Modules and Retroactivity: Theoretical Framework, Analysis, and Design

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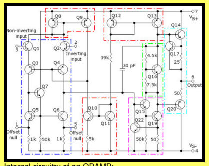
Abstract: A new theoretical approach to interconnections and modularity, based on an extension of the classical control paradigm is proposed. This new approach allows to precisely formulate and quantify the equivalent notion of impedance, which we call retroactivity, in biochemical networks. Just as in electrical circuit theory, high-gain negative feedback combined with large input gains are used in order to achieve insulation. Two biological realizations of the proposed insulation mechanism are analyzed.

Modularity: A fundamental property

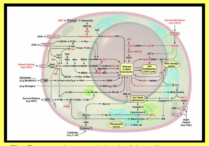


Internal circuitry of an OPAMP:
It is composed of well defined modules

Modularity guarantees that the input/output behavior of a component (a module) does not change upon interconnection.

Electronics and Control Systems Engineering rely on modularity to predict the behavior of a complex network by the behavior of the composing subsystems.

Result: Computers, Videos, cell phones…



The Emergent integrated circuit of the cell
[Hanahan & Weinberg (2000)]

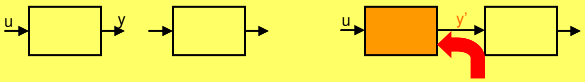
Functional modules seem to recur also in biological networks (e.g. Alon (2007)). But…

Under what conditions can they be interconnected and still maintain their behavior unchanged?

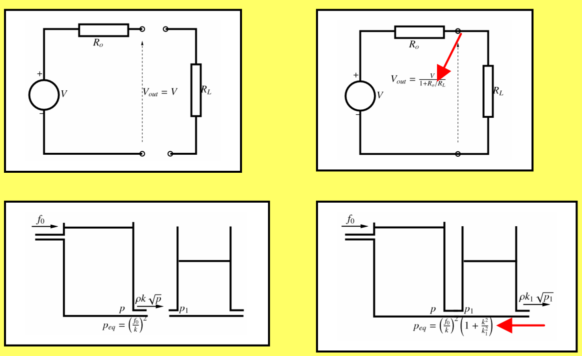
If these conditions are not always verified, what mechanism can be used to interconnect modules without altering their behavior? Does nature already employ such mechanisms?

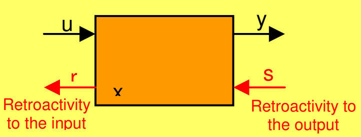
A systems theory with retroactivity

The term "retroactivity" in the context of bio-molecular systems was introduced before by J. Saez-Rodriguez et al. (2004 and 2005)



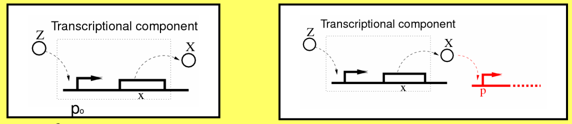
Examples: Interconnection changes the output of the upstream component



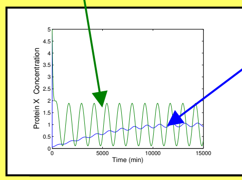


A new system model that incorporates the behavior change due to the interconnection

Retroactivity in transcriptional components



$\frac{dX}{dt} = k(t) - \delta X \quad k(t) = 1 + sin(\omega t)$



X+p $\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}}$ C,

$p + C = p_{TOT}$

$$\frac{dX}{dt} = k(t) - \delta X + k_{off}C - k_{on}(p_{TOT} - C)X$$
$$\frac{dC}{dt} = -k_{off}C + k_{on}(p_{TOT} - C)X,$$

S

The binding sites p drain the output X

Quantification of the retroactivity

Use separation of time scale between the X production and decay processes (internal dynamics) and the binding reaction of X to p (interconnection dynamics)

$k_{off} \gg \delta$ and $k_{on} = k_{off}/k_d$

$$\frac{dy}{dt} = k(t) - \delta(y - C)$$
$$\epsilon\frac{dC}{dt} = -\delta C + \frac{\delta}{k_d}(p_{TOT} - C)(y - C),$$
$$\epsilon = \delta/k_{off}$$
$$y = X + C \text{ (total protein concentration)}$$

$C = \gamma(y)$ (the slow manifold) $\quad \epsilon = 0$

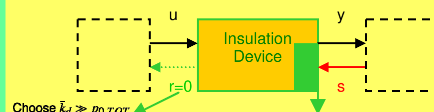
$$\frac{dX}{dt} = (k(t) - \delta X)(1 - \frac{d\gamma(y)}{dy})$$

Dynamics of X after a fast transient

Retroactivity s after a fast transient

$$\mathcal{R}(X, t) = \frac{1}{1 + \frac{(1+X/k_d)^2}{p_{TOT}/k_d}}$$

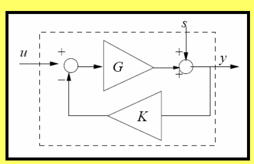
Attenuation of the retroactivity



The insulation device does not alter the dynamics of an upstream system (r=0) and is not altered by s because s is completely attenuated

Choose $\bar{k}_d \gg p_{0,TOT}$ and/or $Z(t) \gg p_{0,TOT}$

S is completely attenuated through amplification Plus negative feedback



$$y = G(u - Ky) + s \Rightarrow y = u\frac{G}{1 + KG} + \frac{s}{1 + KG}$$

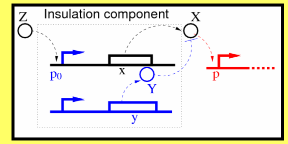
$$\frac{dX}{dt} = Gk(t) - (GKX + \delta X)(1 - \frac{d\gamma(y)}{dy})$$
$$\frac{dX_r}{dt} = Gk(t) - (GKX + \delta X)$$

as G grows $X(t) \to X_r(t)$

Biological realizations of insulation devices

Need to realize a large input amplification gain and a large output negative feedback

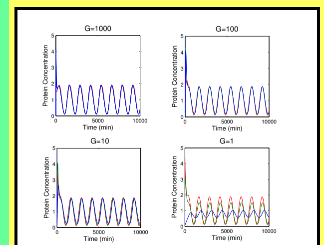
Design 1: Amplification through strong, non-leaky promoter and negative feedback through enhanced degradation via a protease



$$X + Y \underset{\eta}{\overset{\eta}{\rightleftharpoons}} W \xrightarrow{\beta} Y$$

$$\frac{dZ}{dt} = k(t) - \delta Z + k_- Z_p - k_+ Z(p_{0,TOT} - Z_p)$$
$$\frac{dZ_p}{dt} = k_+ Z(p_{0,TOT} - Z_p) - k_- Z_p$$
$$\frac{dm_X}{dt} = GZ_p - \delta_1 m_X$$
$$\frac{dX}{dt} = \nu m_X - \eta YX + \eta W - \delta_2 X + k_{on}C - k_{off}X(p_{TOT} - C)$$
$$\frac{dW}{dt} = \eta XY - \eta W - \beta W$$
$$\frac{dY}{dt} = -\eta YX + \beta W + \alpha G - \gamma Y + \eta W$$

r
s



Red: Z concentration; Green: X concentration with no sites p; Blue: X concentration with sites p

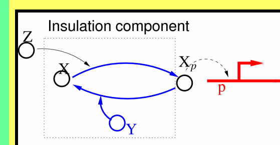
To make r small: $p_{0,TOT}/\bar{k}_d \ll 1, \bar{k}_d = k_-/k_+$

To attenuate s: G large

Values of the gain for which the retroactivity to the output s is well attenuated are G=100,1000, which may be difficult to realize *in vivo.*

Design 2: Amplification through phosphorylation and negative feedback through dephosphorylation

$$X + Z \underset{\beta_2}{\overset{\beta_1}{\rightleftharpoons}} C_1 \xrightarrow{k_1} X_p + Z$$
$$Y + X_p \underset{a_2}{\overset{a_1}{\rightleftharpoons}} C_2 \xrightarrow{k_2} X + Y$$
$$Y_{TOT} = Y + C_2, \; X_{TOT} = X + X_p + C_1 + C_2$$



$$\frac{dZ}{dt} = k(t) - \delta Z - \beta_1 Z(X_{TOT} - X_p - C_1 - C_2) + (\beta_2 + k_1)C_1$$
$$\frac{dC_1}{dt} = -(\beta_2 + k_1)C_1 + \beta_1 Z(X_{TOT} - X_p - C_1 - C_2)$$
$$\frac{dC_2}{dt} = -(k_2 + \alpha_2)C_2 + \alpha_1 X_p(Y_{TOT} - C_2)$$
$$\frac{dX_p}{dt} = k_1 C_1 + \alpha_2 C_2 - \alpha_1 X_p(Y_{TOT} - C_2) + k_{on}C - k_{off}X_p(p_{TOT} - C)$$
$$\frac{dC}{dt} = -k_{on}C + k_{off}X_p(p_{TOT} - C)$$

r
s

Phosphorylation and dephosphosrylation reactions are much faster than protein production and decay

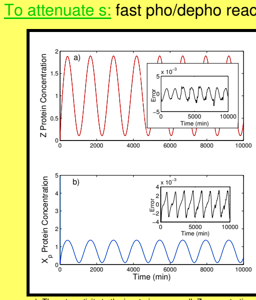
$\beta_i = \delta b_i/\epsilon, \alpha_i = \delta a_i/\epsilon, k_i = \delta c_i/\epsilon,$
$k_{on} = k_{off}/k_d, k_{off}\epsilon = \delta,$and $z = Z + C_1$

$$\frac{dz}{dt} = k(t) - \delta(z - C_1)$$
$$\epsilon\frac{dC_1}{dt} = -\delta(b_2 + c_1)C_1 + \delta b_1(z - C_1)(X_{TOT} - X_p - C_1 - C_2)$$
$$\epsilon\frac{dC_2}{dt} = -\delta(c_2 + a_2)C_2 + \delta a_1 X_p(Y_{TOT} - C_2)$$
$$\epsilon\frac{dX_p}{dt} = \delta c_1 C_1 + a_2 C_2 - a_1 X_p(Y_{TOT} - C_2) + \delta C - \delta/k_d(p_{TOT} - C)X_p$$
$$\epsilon\frac{dC}{dt} = -\delta C + \delta/k_d(p_{TOT} - C)X_p$$

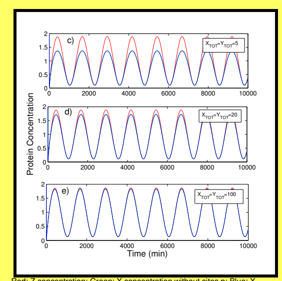
When ε=0, the retroactivity to the output s disappear

To make r small: $X_{TOT} \ll \gamma = (\beta_2 + k_2)/\beta_1$

To attenuate s: fast pho/depho reactions



a): The retroactivity to the input r is very small. Z concentration with (red) an without (black) sites p₀ is the same.
b): The retroactivity to the output s is completely attenuated. X concentration with (blue) and without (green) sites p is the same.



Red: Z concentration; Green: X concentration without sites p; Blue: X concentration with sites p. The only effect of the total concentrations of X and Y is to decrease the nonlinear distortion when they increase.

Phosphorylation/dephosphorylation cycles display a remarkable insulation property by virtue of their fast time scale