¿Puede un ingeniero tunear una célula?

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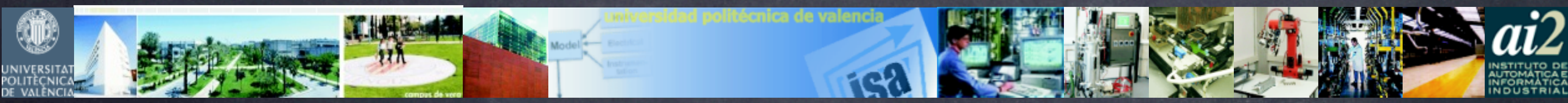

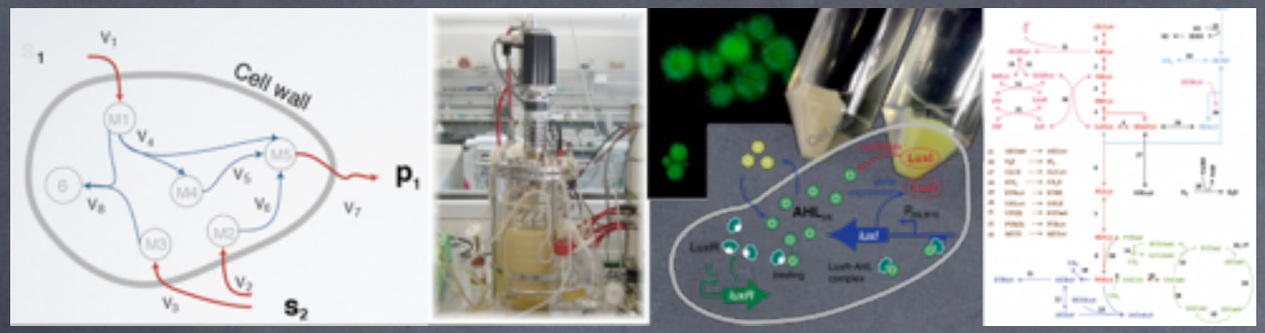

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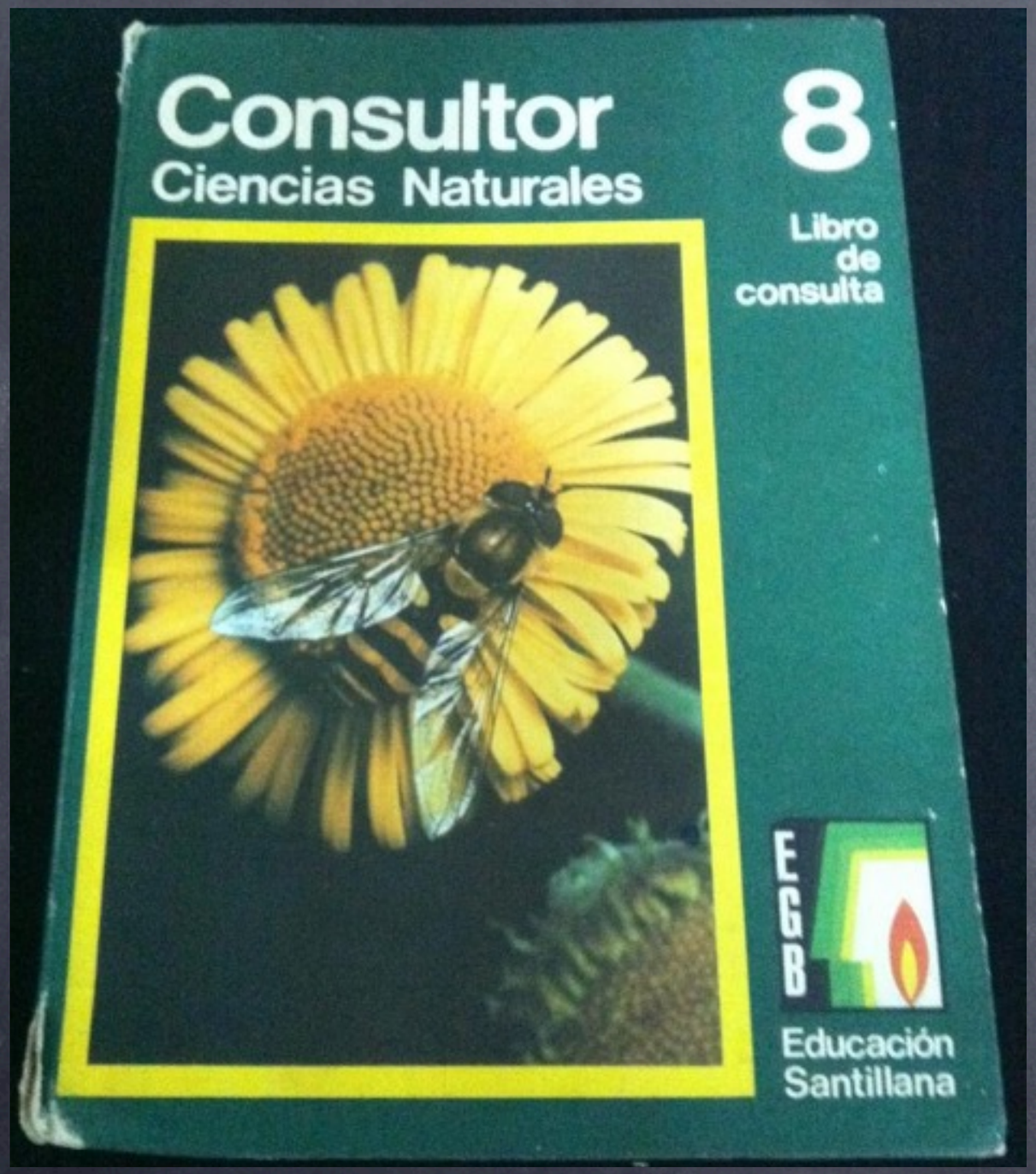


Can a biologist fix a radio?—Or, what I learned while studying apoptosis

As a freshly minted Assistant Professor, I feared that everything in my field would be discovered before I even had a chance to set up my laboratory. Indeed, the field of apoptosis, which I had recently joined, was developing at a mind-boggling speed. Components of the previously mysterious process were being discovered almost weekly, frequent scientific meetings had little overlap in their contents, and it seemed that every issue of *Cell*, *Nature*, or *Science* had to have at least one paper on apoptosis. My fear led me to seek advice from David Papermaster (currently at the University of Connecticut), who I knew to be a person with pronounced common sense and extensive experience. David listened to my outpouring of primal fear and explained why I should not worry.

David said that every field he witnessed during his decades in biological research developed quite similarly. At the first stage, a small number of scientists would somewhat leisurely discuss a problem that would appear esoteric to others, such as whether cell cycle is controlled by an oscillator or whether cells can commit suicide. At this stage the understanding of the problem increases slowly, and scientists are generally nice to each other, a few personal antipathies notwithstanding. Then, an unexpected observation, such as the discovery of cyclins or the finding that apoptosis failure can contribute to cancer, makes many realize that the previously mysterious process can be dissected with available tools and, importantly, that this effort may result in a miracle drug. At once, the field is converted into a Klondike gold rush with all the characteristic dynamics, mentality, and morals. A major driving force becomes the desire to find the nugget that will secure a place in textbooks, guarantee an unrelenting envy of peers, and, at last, solve all financial problems. The assumed proximity of this imaginary nugget easily attracts both financial and human resources, which results in a rapid expansion of the field. The understanding of the biological process increases accordingly and results in crystal clear models that often explain everything and point at targets for future miracle drugs. People at this stage are not necessarily nice, though, as anyone who has read about a gold rush can expect. This description fit the then current state of the apoptosis field rather well, which made me wonder why David was smiling so reassuringly. He took his time to explain.

At some point, David said, the field reaches a stage at which models, that seemed so complete, fall apart, predictions that were considered so obvious are found to be wrong, and attempts to develop wonder drugs largely fail. This stage is characterized by a sense of frustration at the complexity of the process, and by a sinking feeling that despite all that intense digging the promised cure-all may not materialize. In other words, the field hits the wall, even though the intensity of research remains unabated for a while, resulting in thousands of publications, many of which are contradictory or largely descriptive. The flood of publications is explained, in part, by the sheer amount of accumulated information (about 10,000 papers on apoptosis were published yearly over the last few years), which makes reviewers of the manuscripts as confused and overwhelmed as their authors. This stage can be summarized by the paradox that the more facts we learn the less we understand the process we study.

It becomes slowly apparent that even if the anticipated gold deposits exist, finding them is not guaranteed. At this stage, the Chinese saying that it is difficult to find a black cat in a dark room, especially if there is no cat, comes to mind too often. If you want to continue meaningful research at this time of widespread desperation, David said, learn how to make good tools and how to keep your mind clear under adverse circumstances. I am grateful to David for his advice, which gave me hope and, eventually, helped me to enjoy my research even after my field did reach the state he predicted.

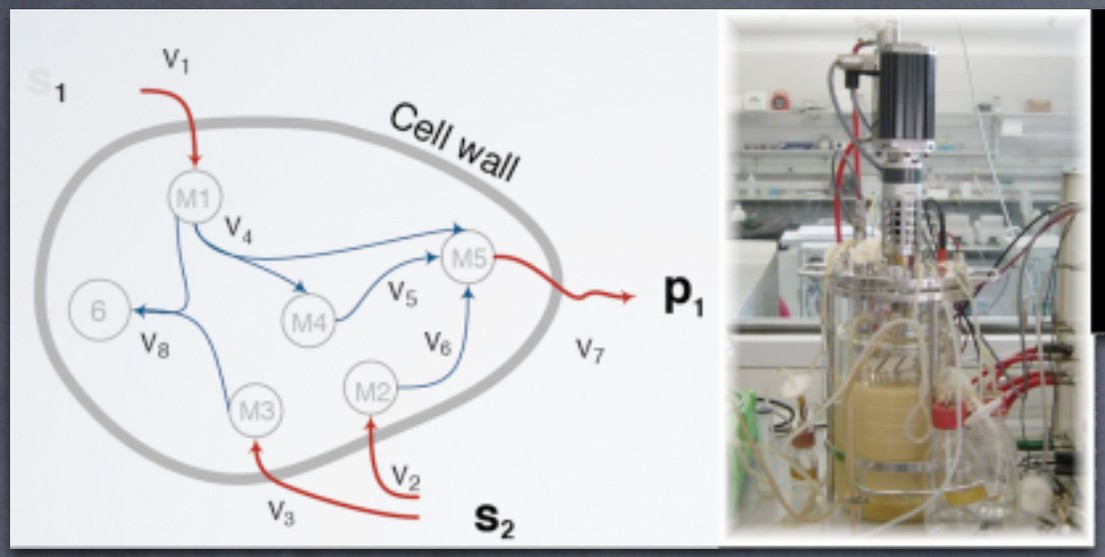
At some point I began to realize that David's paradox has a meaning that is deeper than a survival advice. Indeed, it was puzzling to me why this paradox manifested itself not only in studies of fundamental processes, such as apoptosis or cell cycle, but even in studies of individual proteins. For example, the mystery of what the tumor suppressor p53 actually does seems only to deepen as the number of publications about this protein rises above 23,000.

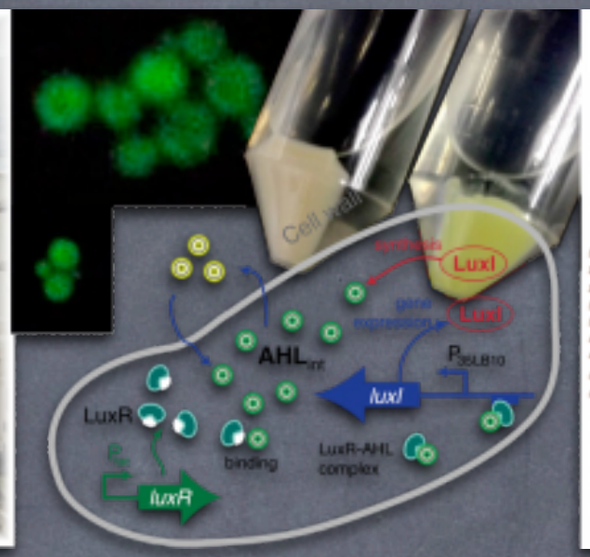
The notion that your work will create more confusion is not particularly stimulating, which made me look for guidance again. Joe Gall at the Carnegie Institution, who started to publish before I was born, and is an author of an excellent series of essays on the history of biology (Gall, 1996), relieved my mental suffering by pointing out that a period of stagnation is eventually interrupted by a new development. As an example, he referred to the studies of cell death that took place in the nineteenth century (Gall, 1996, chapter 29), faded into oblivion, and reemerged a century later with about 60,000 studies on the subject published during a single decade. Even though a prospect of a possible surge in activity in my field was relieving, I started to wonder whether anything could be done to expedite this event, which brought me to think about the nature of David's paradox. The generality of the paradox suggested some common fundamental flaw of how biologists approach problems.

To understand what this flaw is, I decided to follow the advice of my high school mathematics teacher, who recommended testing an approach by applying it to a problem that has a known solution. To abstract from peculiarities of biological experimental systems, I looked for a problem that would involve a reasonably complex but well understood system. Eventually, I thought of the old broken transistor radio that my wife brought

Figure 1. The radio that has been used in this study

Y. Lazebnik, **Can a biologist fix a radio?**, *Cancer Cell,* **2**, 179-182, 2002





La biología ofrece un enorme campo para el análisis, diseño y aplicación de sistemas de control

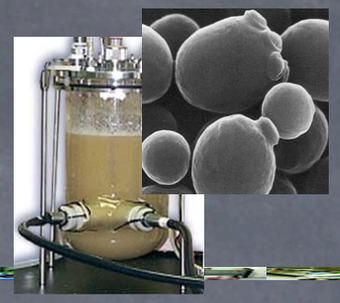
Afrontar los retos de control que surgen en las aplicaciones bio(tecno)lógicas requiere una aproximación multi-escala.

Índice

- Controladores y observadores de biorreacciones:
  - Control de la velocidad específica de reacción en biorreactores *fedbatch*
  - Control de concentración en biorreactores continuos
    - Observadores de velocidades de reacción
- Estimación de flujos metabólicos
- Biología sintética:
  - Control de la expresión de proteínas

Controladores y observadores de biorreacciones

Problemas a resolver

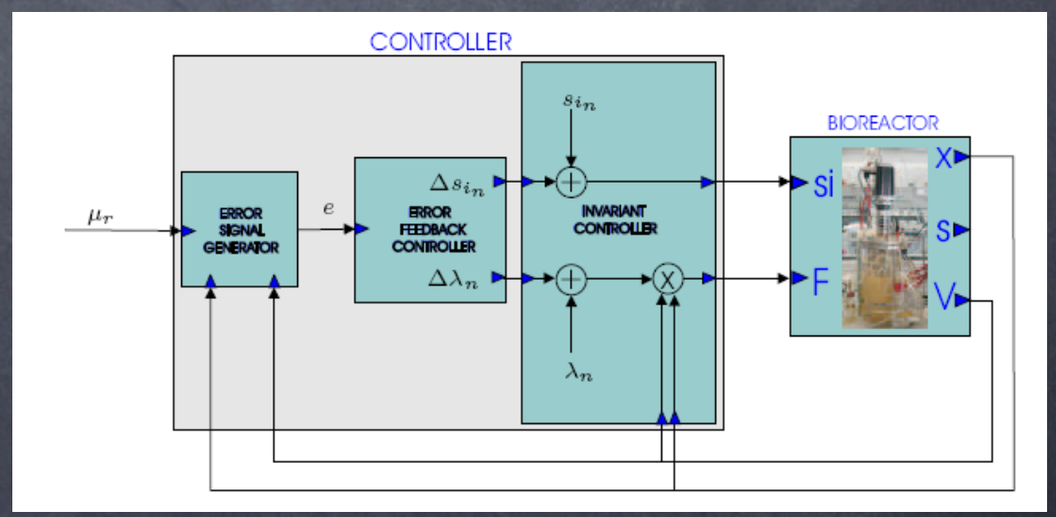


- Problemas que un ingeniero debe resolver:
  - Sensorización hardware y software
  - Análisis dinámico

$$\Sigma_{1a} = \begin{cases} \dot{x} = \mu x - Dx \\ \dot{s} = -y_s \mu x + D(s_i - s) \\ \dot{p} = y_p \mu x - Dp \\ \dot{v} = F \end{cases}$$

$$\mu(s) = \frac{\mu_m s}{k_s + s}$$

  - Control automático: producción óptima de metabolitos (p.e. insulina, biomasa,...)



Control de la velocidad de reacción

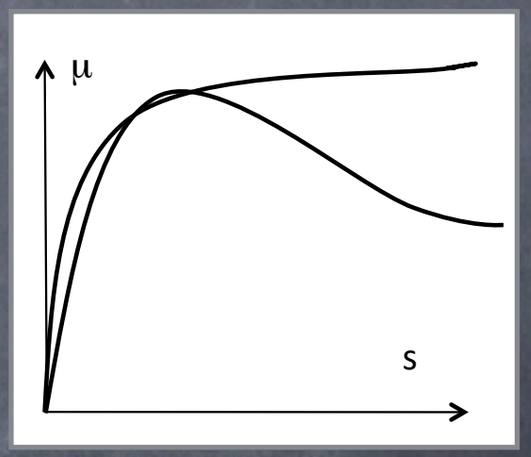
Modelo y objetivos:

- Paradigma: modelo mínimo

Source: Biopolis S.L.

$$D = \frac{F}{v}$$

$$\Sigma = \begin{cases} \dot{x} = \mu(s)x - \dfrac{F}{v}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F}{v}(s_i - s) \\ \dot{v} = F \end{cases}$$



- Medidas: biomasa y volumen
- Parámetros desconocidos, variantes en t
- Estructura de $\mu(s)$ parcialmente desconocida

- Control robusto $\mu(s) = \mu_r$
  - Invarianza y adaptación → Controlador PI no lineal

Ideas principales:

- Modelo de referencia (exosistema):

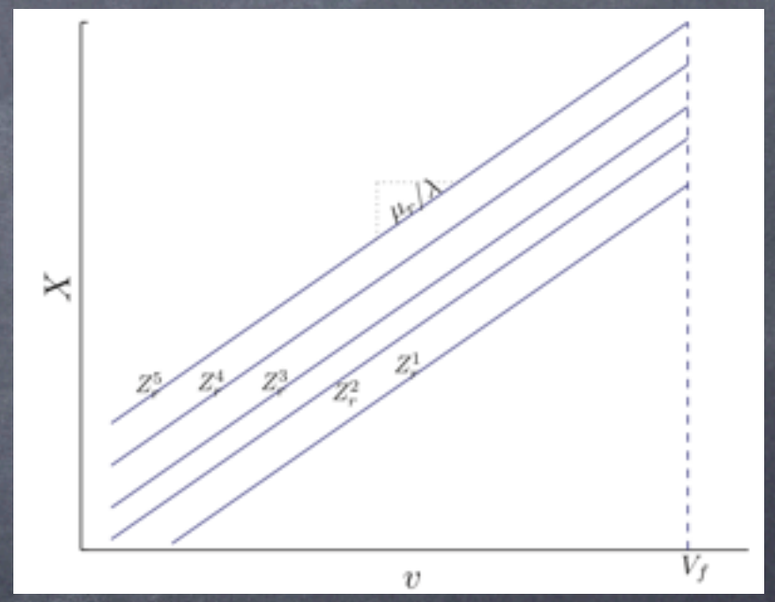
$$\Sigma = \begin{cases} \dot{x} = \mu(s)x - \dfrac{F}{v}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F}{v}(s_i - s) \\ \dot{v} = F \end{cases} \subseteq \Sigma_r \triangleq \begin{cases} \dot{X} = \mu_r X, & X(t_0) = X_{r,0} \\ \dot{s} = 0, & s(t_0) = s_r \\ \dot{v} = \lambda X, & v(t_0) = v_{r,0} \end{cases}$$

$$X = xv$$

$$Z_r = Z_x \cap Z_s$$

$$Z_x = \left\{(X, s, v) | z_x = X - X_{r,0} - \frac{\mu_r}{\lambda}(v - v_{r,0}) = 0\right\}$$

$$Z_s = \{(X, s, v) | z_s = s - s_r = 0\}$$



- Ley de control invariante:

  Sin incertidumbre, la alimentación exponencial $F = \lambda x v$ con $\lambda = \dfrac{y_s\mu_r + m}{s_i - s_r}$ conocido

- ¡Pero esto implica tener un buen modelo!

Ley de control adaptativo:

- Sistema controlado:

$$\Sigma_f : \begin{cases} \dot{x} = \mu(s)x - \lambda_f x^2 \\ \dot{s} = -y_s\mu(s)x - mx + \lambda_f x(s_i - s) \\ \dot{v} = \lambda_f x v. \end{cases}$$

$$F = \lambda_f(t) x v$$

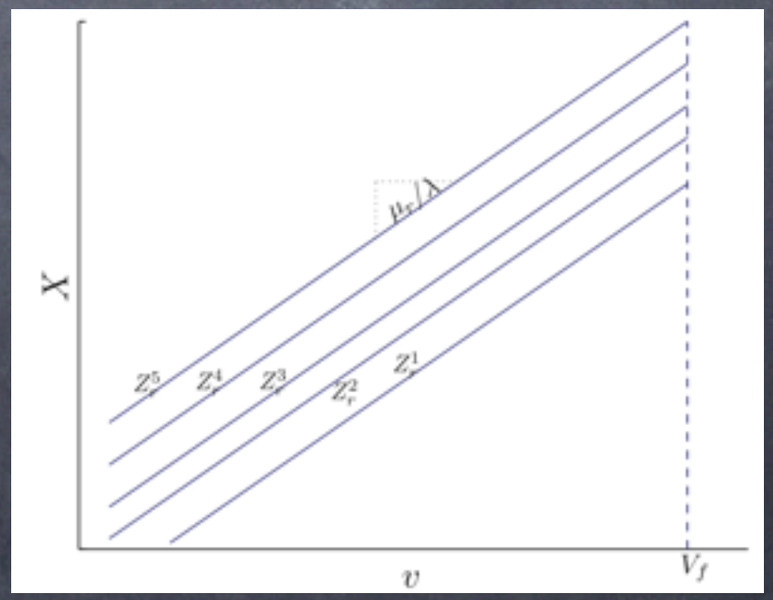
- Idea: adaptar $\lambda_f(t)$ de suerte que la trayectoria del estado sea siempre tangente al manifold objetivo $Z_{\mathcal{X}}$

$$\frac{\partial z_x}{\partial x}\dot{x} + \frac{\partial z_x}{\partial v}\dot{v} + \frac{\partial z_x}{\partial \lambda}\dot{\lambda} = 0$$

$$Z_r = Z_x \cap Z_s$$

$$Z_x = \left\{(X, s, v) | z_x = X - X_{r,0} - \frac{\mu_r}{\lambda}(v - v_{r,0}) = 0\right\}$$

$$Z_s = \{(X, s, v) | z_s = s - s_r = 0\}$$



- Ley de control adaptativo:

$$F = \lambda x v$$

$$\dot{\lambda} = -\lambda^2 \psi(v) x \frac{\mu - \mu_r}{\mu_r}$$
$$\lambda(t_0) = \hat{\lambda}_r$$
$$\psi = \frac{v}{v - v_{r,0}}$$

- Pros y Cons:
  - ✓ Robustez frente a incertidumbre en el proceso
  - ✓ Mínimo conocimiento del proceso
  - – Transitorio lento → añadir acción proporcional
  - – Requiere estimación de la tasa de reacción

→ expresar error como distancia a Z_x

E. Picó-Marco, et al. **Sliding mode scheme for adaptive specific growth rate control in biotechnological fed-batch processes**, *Int. J. of Control*, **78**:2, 128-141, 2005.

→ diseñar observadores de la velocidad de reacción

Adición de realimentación P del error de salida:

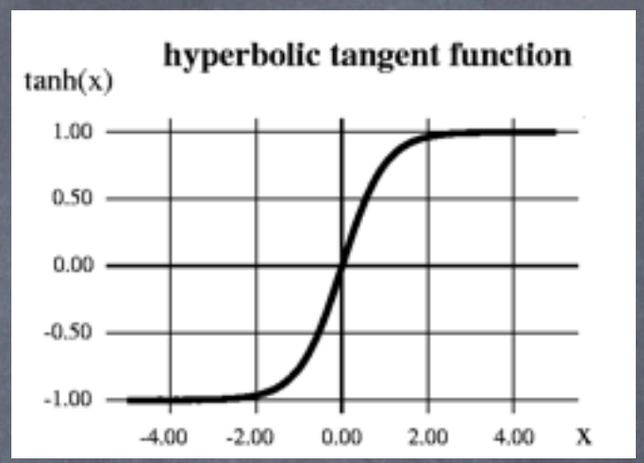
- Idea clave: mantener estructura de control invariante

$$F = \lambda_f(t) x v$$

$$\lambda_f = \lambda(1 - f(\mu - \mu_r))$$

$$\dot{\lambda} = -\lambda^2 \phi(v) x \frac{\mu - \mu_r}{\mu} \quad \lambda(t_0) = \hat{\lambda}_r$$

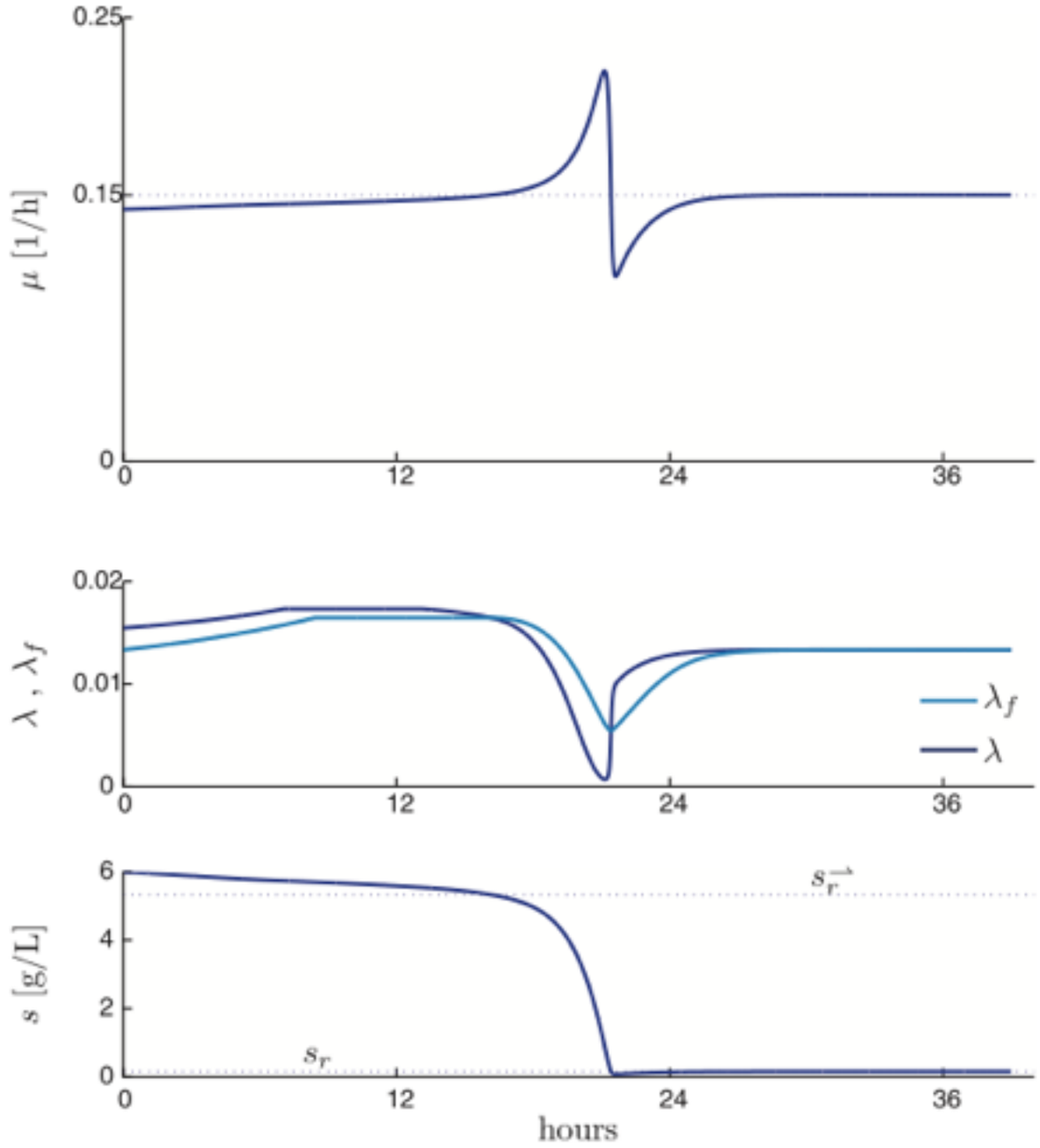
$$f = tanh\left(\frac{k}{\mu_r}(\hat{\mu} - \mu_r)\right)$$

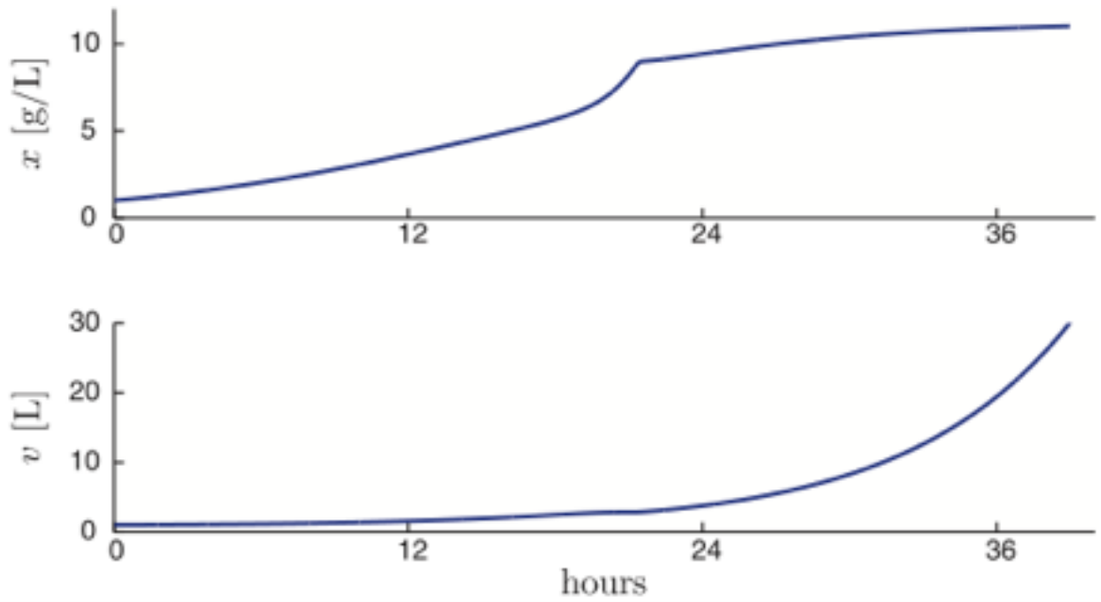


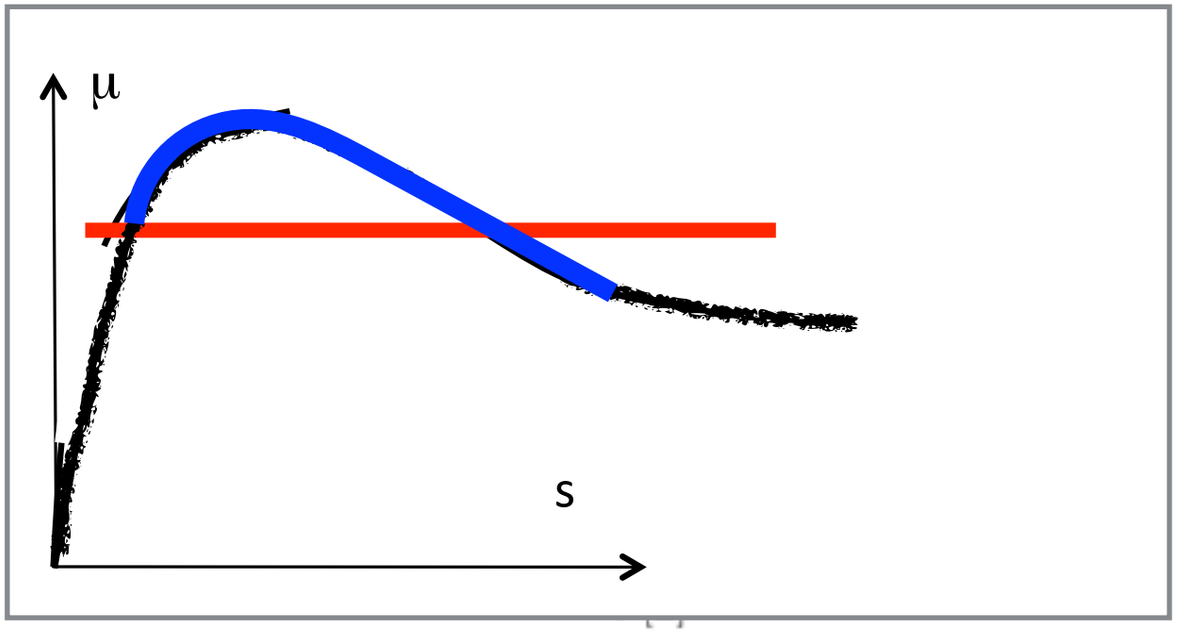
H. De Battista et al., **Nonlinear PI control of fed-batch processes for growth rate regulation**, *Journal of Process Control,* **22**:4, 789-797, 2013

- Estabilidad:
  - ✓ Global: cinética monótona
  - ✓ Global: cinética no monótona débil (una raíz $\mu(s) - \mu_r$)
  - ✓ Local: cinética no monótona

Resultados de simulación







Continuous: PI, Haldane-like kinetics, high initial substrate.

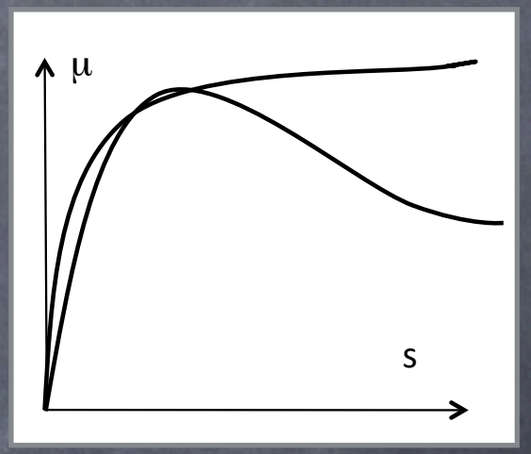
Control de la concentración

Modelo y objetivos:

- Paradigma: modelo mínimo

Source: Biopolis S.L.

$$\Sigma = \begin{cases} \dot{x} = \mu(s)x - \dfrac{F_i}{V}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F_i}{V}(s_i - s) \\ \dot{V} = F_i - F_o \end{cases}$$



- Medidas: biomasa y volumen
- Parámetros desconocidos, variantes en t
- Estructura de $\mu(s)$ parcialmente desconocida

- Control robusto $x = x^\star$
  - Escalado temporal y adaptación → PI no lineal

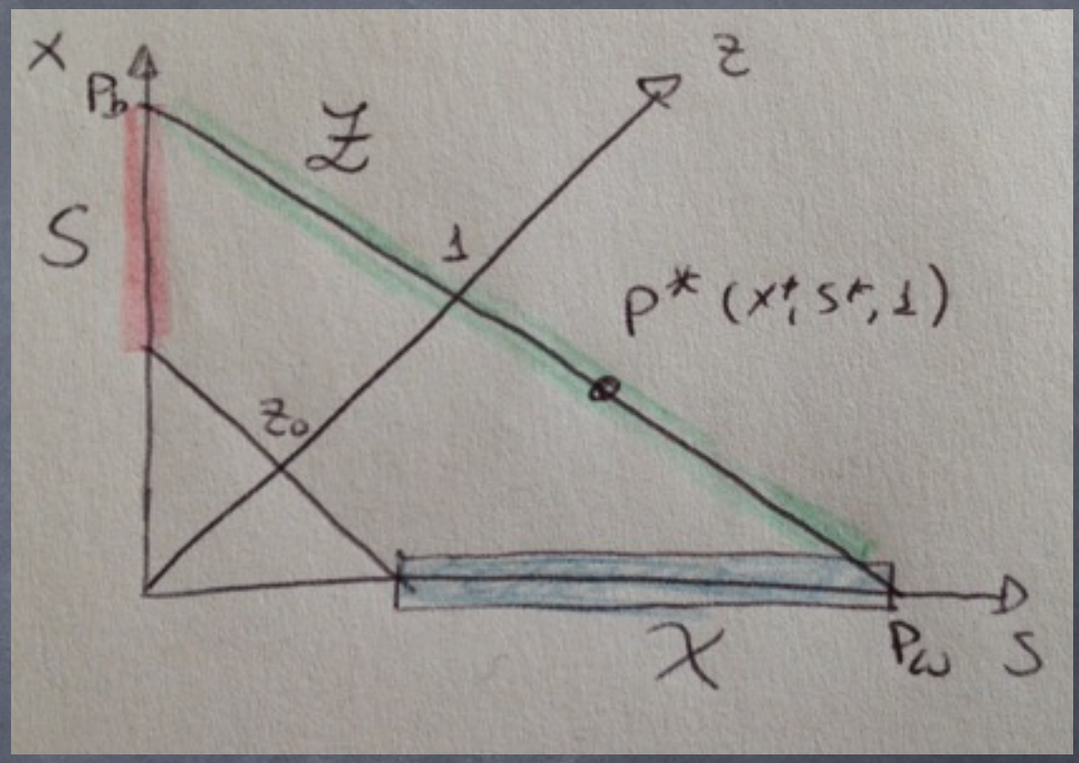
Ideas principales:

- Normalizamos:

$$\dot{x} = \mu(x,s)x - D(t)x \quad x \in \Re_+$$
$$\dot{s} = -y\mu(x,s)x + D(t)(s_i - s)$$

$$x := \frac{yx}{s_i}$$
$$s := \frac{s}{s_i}$$
$$z := x + s$$

$$\dot{x} = \mu(x,s)x - D(t)x \quad x \in \Re_+$$
$$\dot{s} = -\mu(x,s)x + D(t)(1-s) \quad s \in \Re_+$$
$$\dot{z} = D(t)(1-z) \quad z \in \Re_+$$



- Ley de control:

$$D(x,\mu) = \mu x \gamma \qquad \gamma = 1/x^*$$

$$\dot{x} = D(x,\mu)(x^* - x)$$
$$\dot{s} = D(x,\mu)(s^* - s)$$
$$\dot{z} = D(x,\mu)(1-z)$$

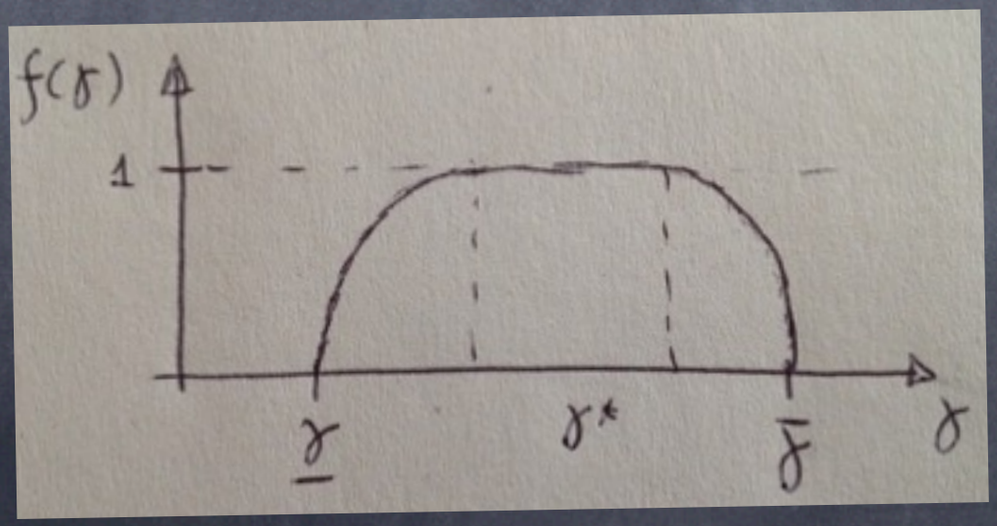
¿Cómo mejorar la ley de control base?

- Adaptación:

$$\begin{aligned}
\dot{x} &= \mu(x,s)x - D(t)x \quad x \in \Re_+ \\
\dot{s} &= -\mu(x,s)x + D(t)(1-s) \quad s \in \Re_+ \\
\dot{z} &= D(t)(1-z) \quad z \in \Re_+
\end{aligned}$$

$$D = \gamma \mu x$$

$$\dot{\gamma} = g\left(\gamma, x, x^{\star}\right) f(\gamma) \longrightarrow \gamma = 1/x^{*}$$



¿Cómo definir la ley de adaptación?

- Cambio de escala temporal:

$$\begin{aligned}\dot{x} &= D(x,\mu)(x^* - x)\\ \dot{s} &= D(x,\mu)(s^* - s)\\ \dot{z} &= D(x,\mu)(1 - z)\end{aligned}$$

$$D = \gamma\mu x$$

$$d\tau = D\,dt$$

$$x' = \frac{1}{D}\dot{x}$$

$$\begin{aligned}x' &= \gamma^{-1} - x\\ s' &= 1 - \gamma^{-1} - s\\ z' &= 1 - z\end{aligned}$$

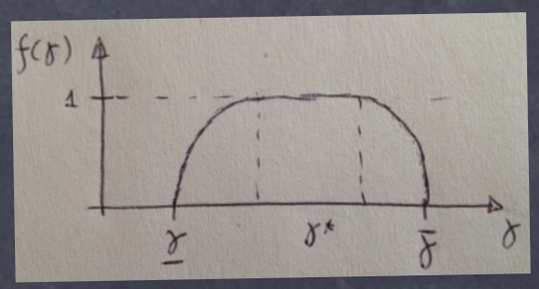
$$\gamma = 1/x^*$$

- PI = adaptar proporcionalmente a la integral de PD

$$x'' = -\frac{\gamma'}{\gamma^2} - x' \rightsquigarrow x'' + ax' + b(x - x^\star) = 0$$

$$\gamma' = -\gamma^2\left[(1-a)x' - b(x - x^\star)\right] f(\gamma)$$

$$f(\gamma) = 1$$



¿Es estable?

- Lyapunov en τ más Stability Preserving Maps :

$$W_1 = \int_0^{\tilde{\gamma}} \frac{h}{f(\frac{\gamma^*}{1-g\gamma^*})} dh$$

$$W_2 = \frac{(b-a+1)}{2}\tilde{x}^2$$

$$W = W_1 + W_2 \longrightarrow \begin{array}{l} a > 1 \\ b > a-1 \end{array}$$

- Control en t original:

$$\dot{\gamma} = -\gamma^2((\mu - D)x(1-a) - Db(x-x^*))f(\gamma) \quad \gamma_0 \in (\underline{\gamma}, \bar{\gamma})$$

$$D(\mu, x) = \gamma\mu x$$

Observadores de tasa de reacción

Modelo y objetivos:

- Modelo (modo fed-batch):

$$\Sigma = \begin{cases} \dot{x} = \mu(s)x - \dfrac{F}{v}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F}{v}(s_i - s) \\ \dot{v} = F \end{cases}$$

$$\mathcal{P} : \begin{cases} \dot{x} = (\mu - D(x,t))x \\ \dot{\mu} = \rho(x, \mu, t)x \end{cases}$$

Aproximaciones básicas

- Observadores de alta ganancia

$$\mathcal{O}_{B\&D} : \begin{cases} \dot{\hat{x}} = \left(\hat{\mu} - D(x,t) + 2\zeta\omega(x - \hat{x})\right)x \\ \dot{\hat{\mu}} = \omega^2(x - \hat{x})x \end{cases}$$

- Observadores de modo deslizante de primer orden

$$\mathcal{O}_{1SM} : \begin{cases} \dot{\hat{x}} = \left(z - D(x,t) + \omega(1+a(x))(x - \hat{x}) + \dfrac{M}{\omega}\,\mathrm{sign}(x - \hat{x})\right)x \\ \dot{z} = \left(\omega^2 a(x)(x - \hat{x}) + M\,\mathrm{sign}(x - \hat{x})\right)x \\ \hat{\mu} = z + \dfrac{M}{\omega}\,\mathrm{sign}(x - \hat{x}) \end{cases}$$

Observadores de modo deslizante de 2º orden

- Idea clave: llevar la derivada un paso atrás respecto a la estimación de μ
- Observador (variación de super-twisting):

$$\mathcal{O}_{2SM}: \begin{cases} \dot{\hat{x}} = \left(\hat{\mu} - D(x,t) + 2\beta(\bar{\rho}|(x-\hat{x})|)^{1/2}\,\mathrm{sign}(x-\hat{x})\right)x \\ \dot{\hat{\mu}} = \left(\alpha\bar{\rho}\,\mathrm{sign}(x-\hat{x})\right)x \end{cases}$$

$$\mathcal{P}_U \begin{cases} \dot{x} = (\mu - D(x,t))x \\ \dot{\mu} \in U\bar{\rho}x \end{cases}$$

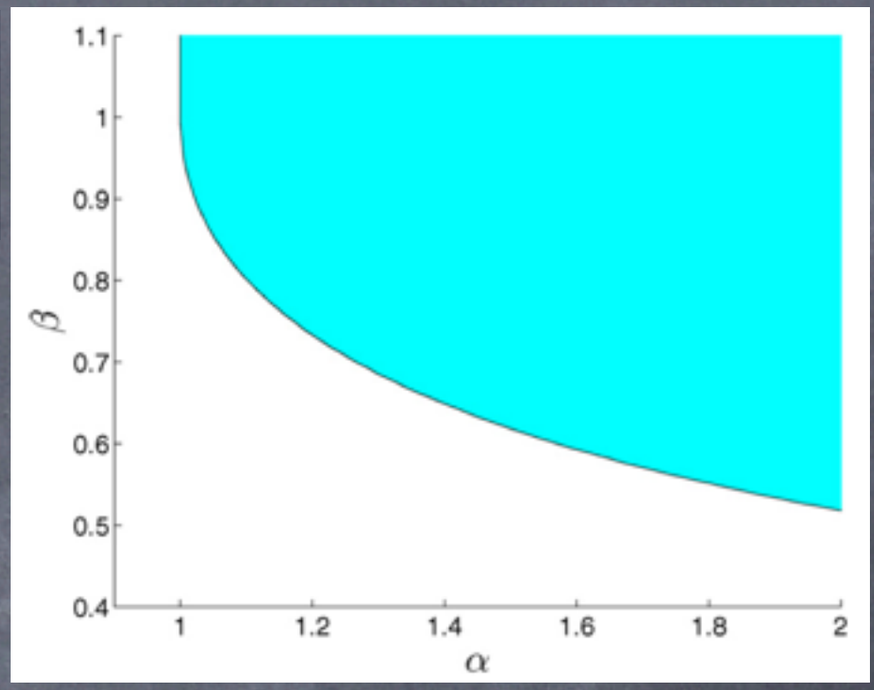
$$\mathcal{P}: \begin{cases} \dot{x} = (\mu - D(x,t))x \\ \dot{\mu} = \rho(x,\mu,t)x \end{cases}$$

H. De Battista et al., **Specific growth rate estimation in (fed-)batch bioreactors using second-order sliding observers**, *J. of Process Control*, **21**:7, 1049-1055, 2011

Estabilidad y ajuste

- Ganancias del observador

$$\mathcal{O}_{2SM}: \begin{cases} \dot{\hat{x}} = \left(\hat{\mu} - D(x,t) + 2\beta(\bar{\rho}|(x-\hat{x})|)^{1/2}\,\mathrm{sign}(x-\hat{x})\right) x \\ \dot{\hat{\mu}} = \left(\alpha\bar{\rho}\,\mathrm{sign}(x-\hat{x})\right) x \end{cases}$$



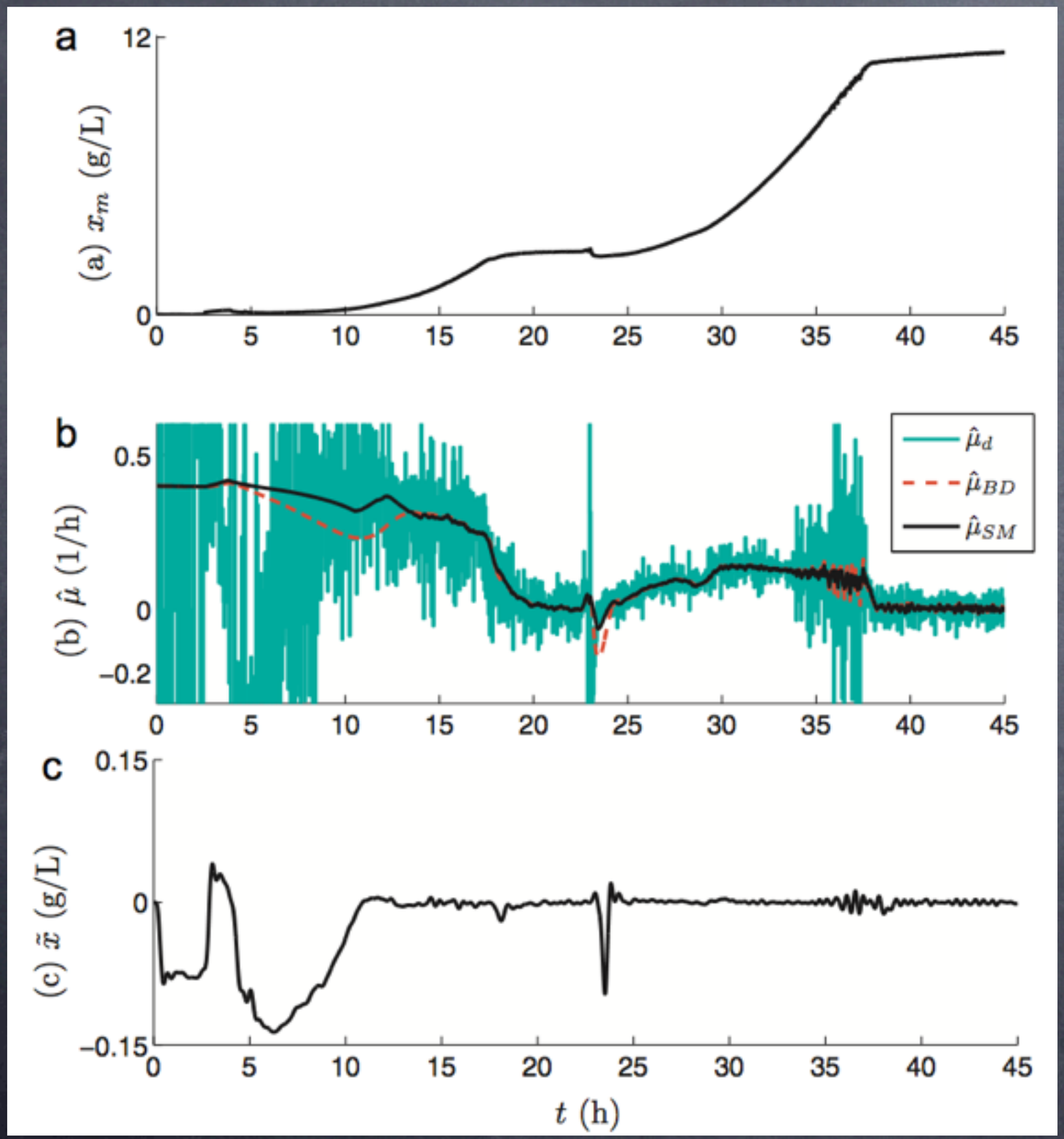
- Ideas clave:
  - Usar cambio de variables:

$$\xi = \begin{bmatrix} (|\bar{\rho}\tilde{x}|)^{1/2}\,\mathrm{sign}\tilde{x} \\ \tilde{\mu} \end{bmatrix} \Rightarrow \dot{\xi} \in \frac{\bar{\rho}x(t)}{|\xi_1|}\mathcal{A}\xi$$

  - Usar LMIs

$$\mathcal{A} = conv(A_1, A_2) \qquad A_1 = \begin{bmatrix} -\beta & 1/2 \\ -(\alpha-1) & 0 \end{bmatrix} \qquad A_2 = \begin{bmatrix} -\beta & 1/2 \\ -(\alpha+1) & 0 \end{bmatrix}$$

Resultados experimentales

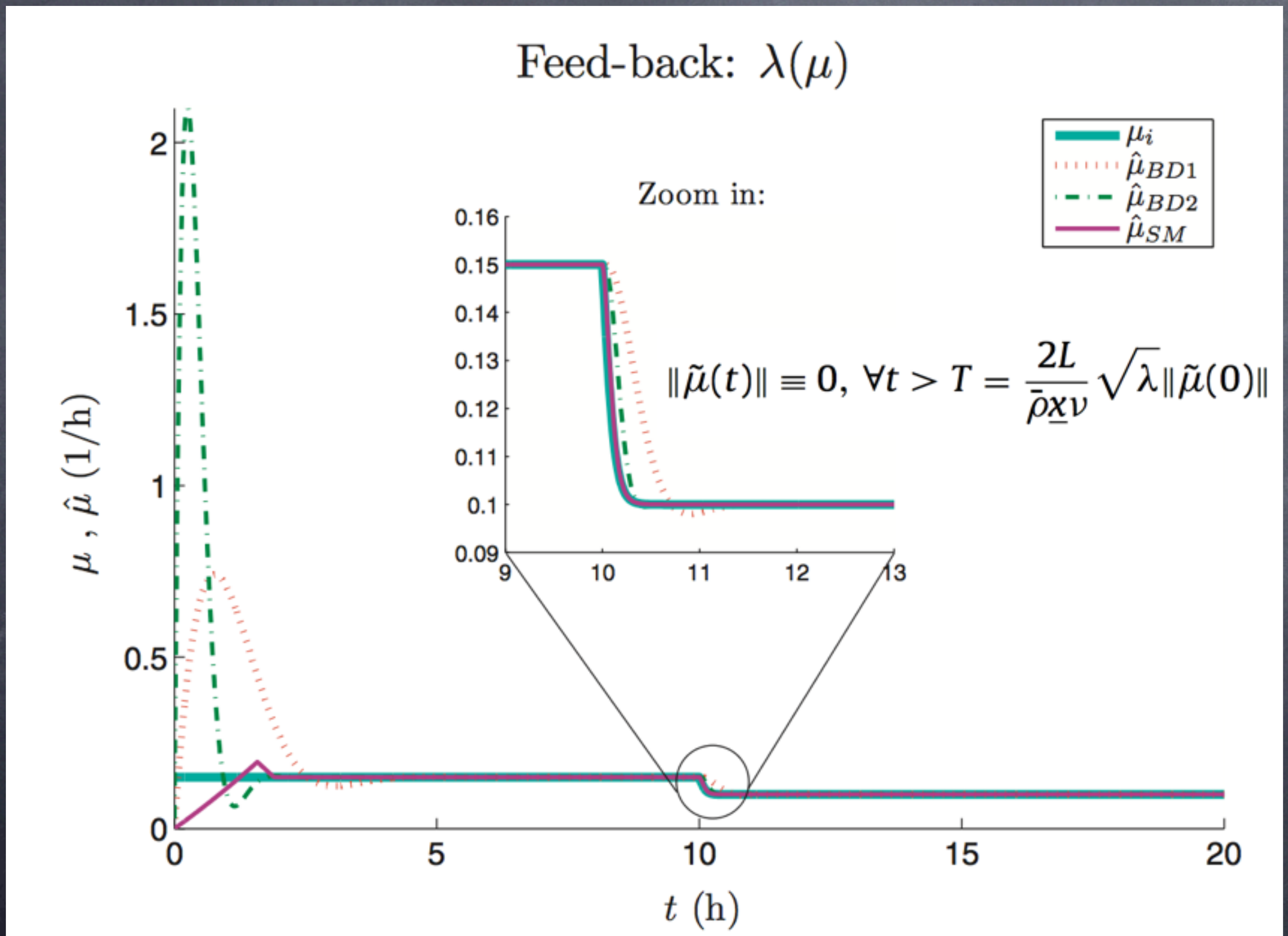


(a) Measured biomass concentration

(b) Estimates of the specific growth rate obtained by sensor output differentiation and using B&D and sliding observers.

(c) Biomass estimation error of the sliding observer.

Simulaciones en bucle cerrado



Deshaciéndose de las LMI?

- Ideas clave:
  - Cambio NL de variables + escalado temporal
  - Escalado temporal: convergencia en t infinito en nuevas variables implica convergencia en t finito en originales
  - Prueba usando *stability preserving maps*
- Observador super-twisting resultante:

$$\dot{\hat{x}} = [\hat{\mu} - D(x,t) + (\eta + k)|x - \hat{x}|^{1/2}\mathrm{sgn}(x - \hat{x}))]\, x$$

$$\dot{\hat{\mu}} = \frac{1 + \eta k}{2}\mathrm{sgn}(x - \hat{x})x$$

$$\eta + k > 2\bar{\rho}$$

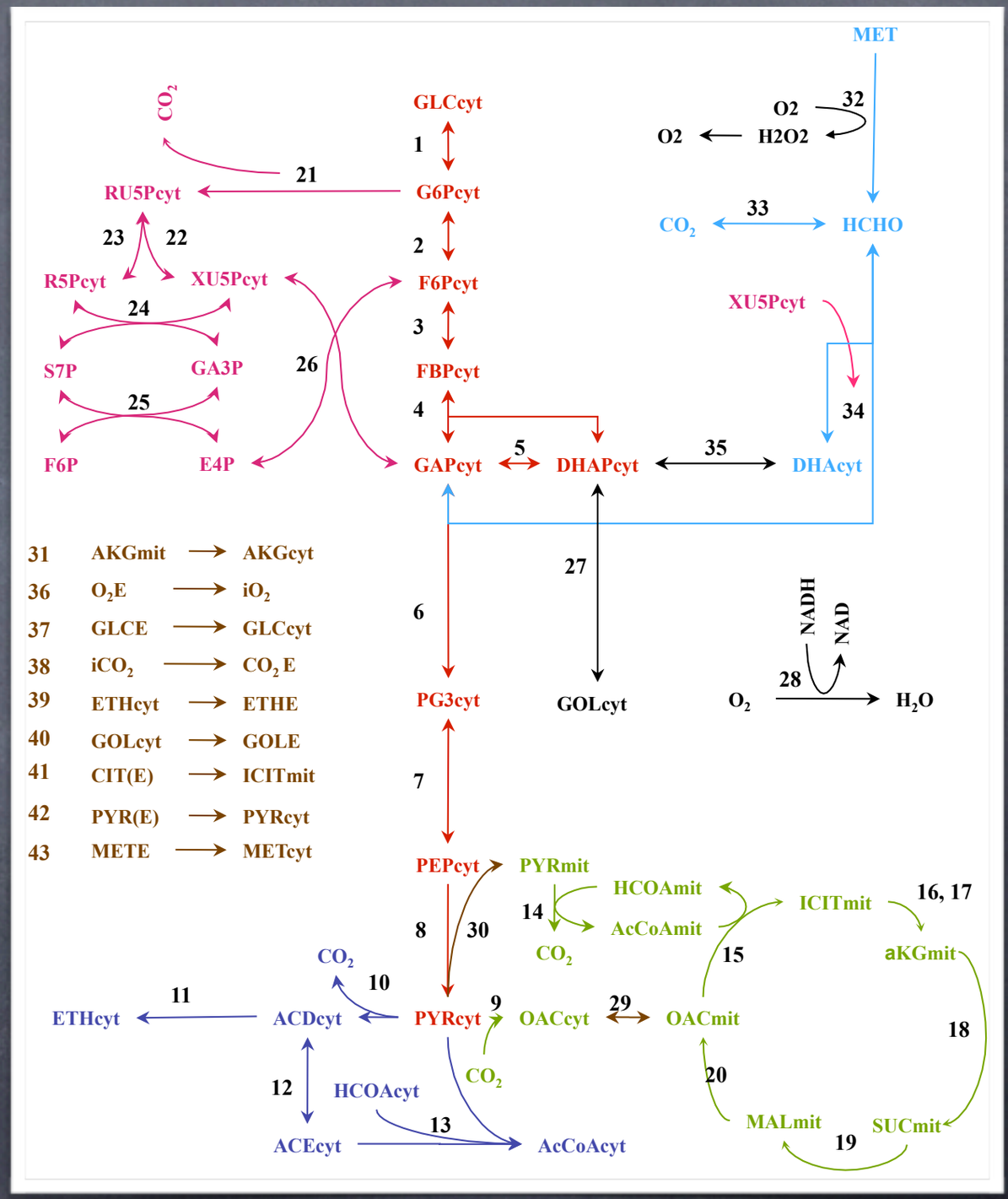
$$\eta k > 2\bar{\rho}^2$$

J. Picó et al., **Stability preserving maps for finite-time convergence: Super-twisting sliding-mode algorithm**, *Automatica*, **49**:2, 534-539, 2013.

Estimación de flujos metabólicos

MFA posibilístico

- Dados:
  - red metabólica (estado estacionario)
  - restricciones (capacidad, irreversibilidad)
- Estimar flujos

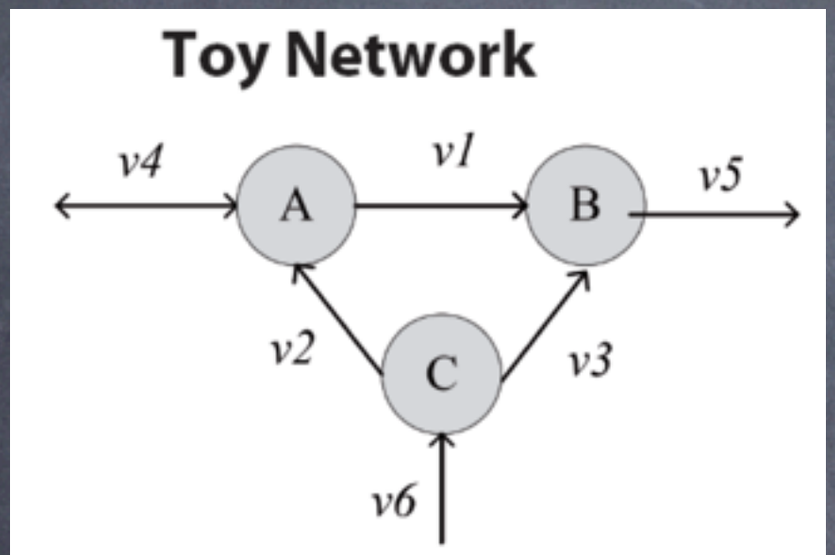


M. Tortajada et al., **Validation of a constraint-based model of *Pichia pastoris* metabolism under data scarcity**, *BMC Systems Biology*, **4**:115, 2010.

Modelos basados en restricciones (BR)

- Combinar:
  1. Conocimiento de la red (estequiometría, irreversibilidad, capacidad,...)
  2. Medidas (e.g. flujos extra-celulares medidos **vm**)

... para estimar la distribución completa de flujos **v**



$$\begin{bmatrix} -1 & 1 & 0 & -1 & 0 & 0 \\ 1 & 0 & 1 & 0 & -1 & 0 \\ 0 & -1 & -1 & 0 & 0 & 1 \end{bmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

F. Llaneras and J. Picó, **Stoichiometric modelling of cell metabolism**, *J Biosci Bioeng* **105**:1, 1-11, 2008.

- **Métodos clásicos**: tipo Mínimos cuadrados, Monte Carlo
  - Punto de vista probabilístico (normalidad de los datos)
  - Computacionalmente exigentes

Ideas clave

- Resolver un modelo BR equivale a un Problema de Satisfacción de Restricciones (CSP)
  - Factibilidad: en que medida modelo y medidas son compatibles?

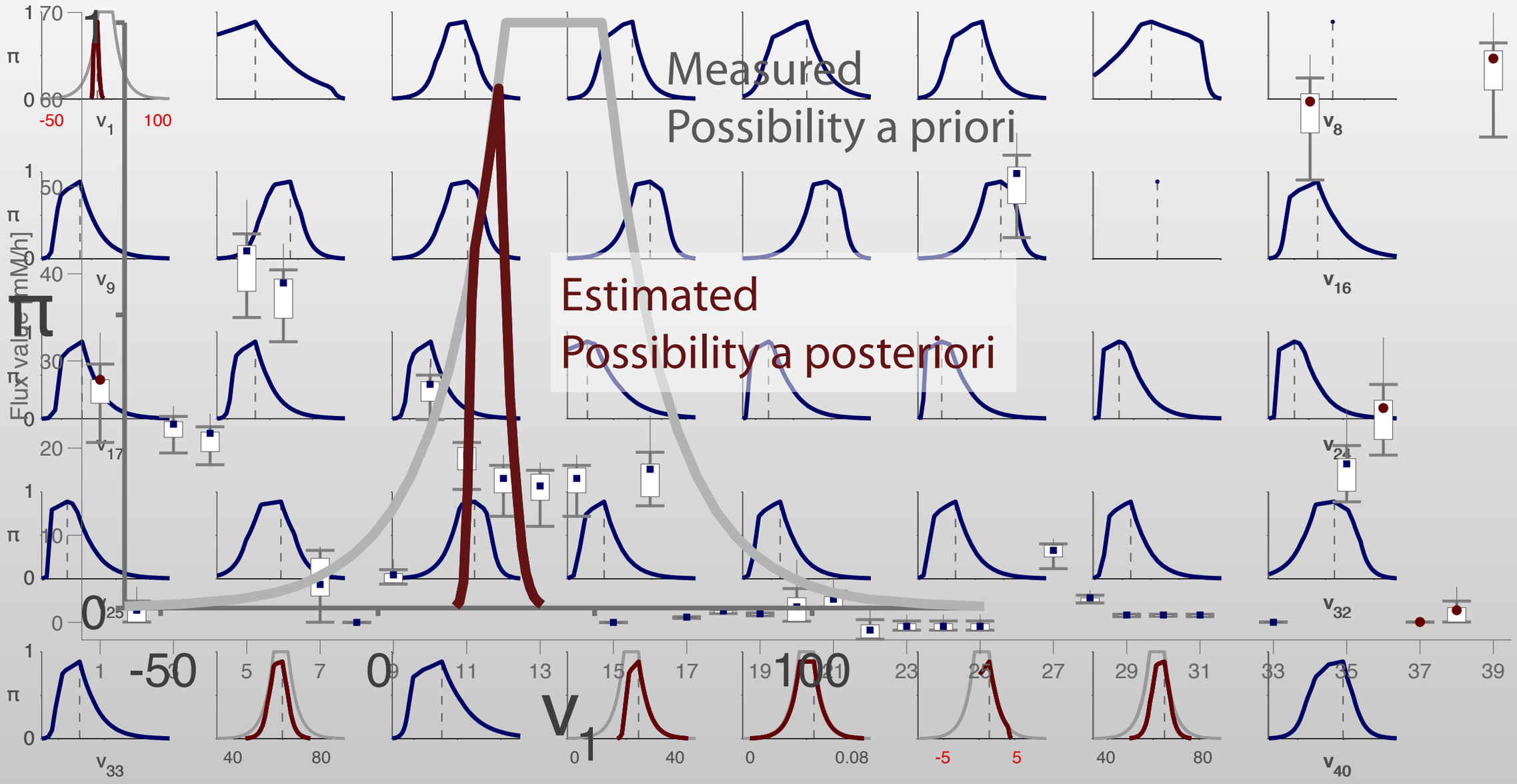
    Dado un conjunto de medidas $\hat{v}_m$ de los flujos medibles v_m,encontrar el conjunto (v_u, v_m) de flujos factibles que satisfacen las restricciones del modelo, y son compatibles con las medidas.

  - Cada solución factible (v_u, v_m) es una distribución de flujo factible

- Grado de factibilidad ⟹ Teoría de posibilidad

F. Llaneras et al., **A possibilistic framework for constraint-based metabolic flux analysis**, *BMC Systems Biology,* **3**:79, 2009.

Resultados



6 measured fluxes
v1, v34, v36, v37, v38, v39

Poss. distributions
Poss. distributions
(measured fluxes)

Box-plots cond. possibility
$\pi = 1, 0.8, 0.5, 0.1$

Biología Sintética

¿Que es la Biología Sintética?

- la ingeniería de la biología: (re)diseño y construcción de nuevos dispositivos y sistemas biológicos a escala celular, con el fin de realizar nuevas funciones de utilidad práctica.

- Disciplina ingenieril:
  - deseo de construir dispositivos que no existen
  - orientación práctica
  - uso de principios y metodologías ingenieriles en el diseño, construcción y caracterización de sistemas biológicos.

iGEM

Synthetic Biology

based on standard parts

- About
- What is iGEM?
- iGEM Values
- Previous Competitions
- Leadership
- Staff
- Financials
- FAQ
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Programs

- iGEM Competition
- Labs Program

In Memory of Austen Heinz
26 May 2015
[read more]

Welcome to iGEM

The iGEM Foundation is dedicated to education and competition, advancement of synthetic biology, and the development of open community and collaboration.

The main prog
Genetically En
Competition is
Biology. Since
experienced e
unique compet

iGEM is also m
a long history
development o

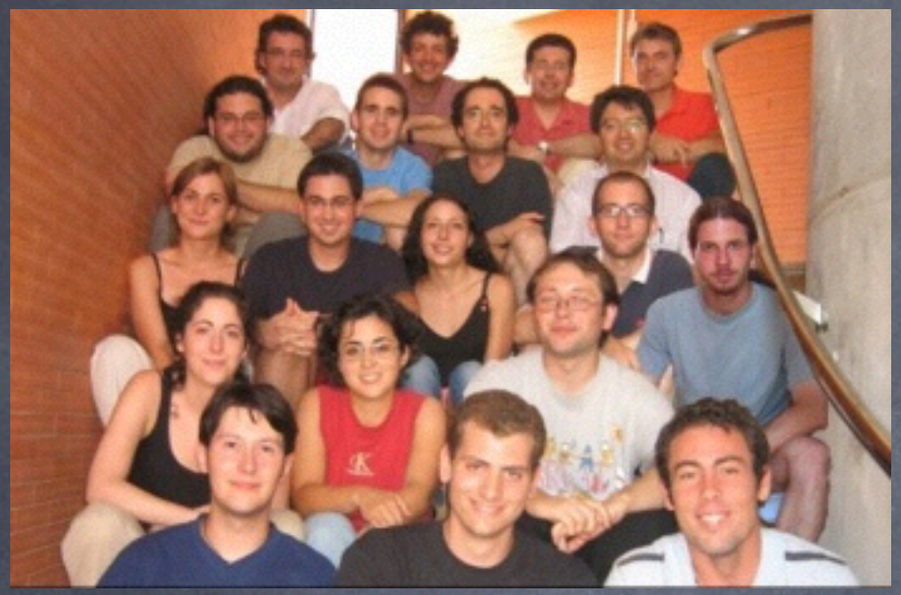
iGEM 2015 Competition

We look forward to welcoming both newcomers and returning iGEM teams! For the most up-to-date information, keep an eye

Giant Jami

September 24
With no regis

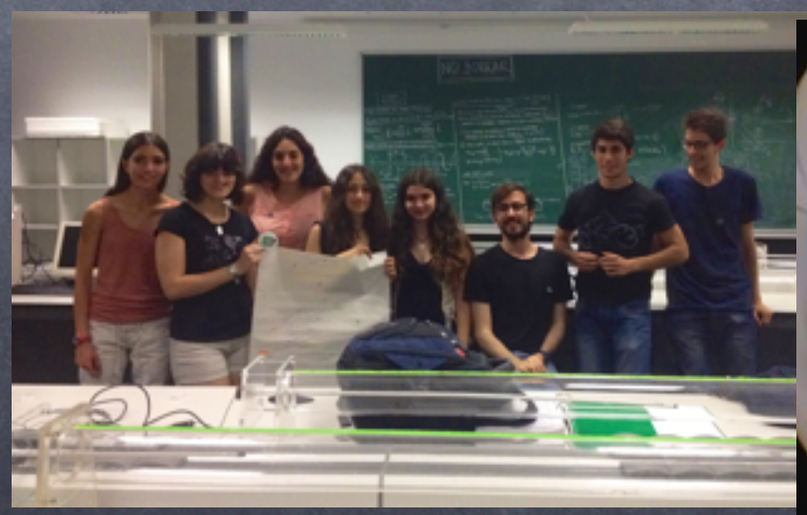
iGEM en la UPV



2007:Making E. coli tasting flavors

2013:Wormboys (UV-UPV)
Prize: Best New Application

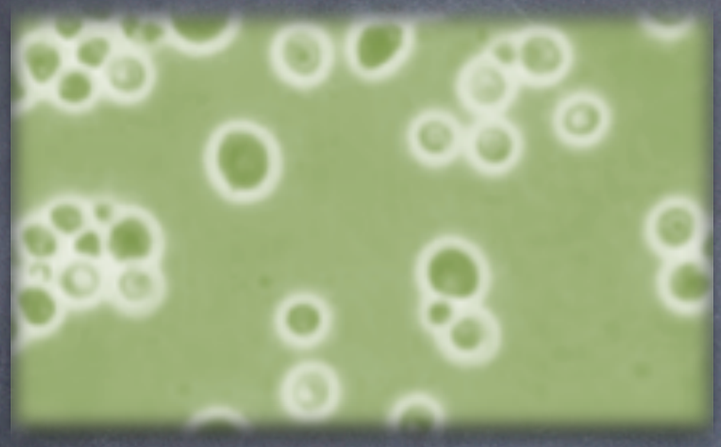
2014:SexyPlant
Prize: Best Parts Collection



2015: BioPharma

Realimentación y control celular para el control de variabilidad en la expresión de proteínas

- Objetivo: regular expresión (producción) de proteínas para evitar heterogeneidad sobre poblaciones celulares



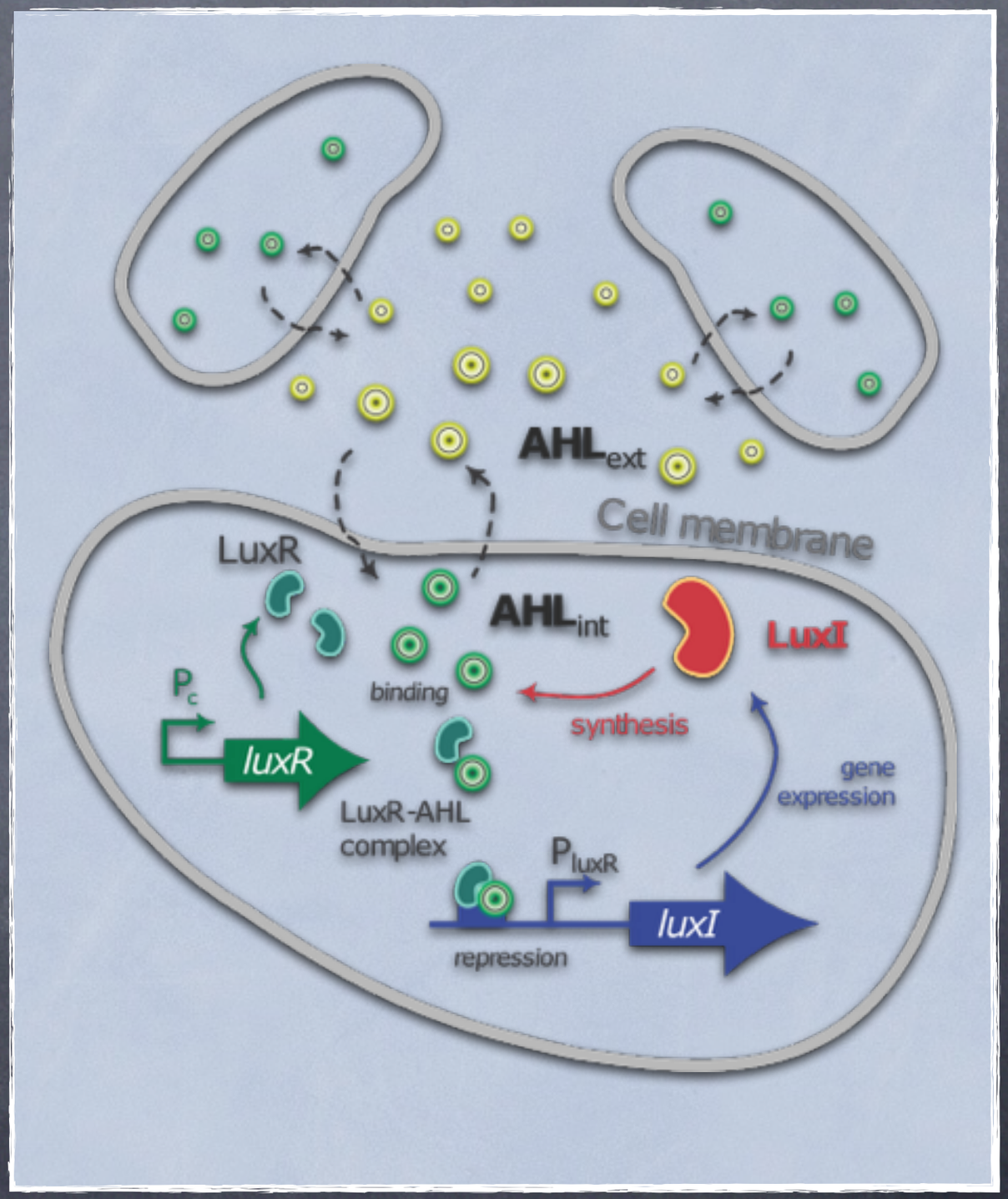
Source: M. Tortajada (Biopolis S.L.)

Source: Biopolis S.L.

- Sub-objetivos prácticos :
  - Regular el valor medio de producción
  - Minimizar la varianza de la producción
- Métodos básicos de diseño:
  - Consensus, estabilidad sobre agentes (contractividad)

Circuito genético sintético de regulación

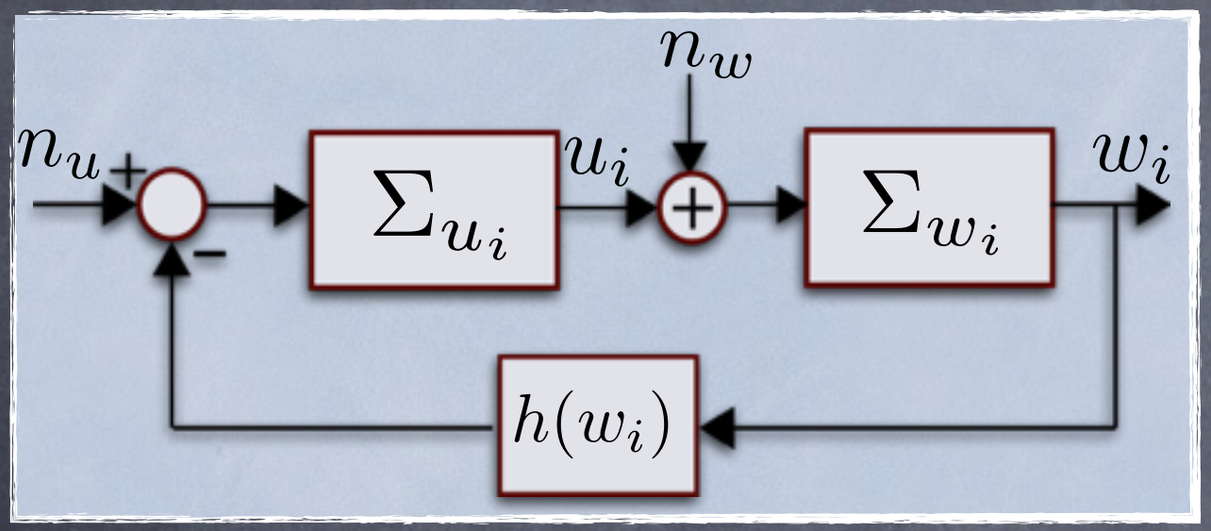
- Combina:
  - comunicación celular basada en *quorum sensing*. (Fuqua, Ann. Rev. Genetics, 2001)
  - realimentación negativa interna. (Egland, J. Bacteriology, 2000)



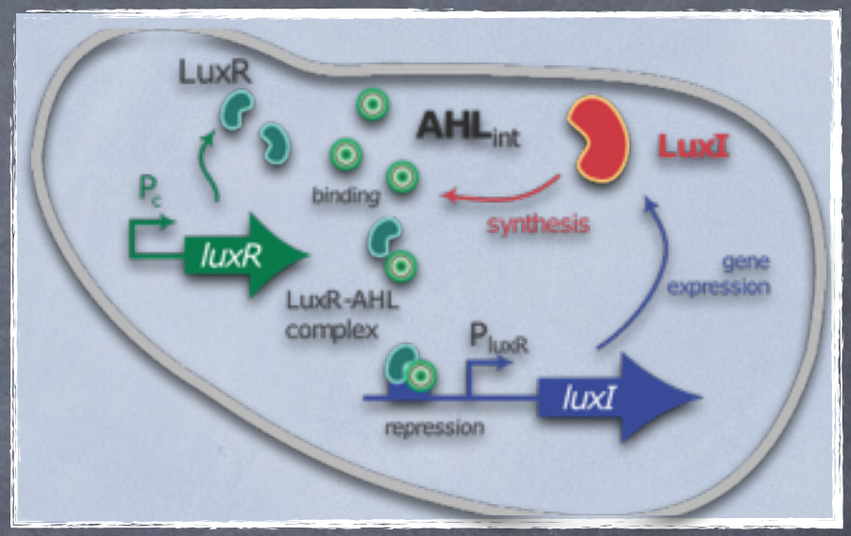
Dinámica celular aislada (modelo simplificado)

- ¿Que podemos conseguir sólo con control en cada célula?

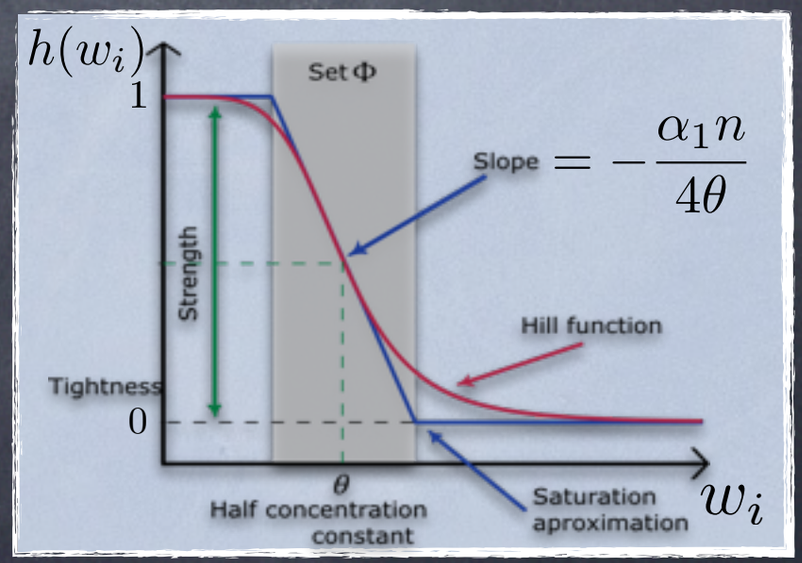
$$\text{Cell}_i : \begin{cases} \frac{du_i}{dt} = \alpha_0 + \alpha_1 h(w_i) - \gamma_1 u_i \\ \frac{dw_i}{dt} = \epsilon\left(\alpha_2 u_i - w_i\right) + d\left(w_e - w_i\right) \end{cases}$$

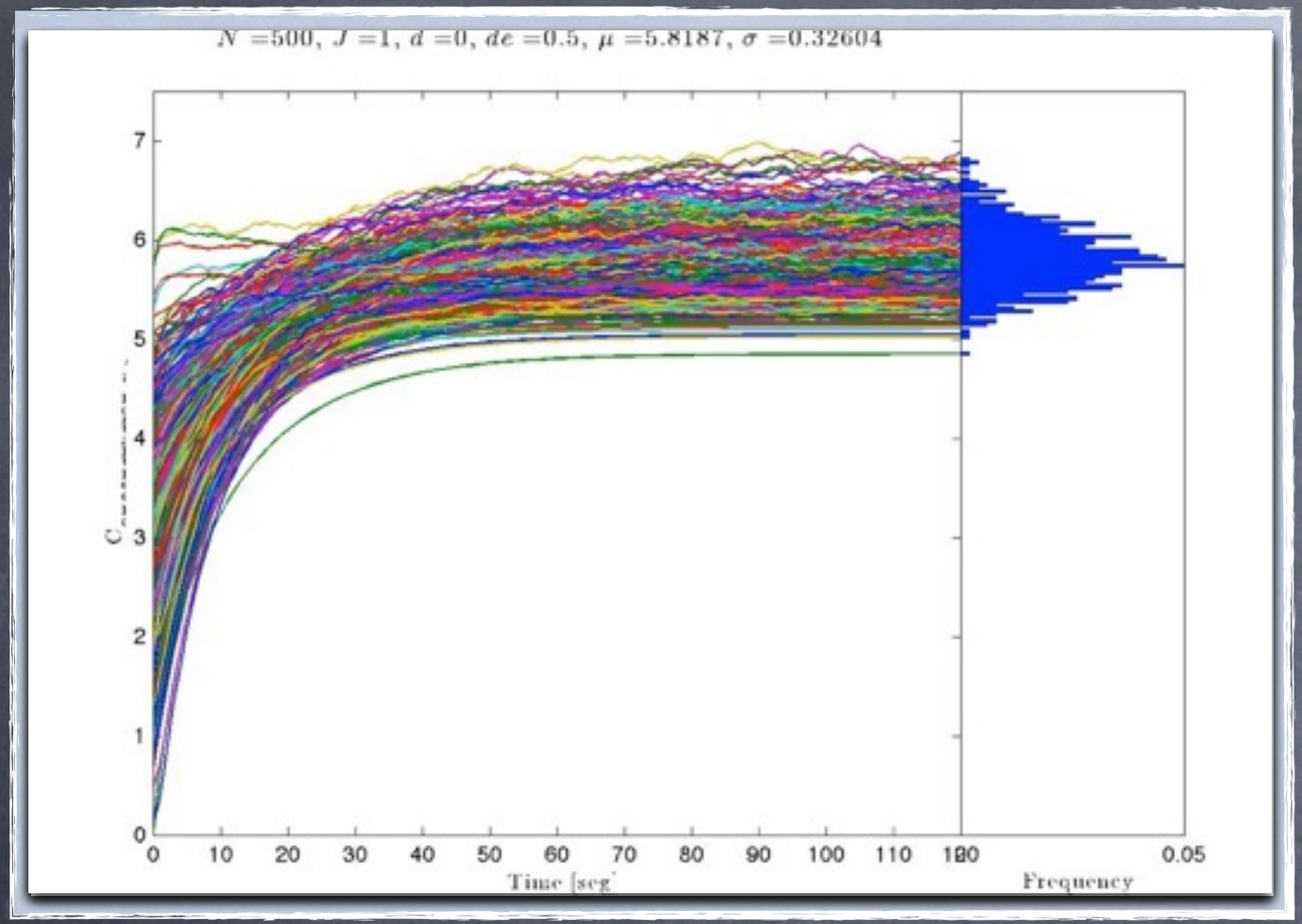


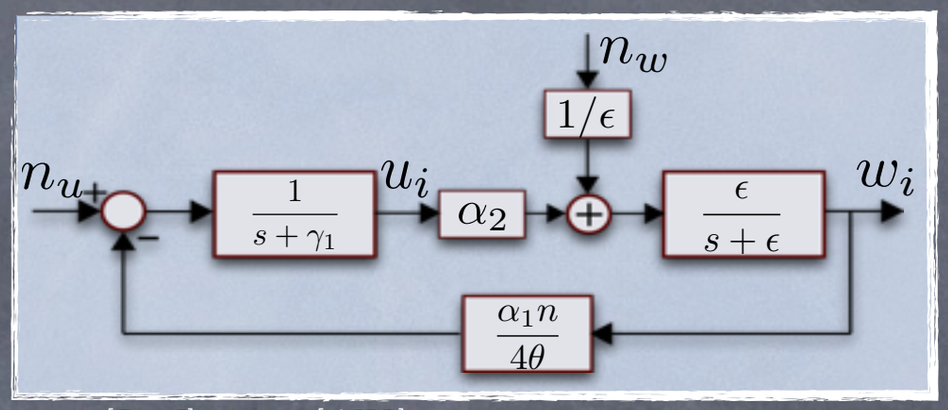
$u_i = [LuxI]_i \quad w_i = [AHL]_i$



- Control alta ganancia-> invarianza
- $w_i = [AHL]_i \longrightarrow \Phi$
- Aproximación lineal en Φ







$u_i = [LuxI]_i \quad w_i = [AHL]_i$

$$FF_{n=1} = 0.018$$
$$FF_{n=2} = 0.012$$
$$FF_{n=3} = 0.008$$

- Dinámica más rápida
- varianza decrece con control más enérgico (mayor n)
- Media y varianza están acopladas

Comunicación al rescate

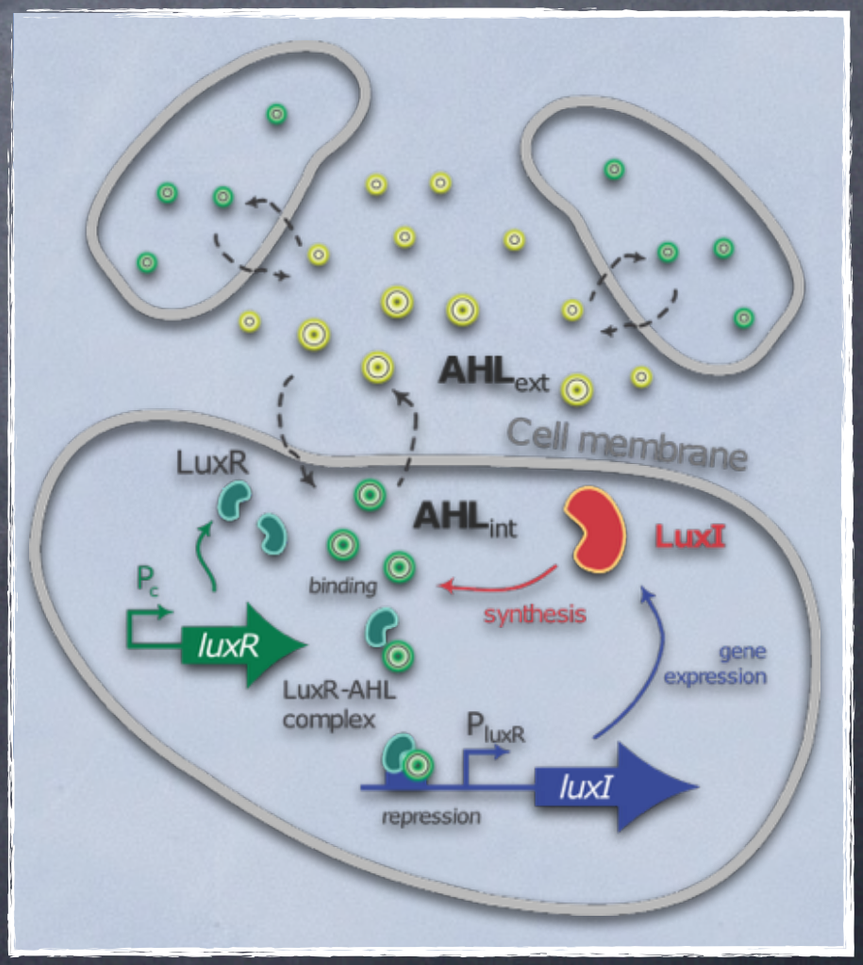
- ¿Qué podemos conseguir añadiendo comunicación?

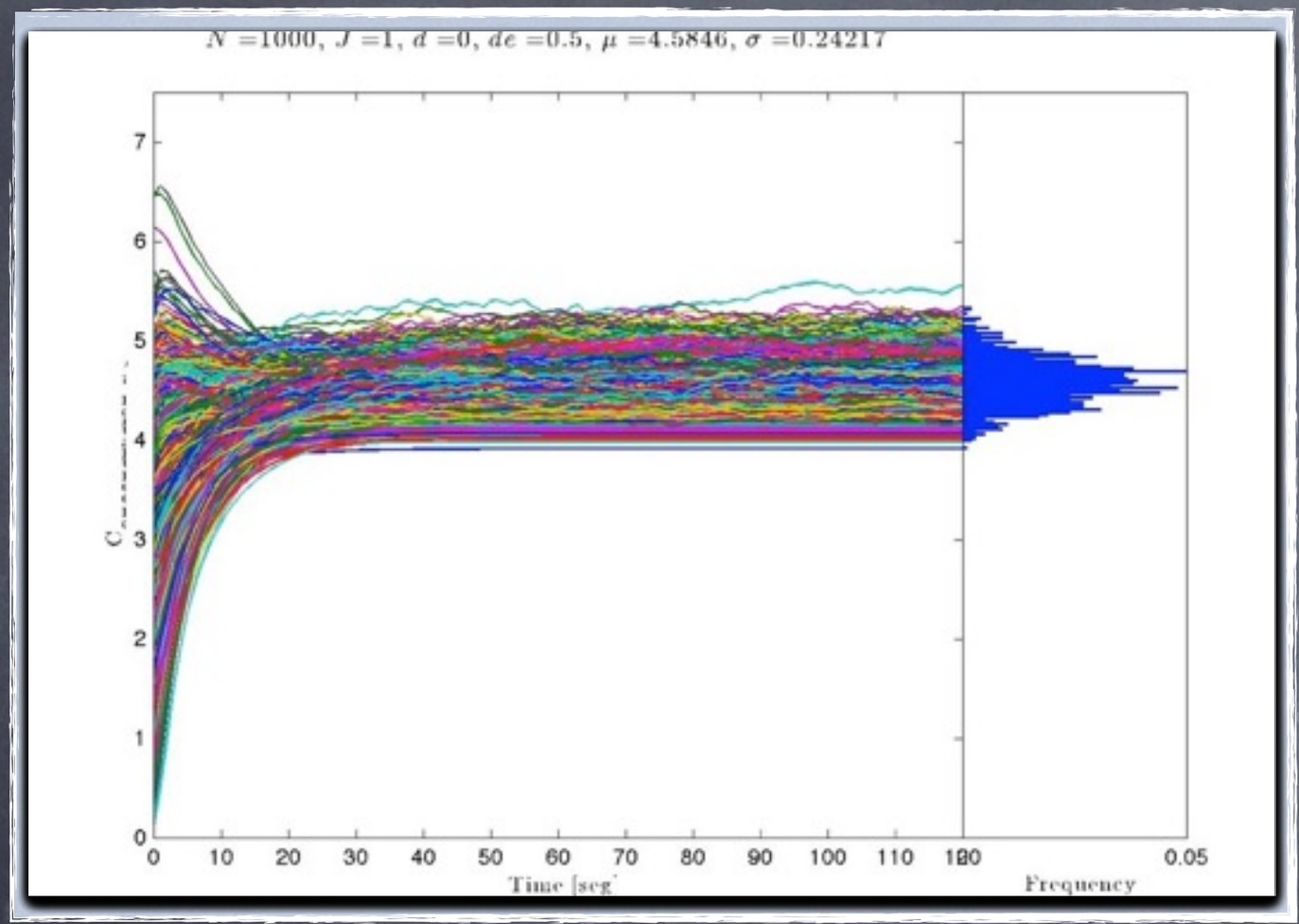
$$\text{Cell}_i : \begin{cases} \frac{du_i}{dt} = \alpha_0 + \alpha_1 h(w_i) - \gamma_1 u_i \\ \frac{dw_i}{dt} = \epsilon\,(\alpha_2 u_i - w_i) + d\,(w_e - w_i) \end{cases}$$

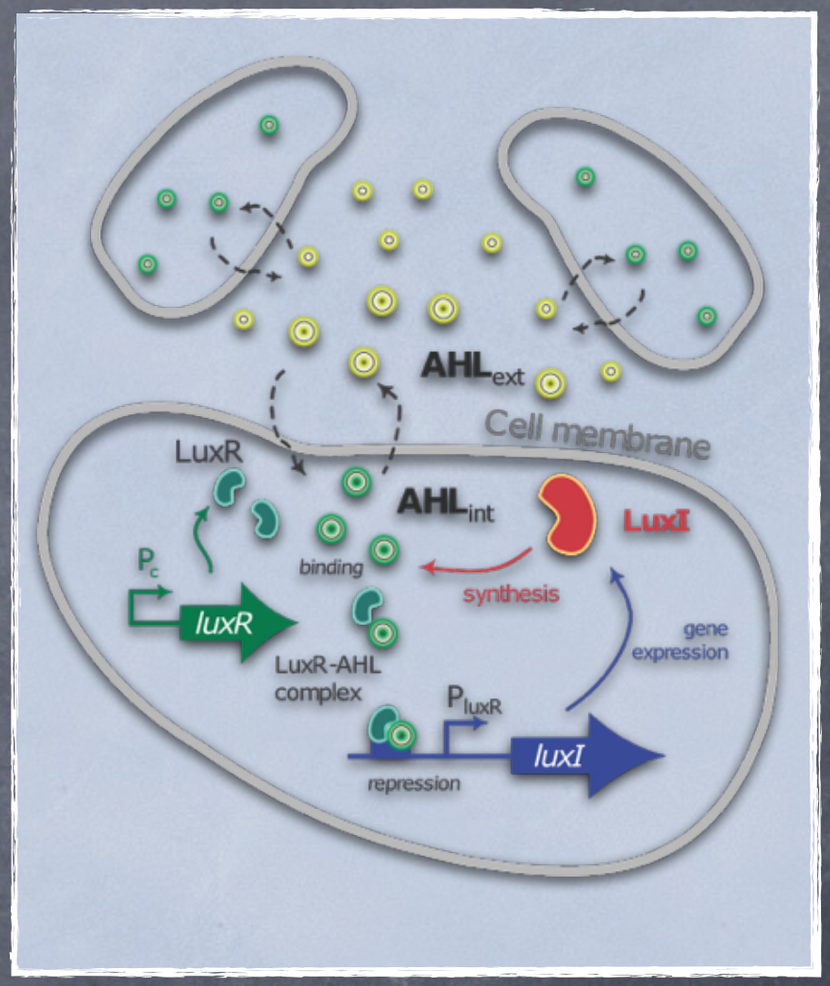
$$\frac{dw_e}{dt} = \frac{d_e}{N}\sum_{i=1}^{N}(w_i - w_e) - \gamma_e w_e = \frac{d_e}{N}\sum_{i=1}^{N} w_i - (d_e + \gamma_e) w_e$$

- Φ aún atractivo e invariante
- Aproximación lineal en Φ

A. Vignoni, D.A. Oyarzún, J. Picó and G.B. Stan, **Control of protein concentrations in heterogeneous cell populations**, *Procs. ECC 2013*, 3633-3639, 2013.

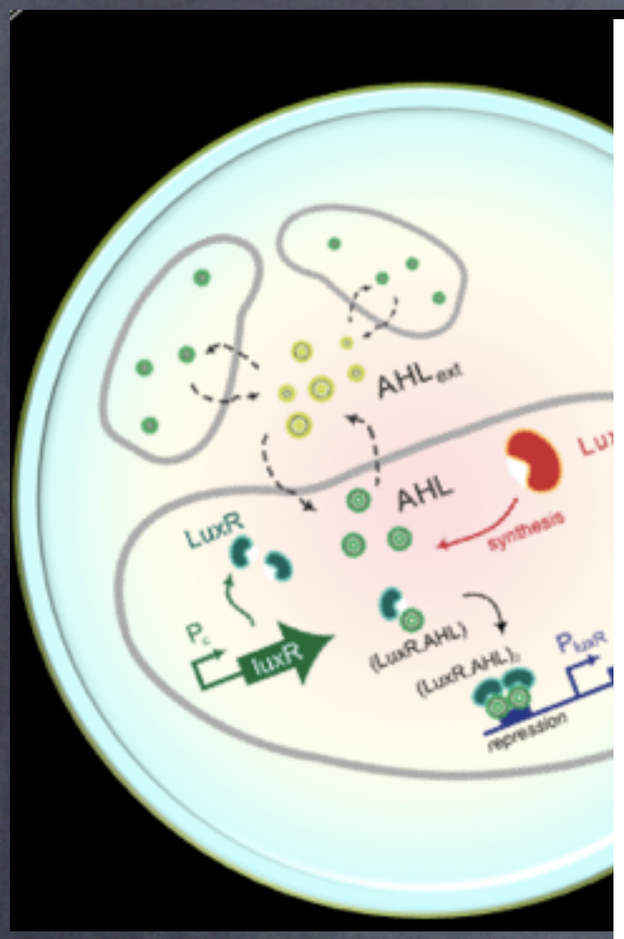




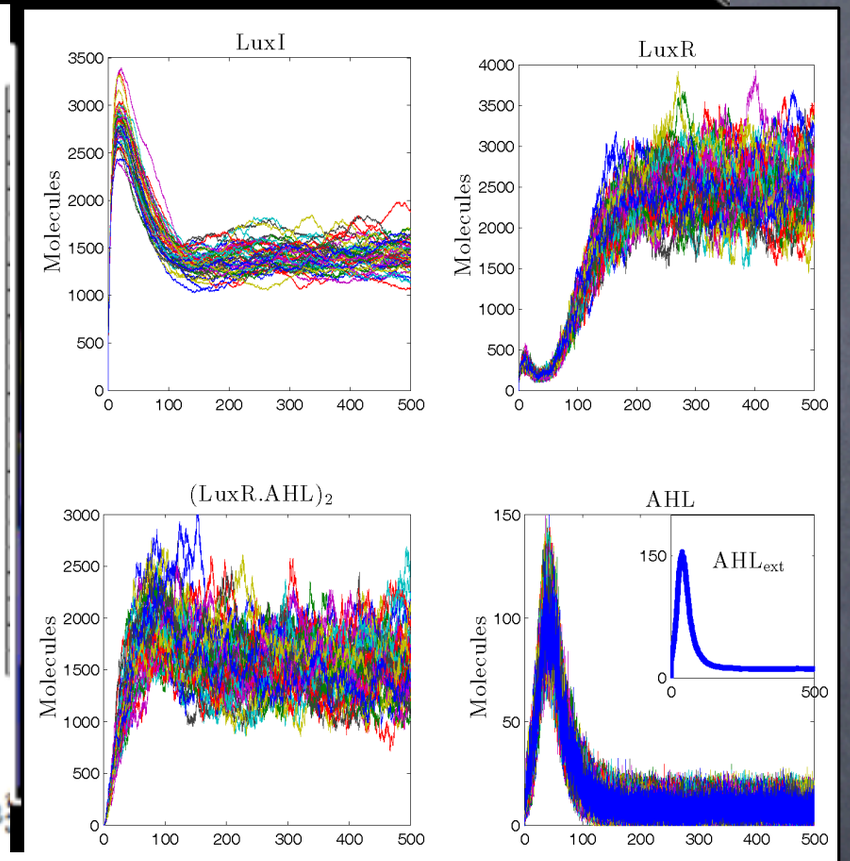


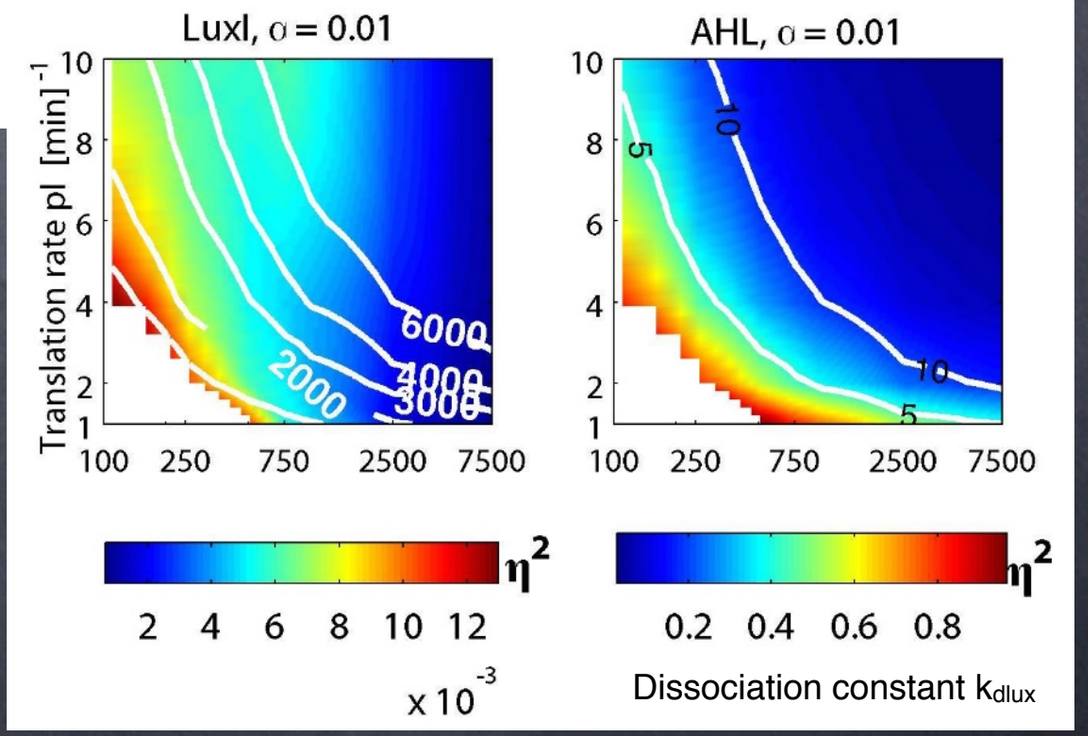
- Varianza decrece con mayor comunicación (mayor d)
- Media y varianza (casi) desacopladas

¿Que más hace falta?



$$\dot{n}_1^i = k_{\mathrm{mLuxI}} n_7^i + \alpha_{\mathrm{mLuxI}} k_{\mathrm{mLuxI}} n_8^i - d_{m_I} n_1^i$$
$$\dot{n}_2^i = k_{\mathrm{mLuxR}} c_n - d_{m_R} n_2^i$$
$$\dot{n}_3^i = k_{\mathrm{LuxI}} n_1^i - d_I n_3^i$$
$$\dot{n}_4^i = k_{\mathrm{LuxR}} n_2^i + k_1^- n_5^i - d_R n_4^i - \frac{k_1^-}{k_{d1}} n_9^i n_4^i$$
$$\dot{n}_5^i = 2k_2^- n_6^i + \frac{k_1^-}{k_{d1}} n_9^i n_4^i - \left(k_1^- + d_{RA} + 2\frac{k_2^-}{k_{d2}} n_5^i \right) n_5^i$$
$$\dot{n}_6^i = k_{\mathrm{lux}}^- n_8^i + \frac{k_2^-}{k_{d2}} (n_5^i)^2 - \left(k_2^- + d_{RA_2} + \frac{k_{\mathrm{lux}}^-}{k_{\mathrm{dlux}}} n_7^i \right) n_6^i$$
$$\dot{n}_7^i = k_{\mathrm{lux}}^- n_8^i - \frac{k_{\mathrm{lux}}^-}{k_{\mathrm{dlux}}} n_6^i n_7^i$$
$$\dot{n}_8^i = -k_{\mathrm{lux}}^- n_8^i + \frac{k_{\mathrm{lux}}^-}{k_{\mathrm{dlux}}} n_6^i n_7^i$$
$$\dot{n}_9^i = D \left(\frac{V_{\mathrm{cell}}}{V_{\mathrm{ext}}} n_{10} - n_9^i \right) - \left(\frac{k_1^-}{k_{d1}} n_4^i + d_A \right) n_9^i + k_1^- n_5^i + k_A n_5^i$$
$$\dot{n}_{10} = D \left(-N \frac{V_{\mathrm{cell}}}{V_{\mathrm{ext}}} n_{10} + \sum_{i=1}^{N} n_9^i \right) - d_{A_e} n_{10}$$





Conclusiones

Conclusiones

- Bioprocesos: escalas múltiples
  - Macroscópica (biorreactor)
  - Metabólica (flujos)
  - Regulación genética
- Ideas útiles de control:
  - Invarianza, adaptación, cambios de escala temporal, modos deslizantes, consensus
  - Análisis estocástico, robustez/incertidumbre
  - Integración de escalas

Entonces…¿puede un ingeniero tunear una célula?

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