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To cite this version:
Michel Fliess, Cédric Join. Dynamic compensation and homeostasis: a feedback control perspective. [Research Report] Ecole polytechnique X. 2018, pp.1-22. hal-01684422v2

HAL Id: hal-01684422
https://hal-polytechnique.archives-ouvertes.fr/hal-01684422v2
Submitted on 15 Jan 2018

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Dynamic compensation and homeostasis:
a feedback control perspective

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Abstract

“Dynamic compensation” is a robustness property where a perturbed biological circuit maintains a suitable output [Karin O., Swisa A., Glaser B., Dor Y., Alon U. (2016). Mol. Syst. Biol., 12: 886]. In spite of several attempts, no fully convincing analysis seems now to be on hand. This communication suggests an explanation via “model-free control” and the corresponding “intelligent” controllers [Fliess M., Join C. (2013). Int. J. Contr., 86, 2228-2252], which are already successfully applied in many concrete situations. As a byproduct this setting provides also a slightly different presentation of homeostasis, or “exact adaptation,” where the working conditions are assumed to be “mild.” Several convincing, but academic, computer simulations are provided and discussed.

Keywords: Systems biology, homeostasis, exact adaptation, dynamic compensation, integral feedback control, PID, model-free control, intelligent proportional controller.
1. Introduction

In systems biology, i.e., an approach of growing importance to theoretical biology (see, e.g., Alon (2006); Klipp et al. (2016); Kremling (2012)), basic control notions, like feedback loops, are becoming more and more popular (see, e.g., Åström et al. (2008); Cowan et al. (2014); Cosentino et al. (2011); Del Vecchio et al. (2015)). This communication intends to show that a peculiar feedback loop permits to clarify the concept of dynamic compensation (DC) of biological circuits, which was recently introduced by Karin et al. (2016). DC is a robustness property. It implies, roughly speaking, that biological systems are able of maintaining a suitable output despite environmental fluctuations. As noticed by Karin et al. (2016) such a property arises naturally in physiological systems. The DC of blood glucose, for instance, with respect to variation in insulin sensitivity and insulin secretion is obtained by controlling the functional mass of pancreatic beta cells.

The already existing and more restricted homeostasis, or exact adaptation, deals only with constant reference trajectories, i.e., setpoints. It is achievable via an integral feedback (see, e.g., Alon et al. (1999); Briat et al. (2016); Miao et al. (2011); Stelling et al. (2004); Yi et al. (2000))

Remark 1.1. PIDs (see, e.g., Åström et al. (2008); O’Dwyer (2009)) read:

\[ u = K_P e + K_I \int e + K_D \dot{e} \]  

where

- \( u, y, y^* \) are respectively the control and output variables, and the reference trajectory.
- \( e = y - y^* \) is the tracking error,
- \( K_P, K_I, K_D \in \mathbb{R} \) are the tuning gains.

To the best of our knowledge, they are, strangely enough, more or less missing
in the literature on theoretical biology\footnote{This is of course less the case in synthetic biology, i.e., a blending between biology and engineering (see, e.g., Del Vecchio et al. (2016) and the references therein).}, although they lead to the most widely used control strategies in industry.

From $K_P = K_D = 0$ in Equation (1), the following integral feedback is deduced:

$$u = K_I \int e$$

(2)

\footnote{A rather comprehensive bibliography of concrete applications is provided by Abouaïssa et al. (2017a).}

Compare Equation (2) with the references above on homeostasis, and Somvanshi et al. (2015). See Abouaïssa et al. (2017b), and the references therein, for an application to ramp metering on freeways in order to avoid traffic congestion.

Conditions for DC have already been investigated by several authors: Karin et al. (2017a,b); Sontag (2017); Villaverde et al. (2017). Parameter identification, which plays a key rôle in most of those studies, leads, according to the own words of Karin et al. (2017b), to some kind of “discrepancy,” which is perhaps not yet fully cleared up. We suggest therefore another roadmap, i.e., intelligent feedback controllers as defined by Fliess et al. (2013). Many concrete applications have already been developed all over the world. Some have been patented. The bibliography contains for obvious reasons only recent works in biotechnology: Bara et al. (2016); Join et al. (2017a); Lafont et al. (2015); MohammadRidha et al. (2018); Tebbani et al. (2016).\footnote{A rather comprehensive bibliography of concrete applications is provided by Abouaïssa et al. (2017a).}

An unexpected byproduct is derived from Remark 1.1 and the comparison in Abouaïssa et al. (2017b) between Equation (2) and our intelligent proportional controller (Fliess et al. 2013). Exact adaptation means now a “satisfactory” behavior thanks to the feedback loop defined by Equation (2) when the working conditions are “mild.” The result by Karin et al. (2016) via a mechanism for DC based on known hormonal circuit reactions, which states that exact adaptation does not guarantee dynamical compensation, remains therefore valid in this new context.
This exploratory research report is organized as follows. Intelligent controllers are summarized in Section 2 where the connection between classic PIs and intelligent proportional controllers is also presented. Section 3, which is heavily influenced by Abouaïssa et al. (2017b), defines dynamic compensation and exact adaptation. Section 4 displays various convincing, but academic, computer experiments. Some concluding remarks may be found in Section 5.

2. Model-free control and intelligent controllers

See Fliess et al. (2013) for full details.

2.1. Generalities

2.1.1. The ultra-local model

The poorly known global description of the plant, which is assumed for simplicity’s sake to be SISO (single-input single output), is replaced by the ultra-local model:

\[ y^{(\nu)} = F + \alpha u \]

where:

- the control and output variables are respectively \( u \) and \( y \);
- the derivation order \( \nu \) is often equal to 1, sometimes to 2; in practice \( \nu \geq 3 \) has never been encountered;
- the constant \( \alpha \in \mathbb{R} \) is chosen by the practitioner such that \( \alpha u \) and \( y^{(\nu)} \) are of the same magnitude; therefore \( \alpha \) does not need to be precisely estimated.

The following comments might be useful:

- Equation (3) is only valid during a short time lapse and must be continuously updated;

\[ 3 \text{For a multivariable extension, see, e.g., Lafont et al. (2015); Menhour et al. (2017).} \]
• $F$ is estimated via the knowledge of the control and output variables $u$ and $y$;

• $F$ subsumes not only the system structure, which most of the time will be nonlinear, but also any external disturbance.

2.1.2. Intelligent controllers

Set $\nu = 2$. Close the loop with the following intelligent proportional-integral-derivative controller, or $iPID$, 

$$u = -\frac{F - \dot{y}^* + K_P e + K_I \int e + K_D \dot{e}}{\alpha}$$

where:

• $e = y - y^*$ is the tracking error,

• $K_P, K_I, K_D \in \mathbb{R}$ are the tuning gains.

When $K_I = 0$, we obtain the intelligent proportional-derivative controller, or $iPD$, 

$$u = -\frac{F - \dot{y}^* + K_P e + K_D \dot{e}}{\alpha}$$

When $\nu = 1$ and $K_I = K_D = 0$, we obtain the intelligent proportional controller, or $iP$, which is the most important one, 

$$u = -\frac{F - \dot{y}^* + K_P e}{\alpha}$$

Combining Equations (3) and (6) yields:

$$\dot{e} + K_P e = 0$$

where $F$ does not appear anymore. The tuning of $K_P$ is therefore straightforward.

Remark 2.1. See Join et al. (2017b) for a comment on those various controllers.
2.1.3. Estimation of $F$

Assume that $F$ in Equation (3) is “well” approximated by a piecewise constant function $F_{\text{est}}$. The estimation techniques below are borrowed from Fliess et al. (2003, 2008) and Sira-Ramírez et al. (2014). Let us summarize two types of computations:

1. Rewrite Equation (3) in the operational domain (see, e.g., Erdélyi (1962)):

$$sY = \frac{\Phi}{s} + \alpha U + y(0)$$

where $\Phi$ is a constant. We get rid of the initial condition $y(0)$ by multiplying both sides on the left by $\frac{d}{ds}$:

$$Y + s\frac{dY}{ds} = -\frac{\Phi}{s^2} + \alpha \frac{dU}{ds}$$

Noise attenuation is achieved by multiplying both sides on the left by $s^{-2}$, since integration with respect to time is a lowpass filter. It yields in the time domain the realtime estimate, thanks to the equivalence between $\frac{d}{ds}$ and the multiplication by $-t$,

$$F_{\text{est}}(t) = -\frac{6}{\tau\pi} \int_{t-\tau}^{t} [(\tau - 2\sigma)y(\sigma) + \alpha\sigma(\tau - \sigma)u(\sigma)] d\sigma$$  \hspace{1cm} (8)

where $\tau > 0$ might be quite small. This integral may of course be replaced in practice by a classic digital filter.

2. Close the loop with the iP (6). It yields:

$$F_{\text{est}}(t) = \frac{1}{\tau} \left[ \int_{t-\tau}^{t} (\dot{y}^* - \alpha u - K_P e) d\sigma \right]$$

**Remark 2.2.** From a hardware standpoint, a real-time implementation of our intelligent controllers is also cheap and easy (Join et al. 2013).

2.2. PI and iP

Consider the classic continuous-time PI controller

$$u(t) = k_p e(t) + k_i \int e(\tau)d\tau$$  \hspace{1cm} (9)

\footnote{This is a weak assumption (see, e.g., Bourbaki (1976).}
A crude sampling of the integral $\int e(\tau)d\tau$ through a Riemann sum $\mathcal{I}(t)$ leads to

$$\int e(\tau)d\tau \simeq \mathcal{I}(t) = \mathcal{I}(t-h) + he(t)$$

where $h$ is the sampling interval. The corresponding discrete form of Equation (9) reads:

$$u(t) = k_p e(t) + k_i I(t) = k_p e(t) + k_i I(t-h) + k_i he(t)$$

Combining the above equation with

$$u(t-h) = k_p e(t-h) + k_i I(t-h)$$

yields

$$u(t) = u(t-h) + k_p (e(t) - e(t-h)) + k_i he(t) \quad (10)$$

**Remark 2.3.** A trivial sampling of the “velocity form” of Equation (9) yields

$$\dot{u}(t) = k_p \dot{e}(t) + k_i e(t) \quad (11)$$

yields

$$u(t) - u(t-h) = k_p \left( \frac{e(t) - e(t-h)}{h} \right) + k_i e(t) \quad (12)$$

which is equivalent to Equation (10).

**Remark 2.4.** This path breaking result was first stated by d’Andréa-Novel et al. (2010):

$$k_p = -\frac{1}{\alpha h}, \quad k_i = -\frac{K_p}{\alpha h} \quad (13)$$
It is straightforward to extend it to the same type of equivalence between PIDs and iPDs.

It explains apparently for the first time the ubiquity of PIs and PIDs in the industrial world.

3. Exact adaptation and dynamic compensation

Equation (11) shows that integral and proportional-integral controllers are close when

1. \( \dot{e} \) remains small,
2. the reference trajectory \( y^* \) starts at the initial condition \( y(0) \) or, at least, at a point in a neighborhood,
3. the measurement noise corruption is low.

The following conditions might be helpful:

- the reference trajectory \( y^* \) is “slowly” varying, and starts at the initial condition \( y(0) \) or, at least, at a point in its neighborhood\(^5\)
- the disturbances and the corrupting noises are rather mild.

Then the performances of the integral controller should be decent: this is exact adaptation, or homeostasis. When the above conditions are not satisfied, dynamic compensation means that one at least of the feedback loops in Section 2.1 is negative, i.e., fluctuations around the reference trajectory due to perturbations and input changes are attenuated\(^6\)

\(^5\)Setpoints are therefore recovered.

\(^6\)The wording “negative feedback” is today common in biology, but, to some extent, neglected in engineering, where it was quite popular long time ago (see, e.g., Küpfmüller et al. (2017)). Historical details are given by Zeron (2008) and Del Vecchio et al. (2015).
4. Two computer experiments

The two academic examples below provide easily implementable numerical examples. They are characterized by the following features:

- \( K_I = 0.5 \) (resp. \( K_I = 1 \)) for the integral feedback in the linear (resp. nonlinear) case.
- \( \alpha = K_P = 1 \) for the the iP in both cases.
- The sampling period is 10ms.
- In order to be more realistic, the output is corrupted additively by a zero-mean white Gaussian noise of standard deviation 0.01.

4.1. Linear case

Consider the input-output system defined by the transfer function

\[
\frac{2(s + 1)}{s^2 + s + 1}
\]

Several reference trajectories are examined:

- (i) Setpoint and 50% efficiency loss of the actuator: see Figures 1 and 2.
- (ii) Slow connection between two setpoints: see Figures 3 and 4.
- (iii) Fast connection: see Figures 5 and 6.
- (iv) Complex reference trajectory: see Figures 7 and 8.

In the first scenario, the control efficiency loss is attenuated much faster by the iP than by the integral feedback. The behaviors of the integral feedback and the iP with respect to a slow connection are both good and cannot be really distinguished. The situation change drastically with a fast connection and a complex reference trajectory: the iP becomes vastly superior to the integral feedback. Exact adaptation works well only in the second scenario, whereas dynamic compensation yields always excellent results.
Figure 1: Integral feedback, constant reference trajectory, control efficiency loss

Figure 2: iP, constant reference trajectory, control efficiency loss
Figure 3: Integral feedback, slow connection

Figure 4: iP, slow connection
Figure 5: Integral feedback, fast connection

Figure 6: iP, fast connection
Figure 7: Integral connection, complex reference trajectory

Figure 8: iP, complex reference trajectory
4.2. Nonlinear case

Consider

\[ \dot{y} + y = u^3 + P_{\text{pert}} \]

where \( P_{\text{pert}} \) is a perturbation. Introduce three scenarios:

(i) Setpoint without any perturbation, \( i.e., P_{\text{pert}} = 0 \): see Figures 9 and 10.

(ii) Setpoint with a sine wave perturbation which starts at \( t = 25s, i.e., \)

\[ P_{\text{pert}}(t) = 0.2 \sin\left(\frac{2\pi}{5}(t - 25)\right) \] if \( t \geq 25s \), and \( P_{\text{pert}}(t) = 0 \) if \( t \leq 25s \):

see Figures 11 and 12.

(iii) Non-constant reference trajectory without any perturbation, \( i.e., P_{\text{pert}} = 0 \): see Figures 13 and 14.

A clear-cut superiority of the iP with respect to the integral feedback is indisputable. The behavior of dynamic compensation (resp. exact adaptation) is always (resp. never) satisfactory.

Remark 4.1. Do not believe that integral feedbacks are never adequate if nonlinearities occur. See

- an example related to ramp metering in Abouaïssa et al. (2017b),
- theoretical investigations in Sontag (2010).

5. Conclusion

In order to be fully convincing, this preliminary announcement on homeostasis extensions needs of course to exhibit true biological examples. In our context noise corruption is also a hot topic (see, e.g., Briat et al. (2016); Sun et al. (2010)). The estimation and identification techniques sketched in Section 2.1 might lead to a better understanding (see also Fliess (2006, 2008)).
Figure 9: Integral feedback, constant reference trajectory, without any perturbation

Figure 10: iP, constant reference trajectory, without any perturbation
Figure 11: Integral feedback, constant reference trajectory, with perturbation

Figure 12: iP, constant reference trajectory, with perturbation
Figure 13: Integral feedback, non-constant reference trajectory, without any perturbation

Figure 14: iP, non-constant reference trajectory, without any perturbation
References


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The first edition was published in 1932. Karl Küpfmüller was its sole author. He died in 1977.


