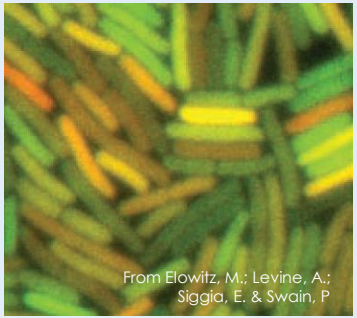
If we want to …



We have to fight with …

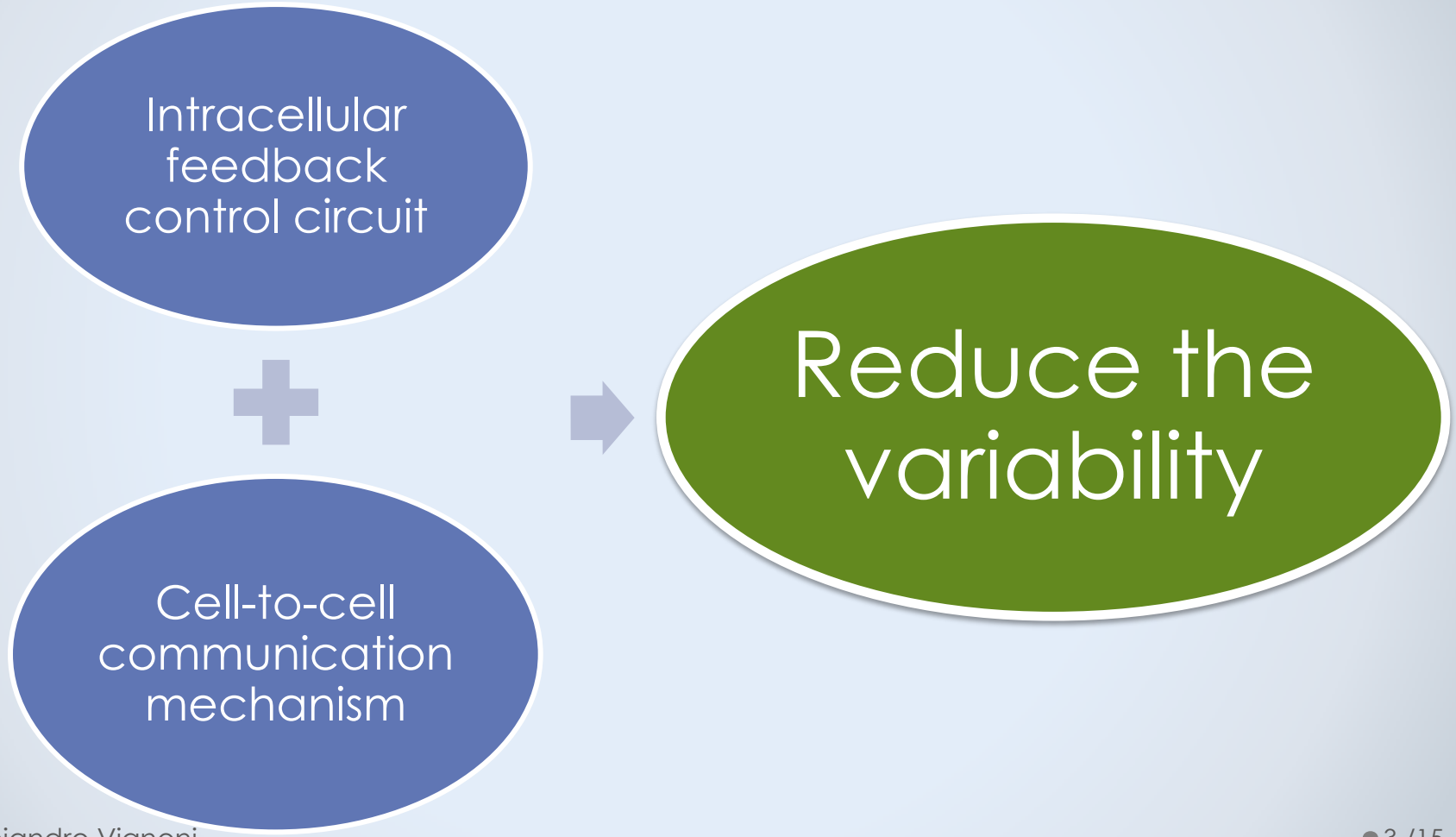
Variability in

gene expression.

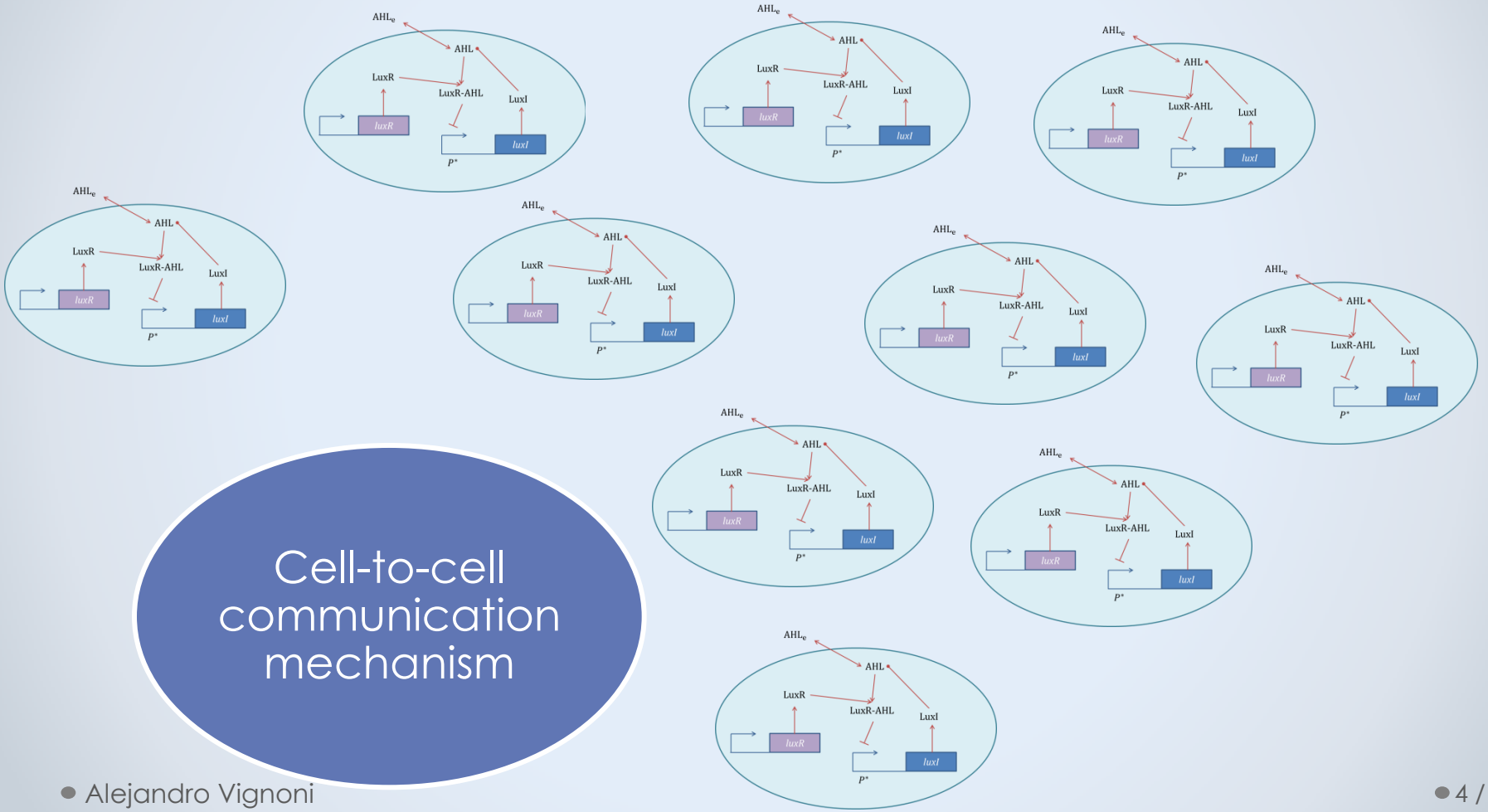


How?

Using a synthetic gene network



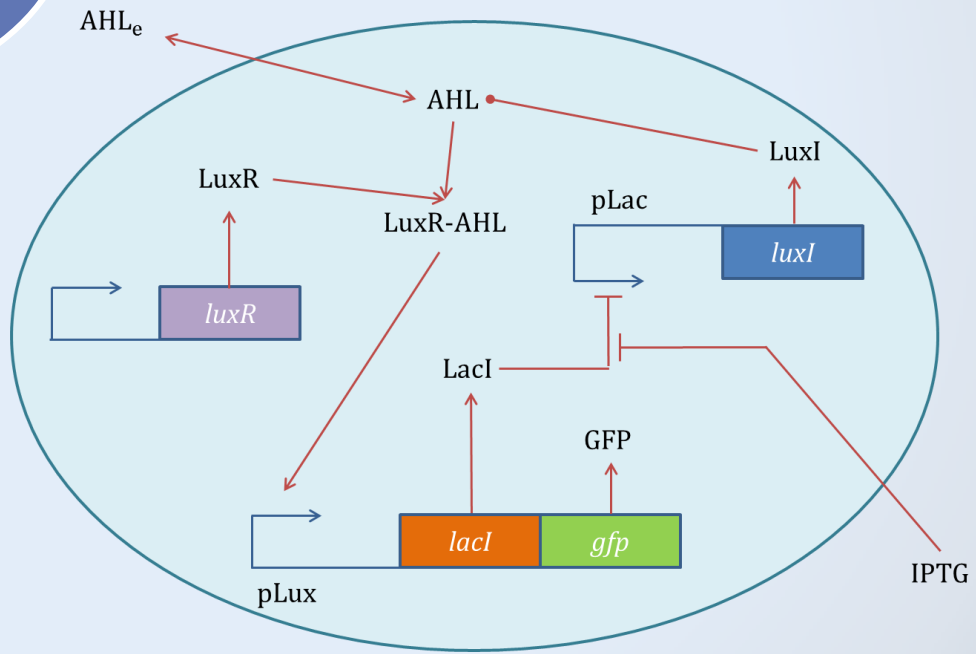
Using a synthetic gene network



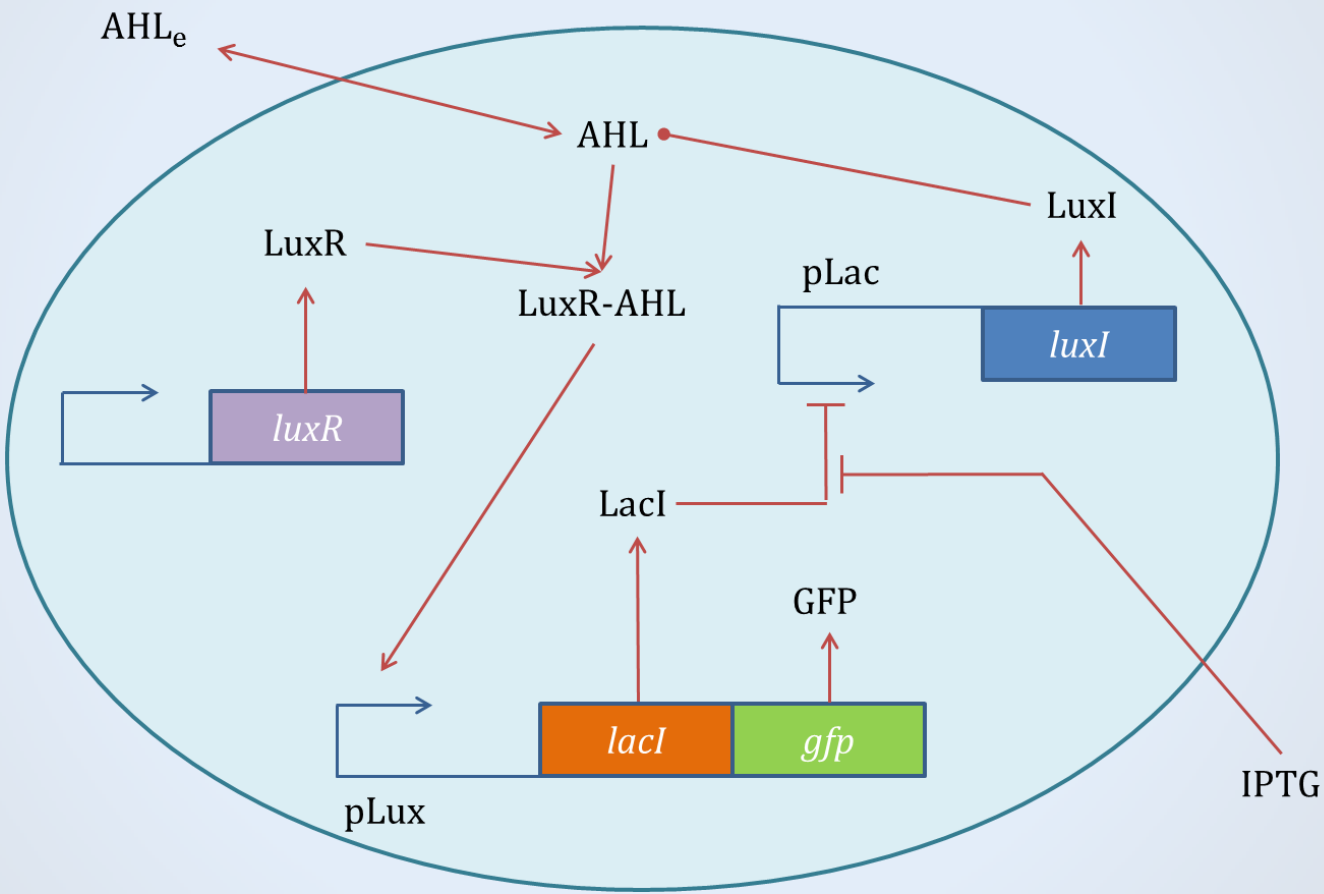
Cell-to-cell communication mechanism

Using a synthetic gene network

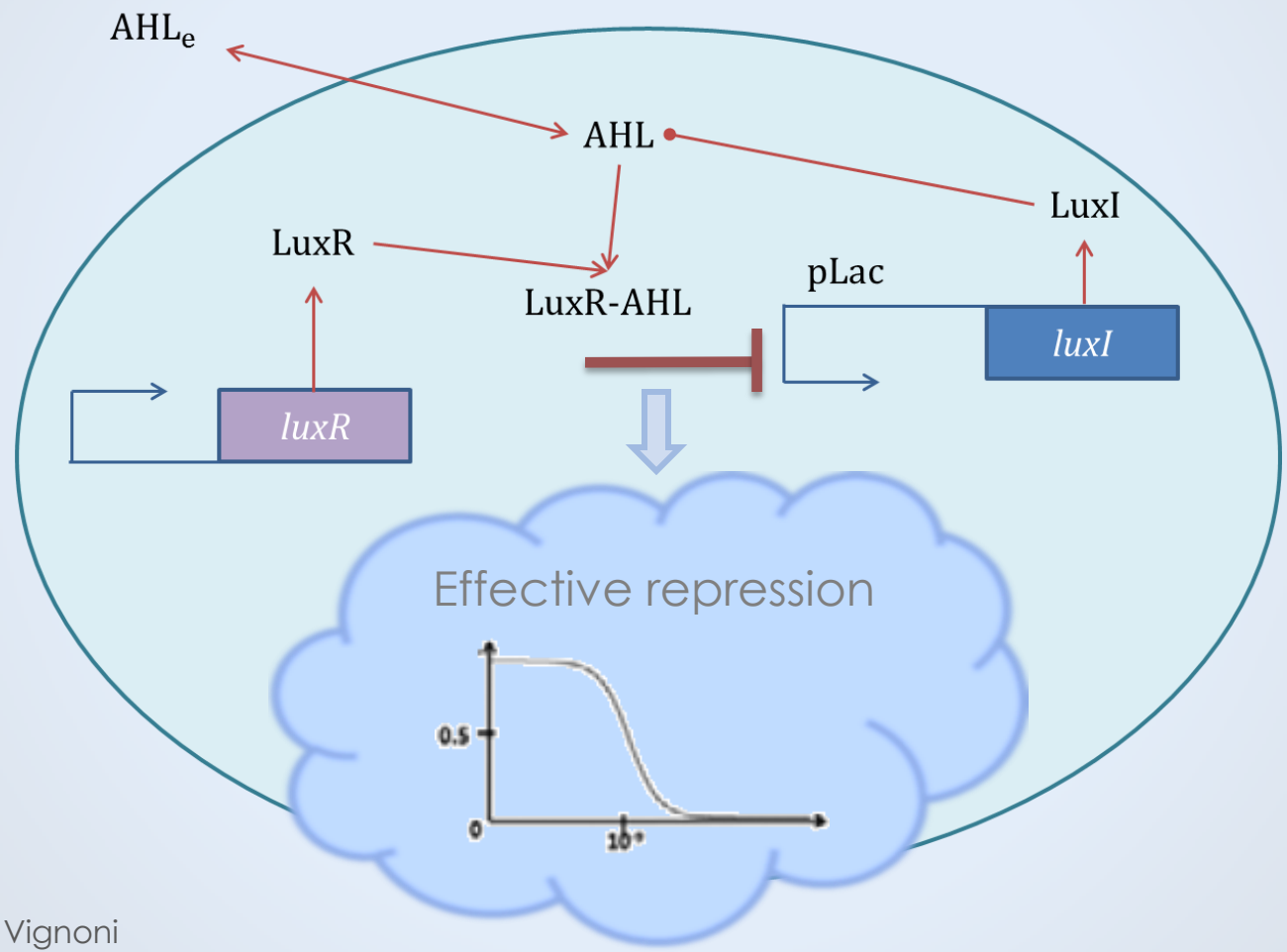
Intracellular feedback control circuit



Genetic circuit

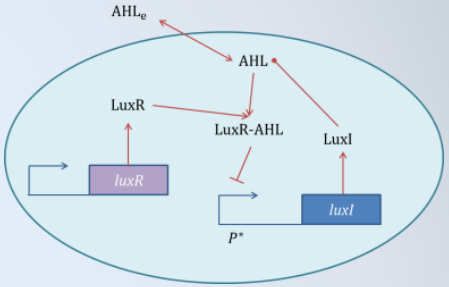


Genetic circuit – Mathematical model



Let's see the **model** of our genetic circuit.

$$Cell_i: \begin{cases} \dfrac{d[LuxI]_i}{dt} = b_i + u([AHL]_i) - \gamma_I [LuxI]_i \\ \dfrac{d[AHL]_i}{dt} = K_A[LuxI]_i + d([AHL]_i - [AHL]_e) - \gamma_A [AHL]_i \end{cases}$$



b_i	→ Basal expression of *LuxI*	K_A	→ AHL synthesis rate.
$u([AHL]_i)$	→ effective repressor hill function	d	→ Membrane permeability
γ_I	→ *LuxI degradation rate*	γ_A	→ *AHL degradation* rate

External AHL dynamic

$$\frac{d[AHL]_e}{dt} = \frac{d_e}{N}\sum_i^N([AHL]_i - [AHL]_e) - \gamma_{Ae}[AHL]_e$$

K_A	→ AHL synthesis rate.	γ_{Ae}	→ External AHL *decay rate*
d_e	→ External membrane permeability	N	→ Number of cells

The effective Hill function: the key element of the model

$$u([AHL]_i)_{hill} = \frac{K_I / K_h^{\eta}}{1 + \left([AHL]_i / K_h\right)^{\eta}}$$

η Hill coefficient

K_h Half concentration constant

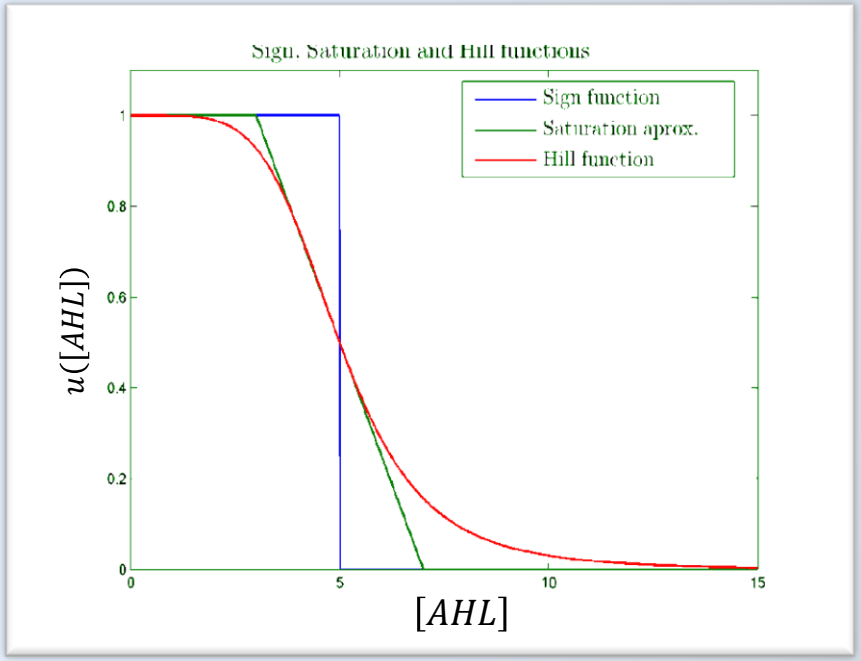
K_I Dynamic range

Control Parameters

S Slope

T Threshold

R Range



For analytical purposes:
Saturation Approximation.

Theoretical analysis and mathematical model

$$Var\{[AHL]\} = f_V(S,T)$$

$$\mathrm{E}\{[AHL]\} = f_E(S,T,R)$$

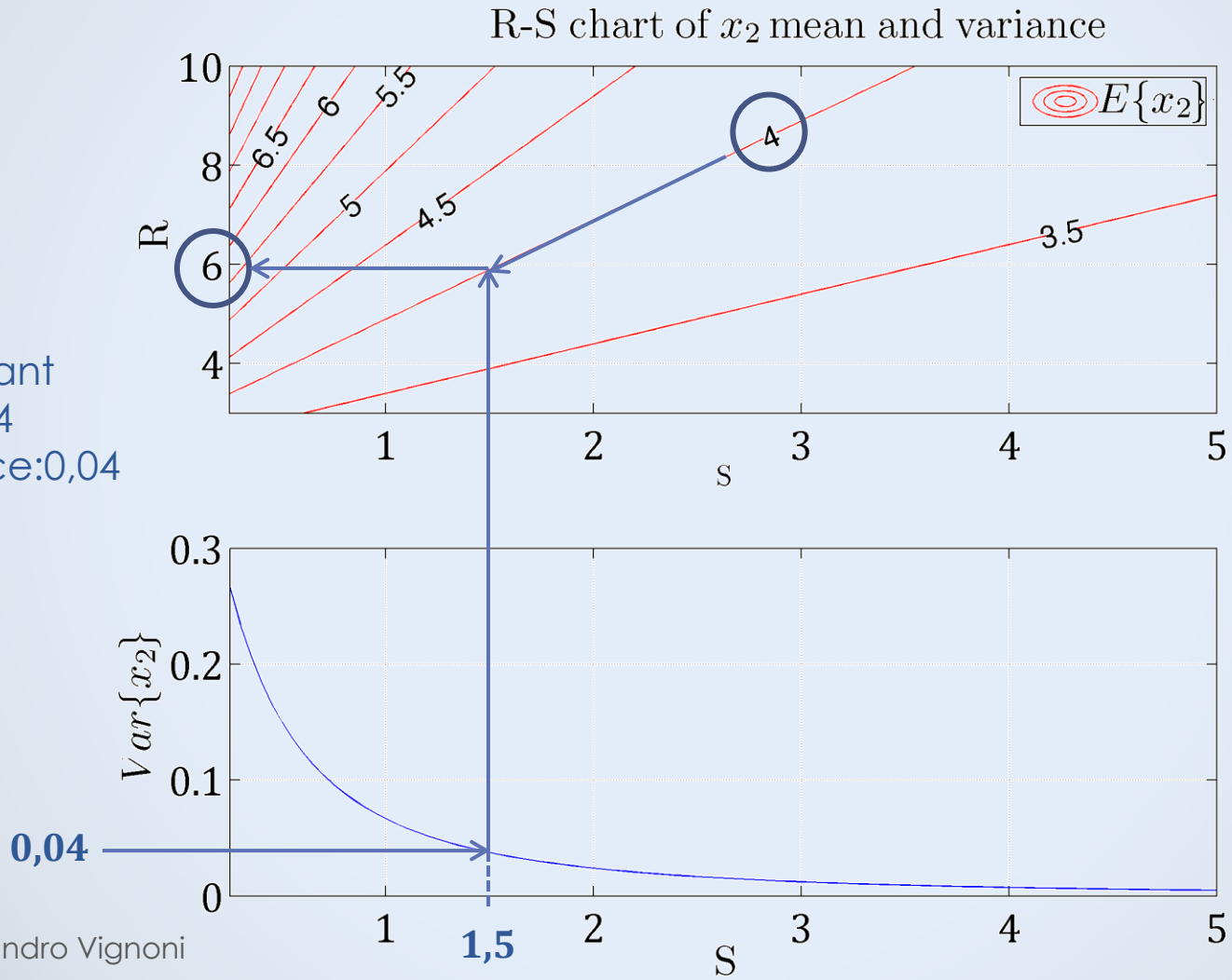
Mean and variance can be controlled independently

We will select the genetic regulation control parameters.

To obtain the desired gene expression variability distribution.

We obtain a R-S chart for the Mean and the Variance

If we want
Mean: 4
Variance:0,04

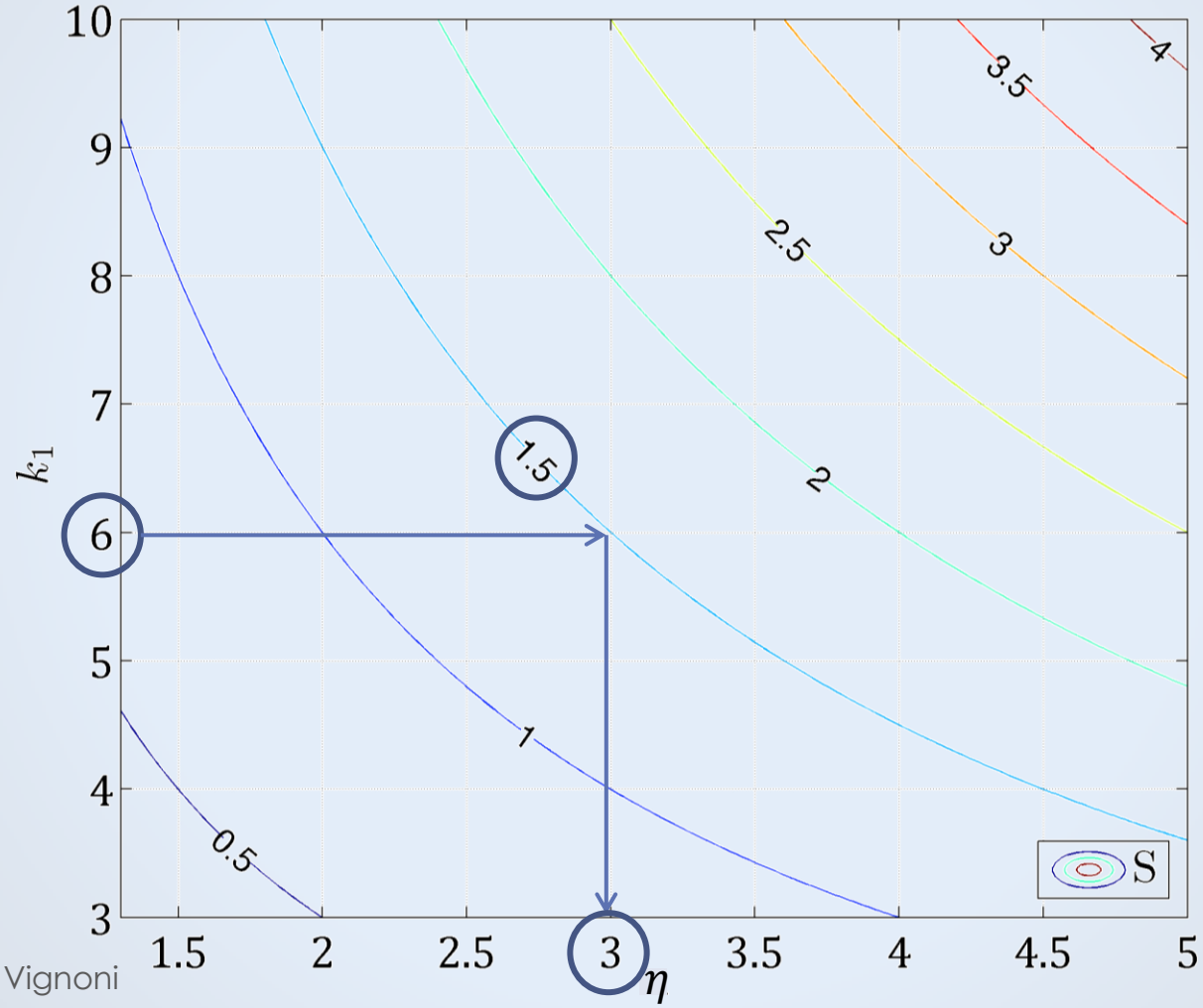


For a fixed T

Chart of control parameters

From the previous chart

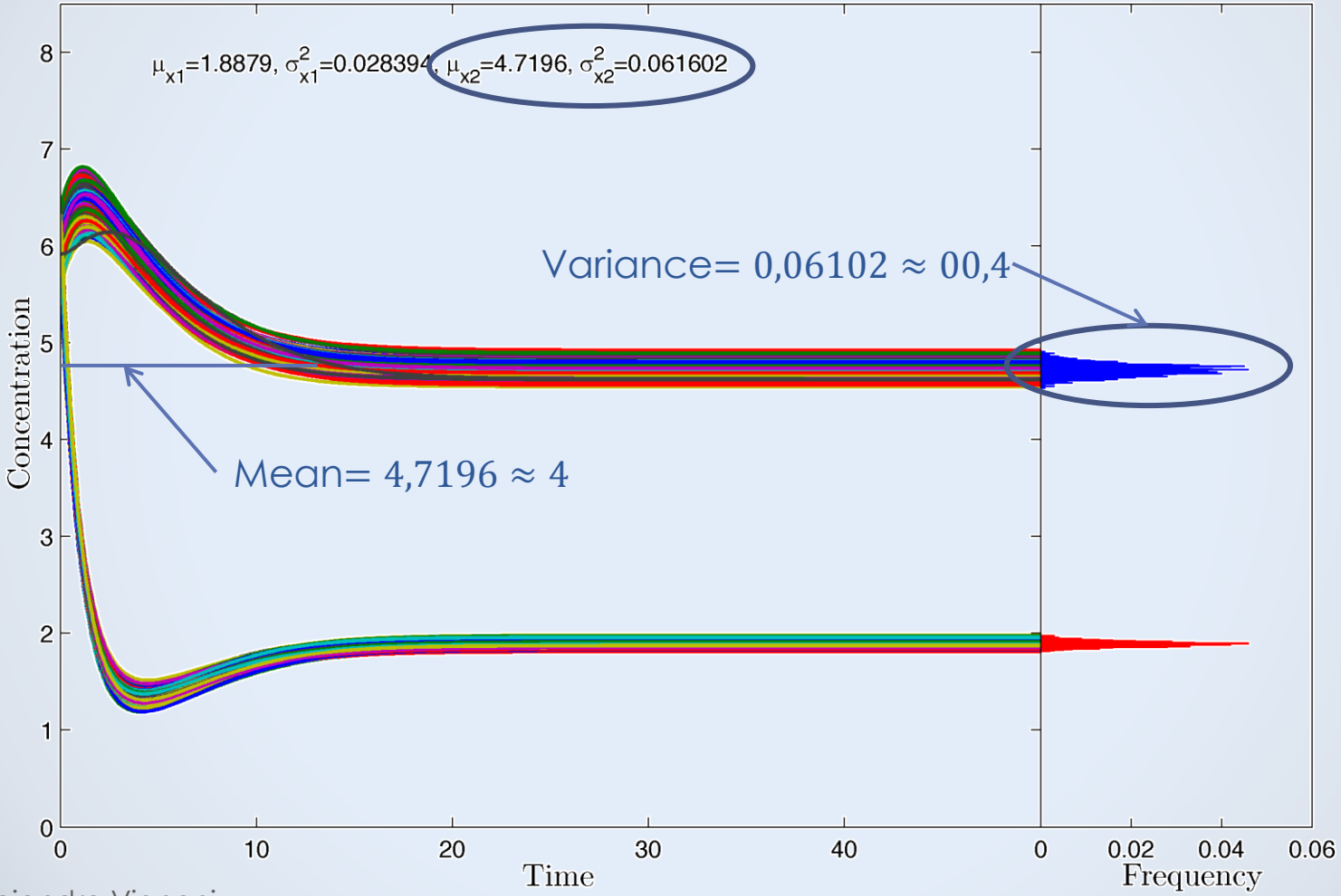
- $R=k_1=6$
- S=1,5



We obtain

- $k_1=6$
- $\eta=3$

We perform a ***simulation experiment*** introducing more stochasticity



Summary

- **Control** of the *mean* and the *variance* of the gene expression noise *can be done*.
- Parameters chart to help the design
- Simulation experiments
- Synthetic biology potential for industrial applications.

Future work

- Improve the model
- Make Experiments: Which parameters can we tune ?

Acknowledgement

Research in this area is partially supported by:

European Union and Spanish government grants FEDER-CICYT DPI2008-06880-C03-01 (Multisysbio) and FEDER-CICYTDPI2011-28112-C04-01

UNIVERSITAT POLITÈCNICA DE VALÈNCIA

The first author thanks grants FPI/2009-21 and PAID-00-11 of UPV.