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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:

$$u = K_P e + K_I \int e + K_D \dot{e} \quad (1)$$

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

25 in the literature on theoretical biology,¹ although they lead to the most widely
26 used control strategies in industry.

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

$$u = K_I \int e \quad (2)$$

27 Compare Equation (2) with the references above on homeostasis, and Somvanshi *et al.*
28 (2015). See Abouaïssa *et al.* (2017b), and the references therein, for an appli-
29 cation to ramp metering on freeways in order to avoid traffic congestion.

30 Conditions for DC have already been investigated by several authors: Karin *et al.*
31 (2017a,b); Sontag (2017); Villaverde *et al.* (2017). Parameter identification,
32 which plays a key rôle in most of those studies, leads, according to the own
33 words of Karin *et al.* (2017b), to some kind of “discrepancy,” which is per-
34 haps not yet fully cleared up. We suggest therefore another roadmap, *i.e.*,
35 *intelligent* feedback controllers as defined by Fliess *et al.* (2013). Many con-
36 crete applications have already been developed all over the world. Some have
37 been patented. The bibliography contains for obvious reasons only recent works
38 in biotechnology: Bara *et al.* (2016); Join *et al.* (2017a); Lafont *et al.* (2015);
39 MohammadRidha *et al.* (2018); Tebbani *et al.* (2016).²

40 An unexpected byproduct is derived from Remark 1.1 and the comparison in
41 Abouaïssa *et al.* (2017b) between Equation (2) and our *intelligent proportional*
42 controller (Fliess *et al.* (2013)). Exact adaptation means now a “satisfactory”
43 behavior thanks to the feedback loop defined by Equation (2) when the working
44 conditions are “mild.” The result by Karin *et al.* (2016) via a mechanism for DC
45 based on known hormonal circuit reactions, which states that exact adaptation
46 does not guarantee dynamical compensation, remains therefore valid in this new
47 context.

¹This 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).

²A rather comprehensive bibliography of concrete applications is provided by Abouaïssa *et al.* (2017a).

48 This exploratory research report is organized as follows. Intelligent con-
 49 trollers are summarized in Section 2, where the connection between classic PIs
 50 and intelligent proportional controllers is also presented. Section 3, which is
 51 heavily influenced by Abouaïssa *et al.* (2017b), defines dynamic compensation
 52 and exact adaptation. Section 4 displays various convincing, but academic,
 53 computer experiments. Some concluding remarks may be found in Section 5.

54 2. Model-free control and intelligent controllers

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

56 2.1. Generalities

57 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),³ is replaced by the
ultra-local model:

$$\boxed{y^{(\nu)} = F + \alpha u} \quad (3)$$

58 where:

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

65 The following comments might be useful:

- 66 • Equation (3) is only valid during a short time lapse and must be continu-
 67 ously updated;

³For a multivariable extension, see, *e.g.*, Lafont *et al.* (2015); Menhour *et al.* (2017).

- 68 • F is estimated via the knowledge of the control and output variables u
- 69 and y ;
- 70 • F subsumes not only the system structure, which most of the time will be
- 71 nonlinear, but also any external disturbance.

72 *2.1.2. Intelligent controllers*

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

$$u = -\frac{F - \dot{y}^* + K_P e + K_I \int e + K_D \dot{e}}{\alpha} \quad (4)$$

73 where:

- 74 • $e = y - y^*$ is the tracking error,
- 75 • $K_P, K_I, K_D \in \mathbb{R}$ are the tuning gains.

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

$$u = -\frac{F - \dot{y}^* + K_P e + K_D \dot{e}}{\alpha} \quad (5)$$

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

$$\boxed{u = -\frac{F - \dot{y}^* + K_P e}{\alpha}} \quad (6)$$

Combining Equations (3) and (6) yields:

$$\dot{e} + K_P e = 0 \quad (7)$$

76 where F does not appear anymore. The tuning of K_P is therefore straightfor-
77 ward.

78 **Remark 2.1.** See Join et al. (2017b) for a comment on those various con-
79 trollers.

80 *2.1.3. Estimation of F*

81 Assume that F in Equation (3) is “well” approximated by a piecewise con-
 82 stant function F_{est} .⁴ The estimation techniques below are borrowed from Fliess *et al.*
 83 (2003, 2008) and Sira-Ramírez *et al.* (2014). Let us summarize two types of
 84 computations:

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

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

where Φ is a constant. We get rid of the initial condition $y(0)$ by multi-
 plying 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 $-t$,

$$F_{\text{est}}(t) = -\frac{6}{\tau^3} \int_{t-\tau}^t [(\tau - 2\sigma)y(\sigma) + \alpha\sigma(\tau - \sigma)u(\sigma)] d\sigma \quad (8)$$

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

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

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

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

89 *2.2. PI and iP*

Consider the classic continuous-time PI controller

$$u(t) = k_p e(t) + k_i \int e(\tau) d\tau \quad (9)$$

⁴This 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:

$$u(t) = k_p e(t) + k_i \mathcal{I}(t) = k_p e(t) + k_i \mathcal{I}(t-h) + k_i h e(t)$$

Combining the above equation with

$$u(t-h) = k_p e(t-h) + k_i \mathcal{I}(t-h)$$

yields

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

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

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

yields

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

⁹⁰ which is equivalent to Equation (10).

Replace in Equation (6) F by $\dot{y}(t) - \alpha u(t-h)$ and therefore by

$$\frac{y(t) - y(t-h)}{h} - \alpha u(t-h)$$

It yields

$$u(t) = u(t-h) - \frac{e(t) - e(t-h)}{h\alpha} - \frac{K_P}{\alpha} e(t) \quad (12)$$

FACT.- Equations (10) and (12) become **identical** if we set

$$k_p = -\frac{1}{\alpha h}, \quad k_i = -\frac{K_P}{\alpha h} \quad (13)$$

⁹¹

⁹² **Remark 2.4.** This path breaking result was first stated by d’Andréa-Novel et al.
⁹³ (2010):

- 94 • It is straightforward to extend it to the same type of equivalence between
95 PIDs and *i*PDs.
- 96 • It explains apparently for the first time the ubiquity of PIs and PIDs in
97 the industrial world.

98 3. Exact adaptation and dynamic compensation

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

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

105 The following conditions might be helpful:

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

109 Then the performances of the integral controller should be decent: this is *ex-*
110 *act adaptation*, or *homeostasis*. When the above conditions are not satisfied,
111 *dynamic compensation* means that one at least of the feedback loops in Sec-
112 tion 2.1 is *negative*, *i.e.*, fluctuations around the reference trajectory due to
113 perturbations and input changes are attenuated.⁶

⁵Setpoints are therefore recovered.

⁶The 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).

114 **4. Two computer experiments**

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

- 117 • $K_I = 0.5$ (resp. $K_I = 1$) for the integral feedback in the linear (resp.
118 nonlinear) case.
- 119 • $\alpha = K_P = 1$ for the the iP (6) in both cases.
- 120 • The sampling period is 10ms.
- 121 • In order to be more realistic, the output is corrupted additively by a zero-
122 mean white Gaussian noise of standard deviation 0.01.

123 *4.1. Linear case*

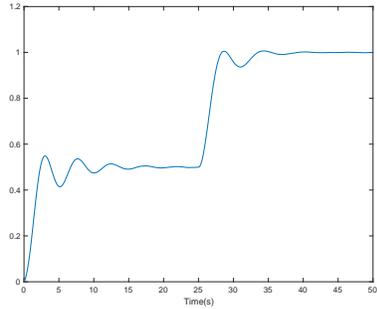
Consider the input-output system defined by the transfer function

$$\frac{2(s+1)}{s^2+s+1}$$

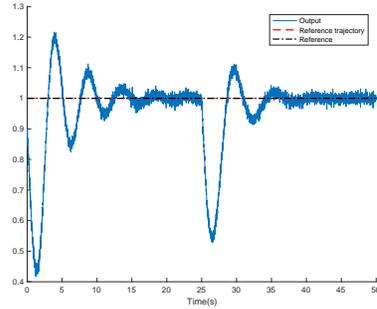
124 Several reference trajectories are examined:

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

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

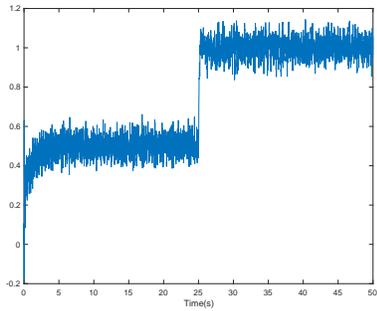


(a) Control

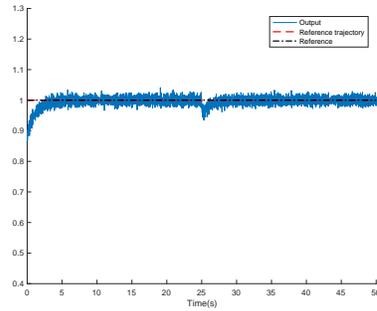


(b) Output

Figure 1: Integral feedback, constant reference trajectory, control efficiency loss

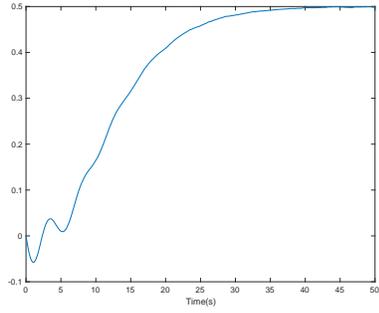


(a) Control

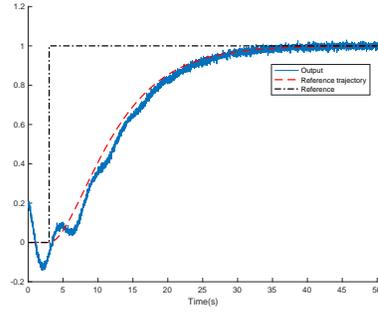


(b) Output

Figure 2: iP, constant reference trajectory, control efficiency loss

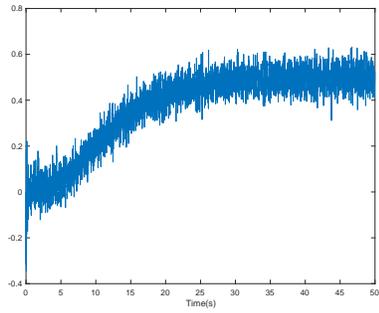


(a) Control

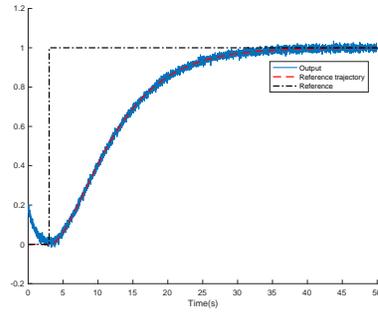


(b) Output

Figure 3: Integral feedback, slow connection

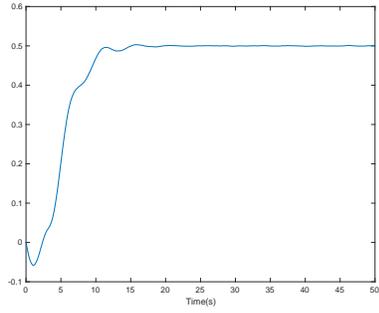


(a) Control

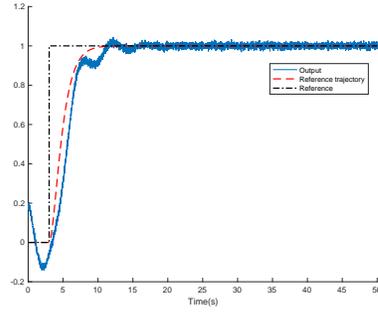


(b) Output

Figure 4: iP, slow connection

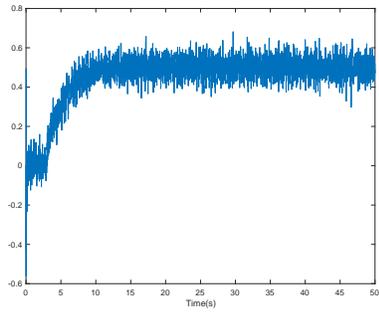


(a) Control

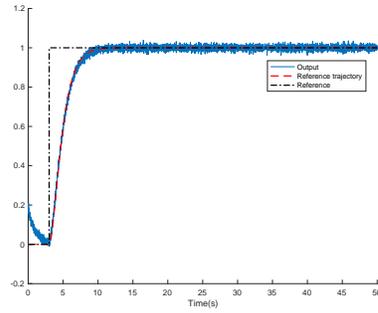


(b) Output

Figure 5: Integral feedback, fast connection

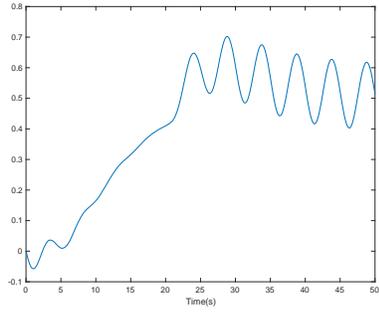


(a) Control

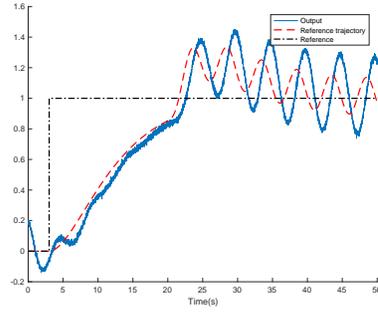


(b) Output

Figure 6: iP, fast connection

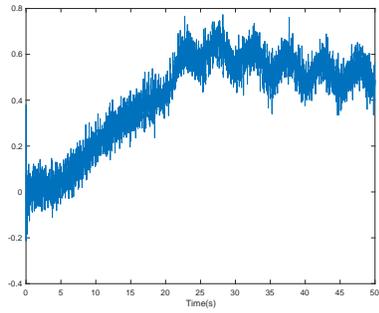


(a) Control

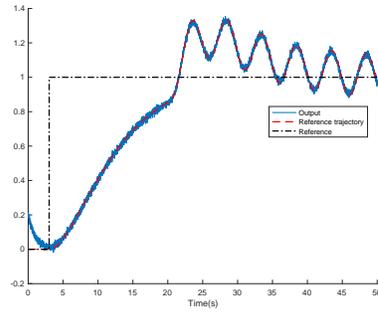


(b) Output

Figure 7: Integral connection, complex reference trajectory



(a) Control



(b) Output

Figure 8: iP, complex reference trajectory

136 *4.2. Nonlinear case*

Consider

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

137 where P_{pert} is a perturbation. Introduce three scenarios:

- 138 (i) Setpoint without any perturbation, *i.e.*, $P_{\text{pert}} = 0$: see Figures 9 and 10.
- 139 (ii) Setpoint with a sine wave perturbation which starts at $t = 25\text{s}$, *i.e.*,
140 $P_{\text{pert}}(t) = 0.2 \sin(\frac{2\pi}{5}(t - 25))$ if $t \geq 25\text{s}$, and $P_{\text{pert}}(t) = 0$ if $t \leq 25\text{s}$:
141 see Figures 11 and 12.
- 142 (iii) Non-constant reference trajectory without any perturbation, *i.e.*, $P_{\text{pert}} =$
143 0 : see Figures 13 and 14.

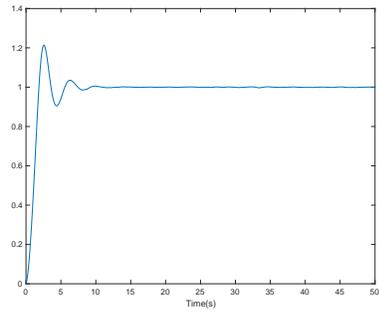
144 A clear-cut superiority of the iP with respect to the integral feedback is indis-
145 putable. The behavior of dynamic compensation (resp. exact adaptation) is
146 always (resp. never) satisfactory.

147 **Remark 4.1.** *Do not believe that integral feedbacks are never adequate if non-*
148 *linearities occur. See*

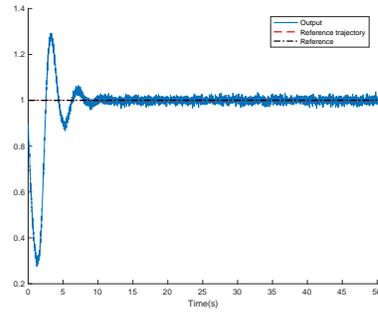
- 149 • *an example related to ramp metering in Abouaiïssa et al. (2017b),*
150 • *theoretical investigations in Sontag (2010).*

151 **5. Conclusion**

152 In order to be fully convincing, this preliminary announcement on homeostasis
153 extensions needs of course to exhibit true biological examples. In our context
154 noise corruption is also a hot topic (see, *e.g.*, Briat *et al.* (2016); Sun *et al.*
155 (2010)). The estimation and identification techniques sketched in Section 2.1
156 might lead to a better understanding (see also Fliess (2006, 2008)).

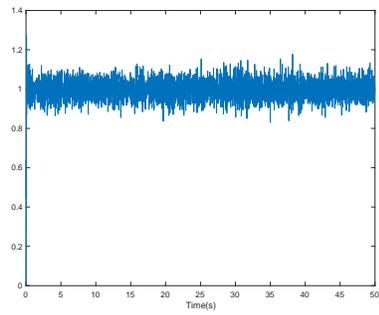


(a) Control

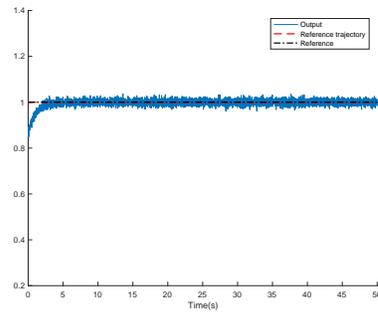


(b) Output

Figure 9: Integral feedback, constant reference trajectory, without any perturbation

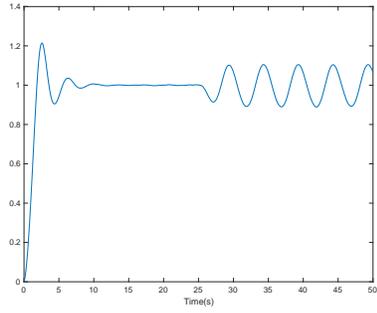


(a) Control

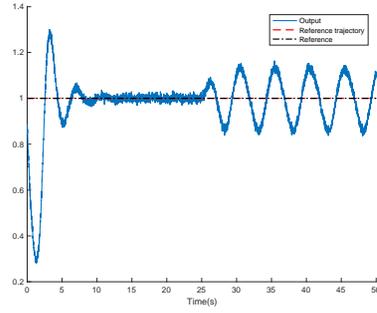


(b) Output

Figure 10: iP, constant reference trajectory, without any perturbation

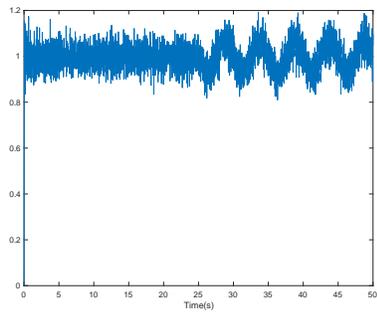


(a) Control

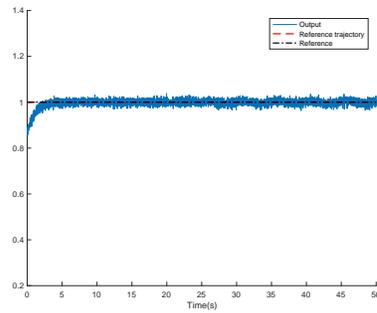


(b) Output

Figure 11: Integral feedback, constant reference trajectory, with perturbation

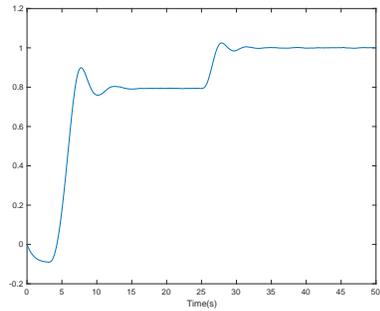


(a) Control

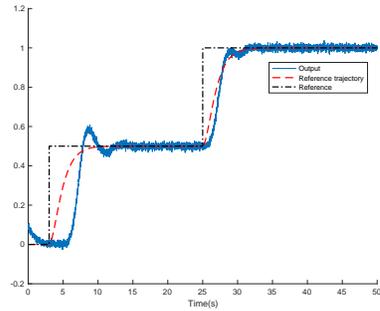


(b) Output

Figure 12: iP, constant reference trajectory, with perturbation

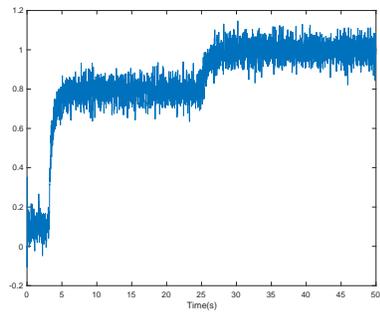


(a) Control

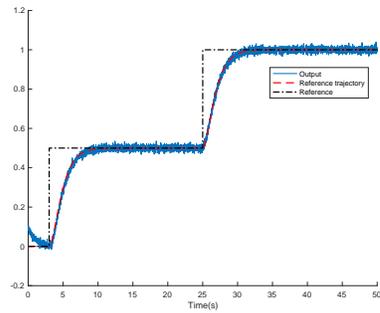


(b) Output

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



(a) Control



(b) Output

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

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