Auto Regulation/Homeostasis

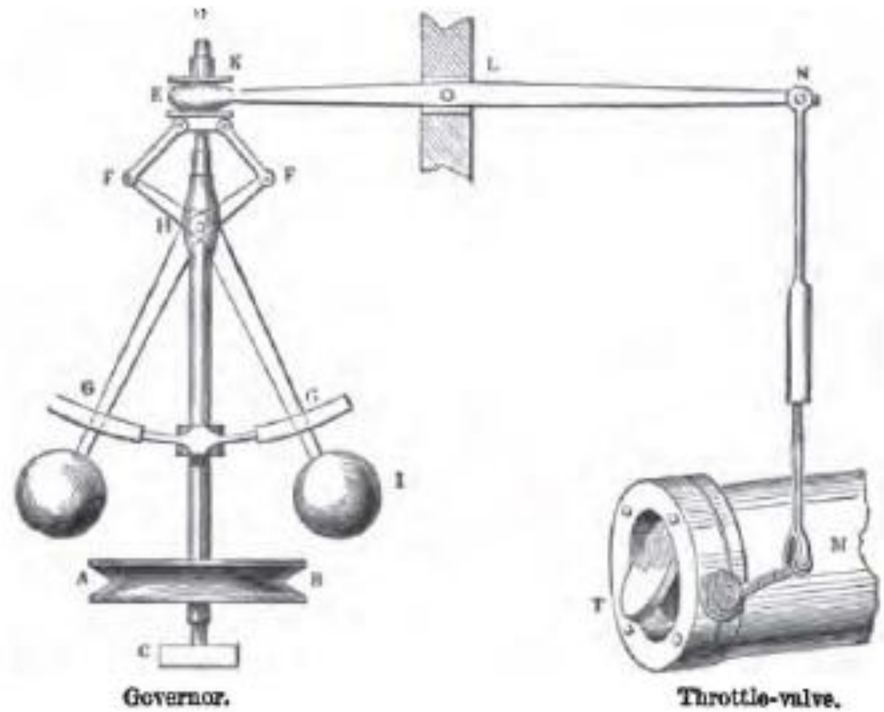
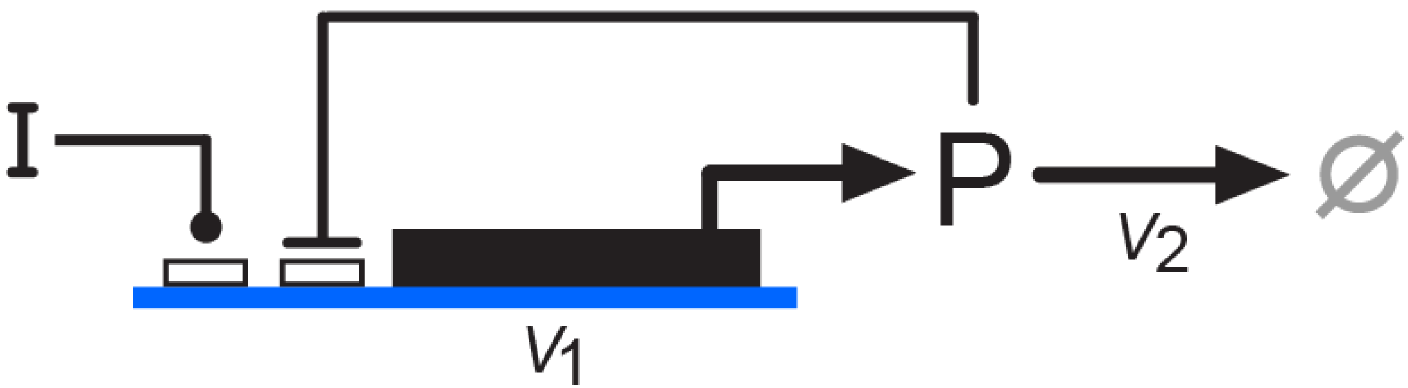


Figure 14.1: A typical governor from J. Farley, A Treatise on the Steam Engine: Historical, Practical, and Descriptive (London: Longman, Rees, Orme, Brown, and Green, 1827, p436

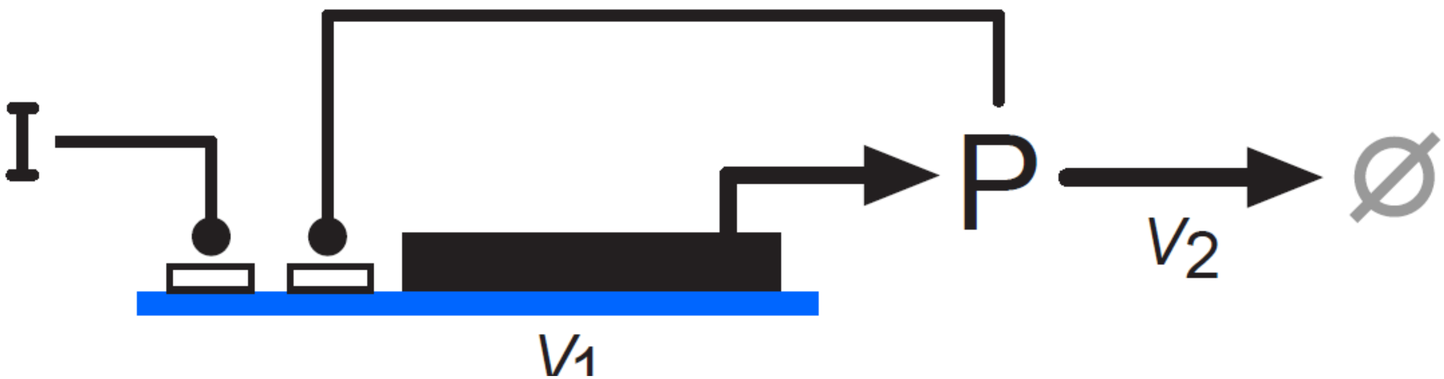
Homeostasis

- A homeostatic system is one that resists internal change when external parameters are perturbed. We will illustrate two such networks: one that shows perfect adaptation and another that near adaptation.
- Perfect adaptation describes a system that recovers from a perturbation without any error (thus perfectly). There are a number of approaches to achieving perfect adaptation, one is via integral control and another, simpler approach, is via coordinate stimulation. In this tutorial we will illustrate perfect adaptation using coordinate stimulation.
- A simpler and perhaps more common method for achieving homeostasis is to use negative feedback to resist external perturbations. Unlike systems which show perfect adaptation, systems which employ negative feedback cannot completely restore a disturbance.

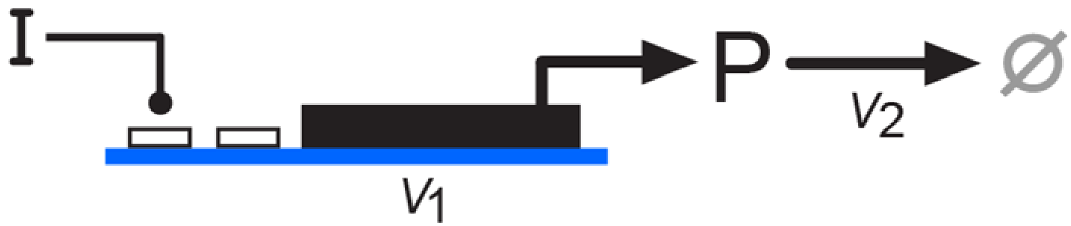
Auto-regulation – Negative Feedback

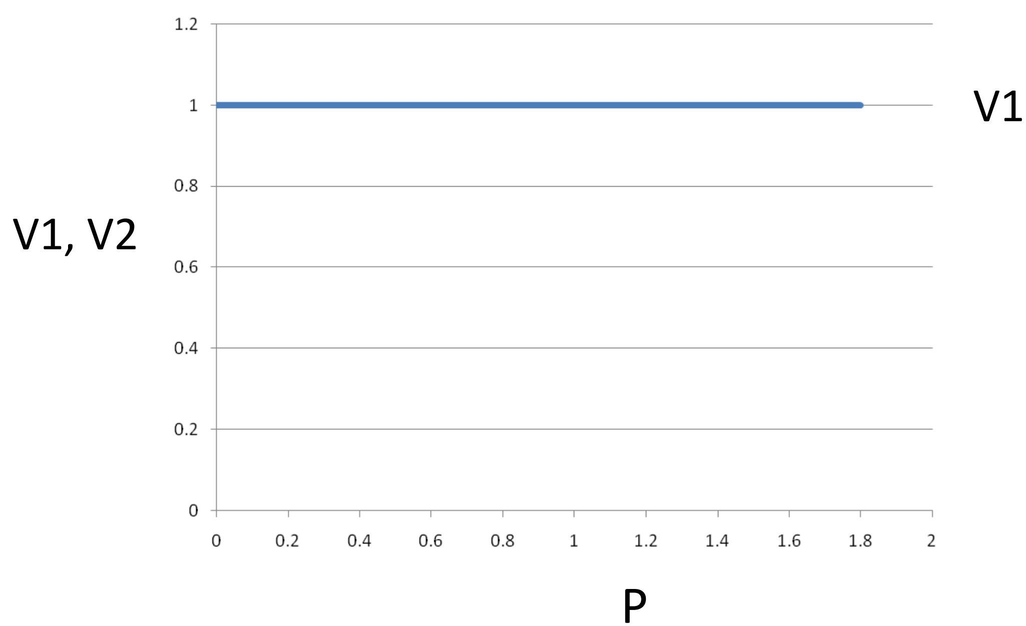


Auto-regulation – Positive Feedback

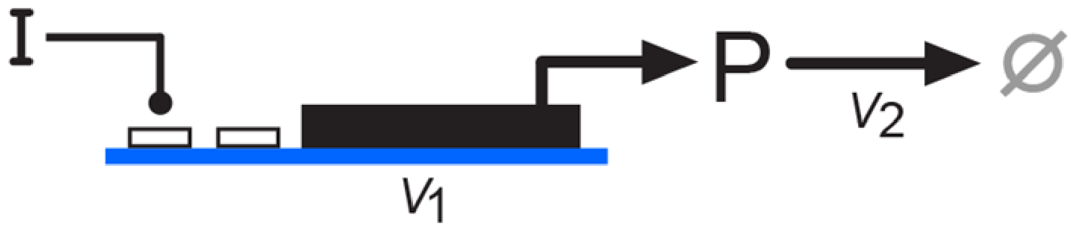


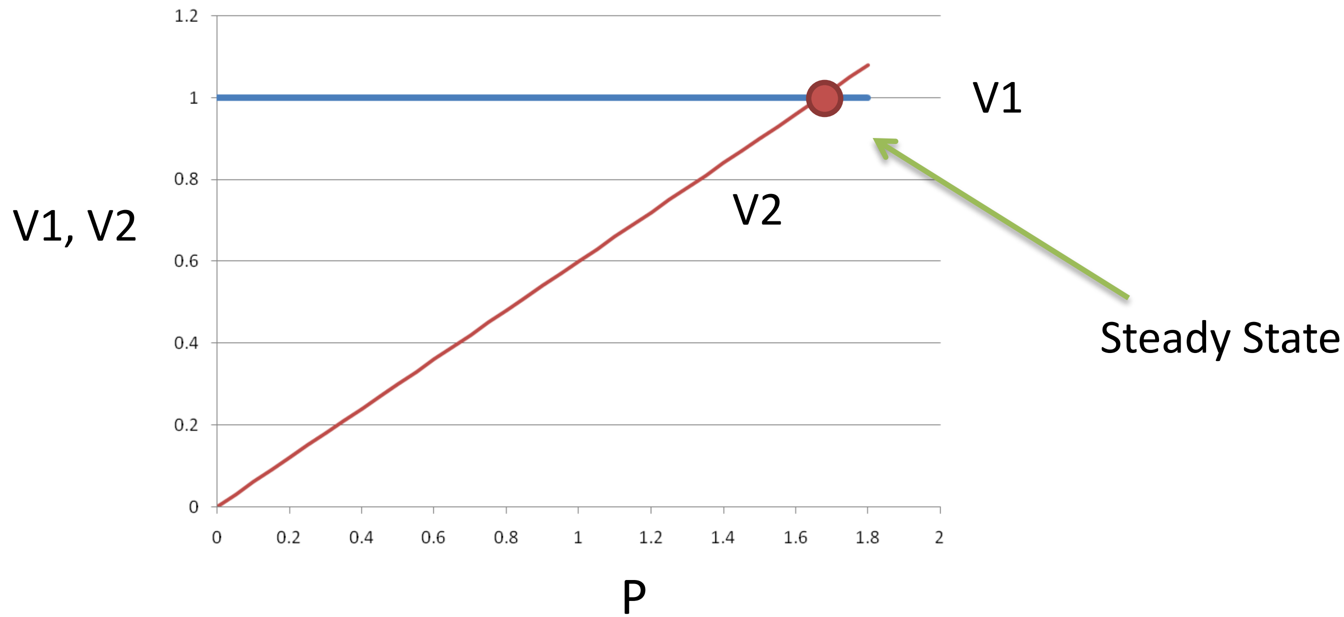
Negative Feedback - Homeostasis



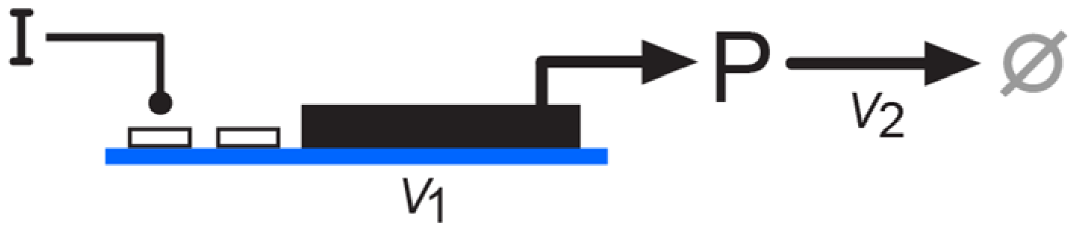


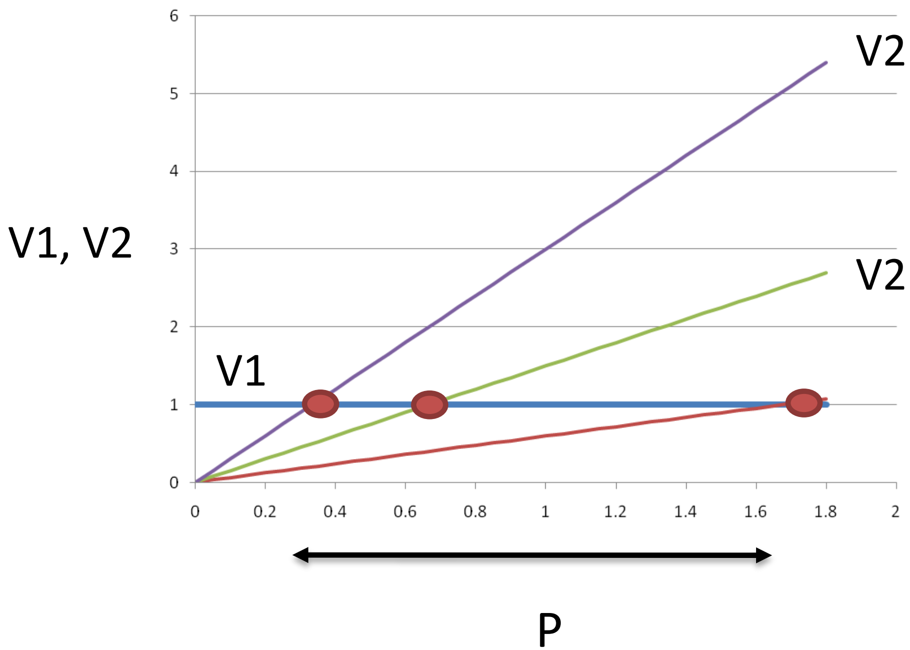
Negative Feedback - Homeostasis





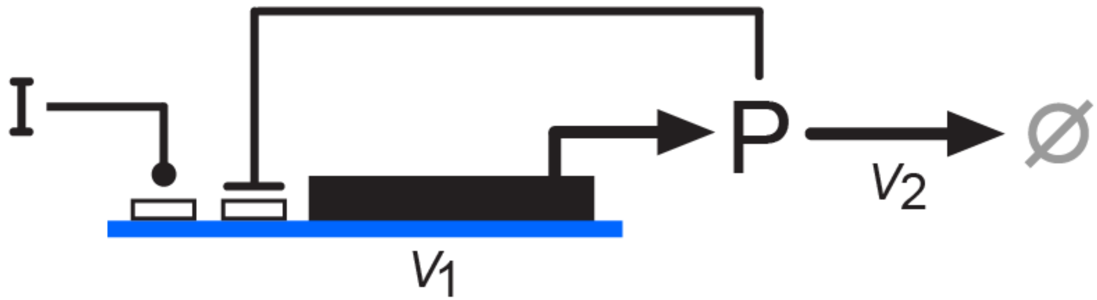
Negative Feedback - Homeostasis

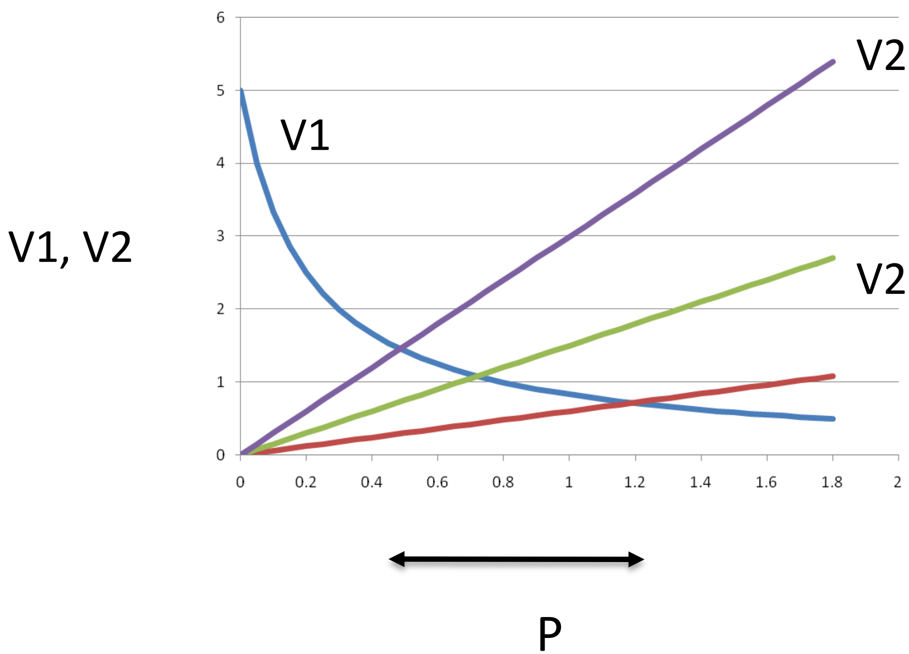




P is very sensitive to changes in V2 (k2)

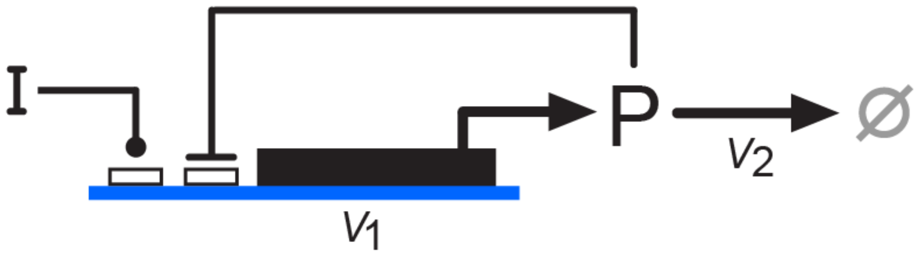
Negative Feedback - Homeostasis

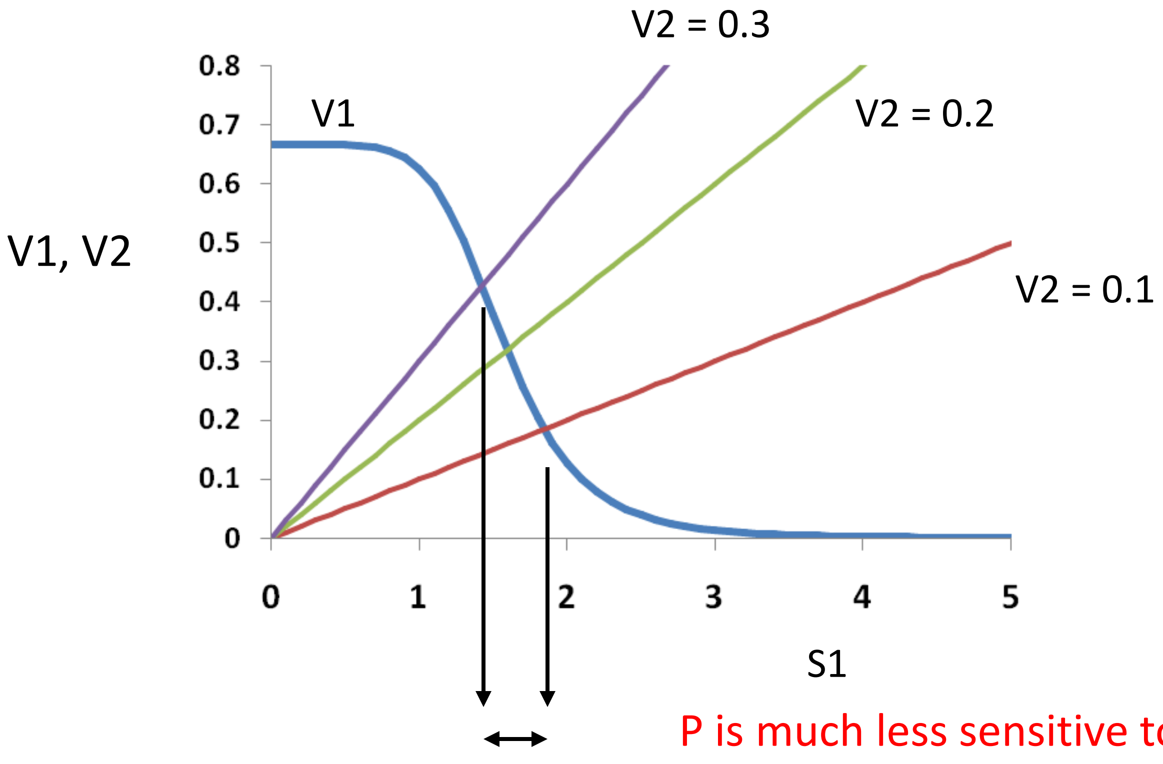




P is less sensitive to changes in V2 (k2)

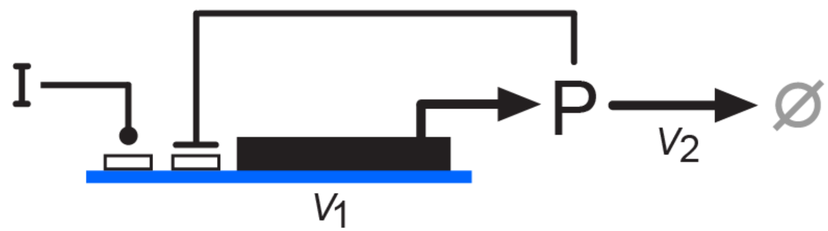
Negative Feedback - Homeostasis





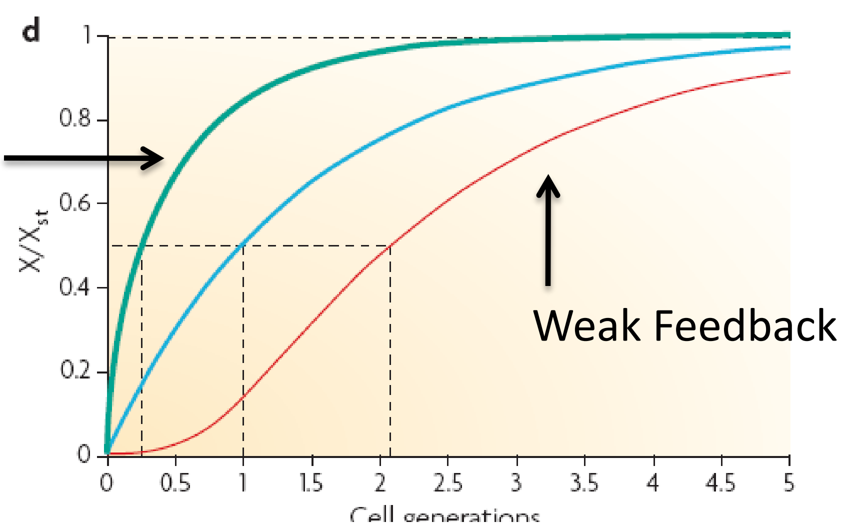
P is much less sensitive to changes in V2 (k2)

Auto-regulation – Negative Feedback Response Accelerator



Strong Feedback
+ strong input
promoter

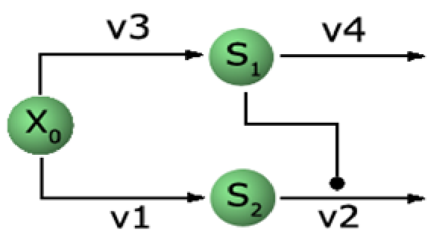
P



Input, I

Perfect Adaptation

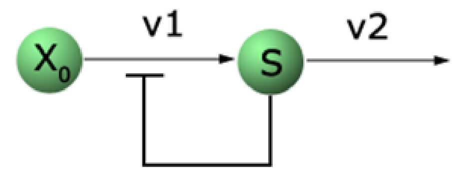
S_2 remains homeostatic



$$v1 = k_1 X_0 \qquad v2 = k_2 S_1 S_2$$

$$v3 = k_3 X_0 \qquad v4 = k_4 S_1$$

S remains homeostatic



$$v1 = \frac{X_0}{K_m + S^4} \qquad v2 = k_1 S$$

Perfect Adaptation **Negative Feedback**

Perfect Adaptation

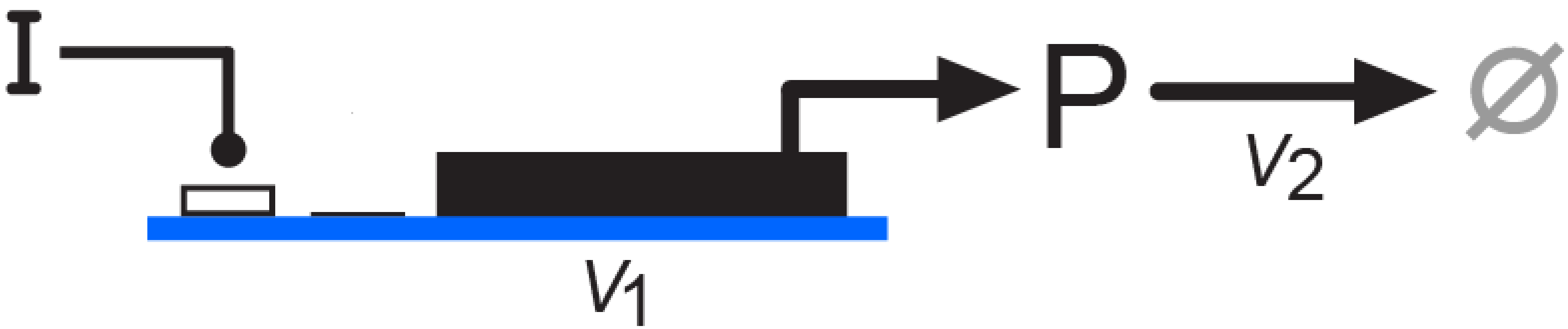
```
p = defn PerfectAdaptation
   $Xo-> S2;  k1*Xo;
   S2 -> $w;  k2*S1*S2;
   $Xo-> S1;  k3*Xo;
   S1 -> $w;  k4*S1;
end;
// initialize
p.k1 = 1; p.k2 = 1;
p.k3 = 1; p.k4 = 1;
p.Xo = 1.0;
```

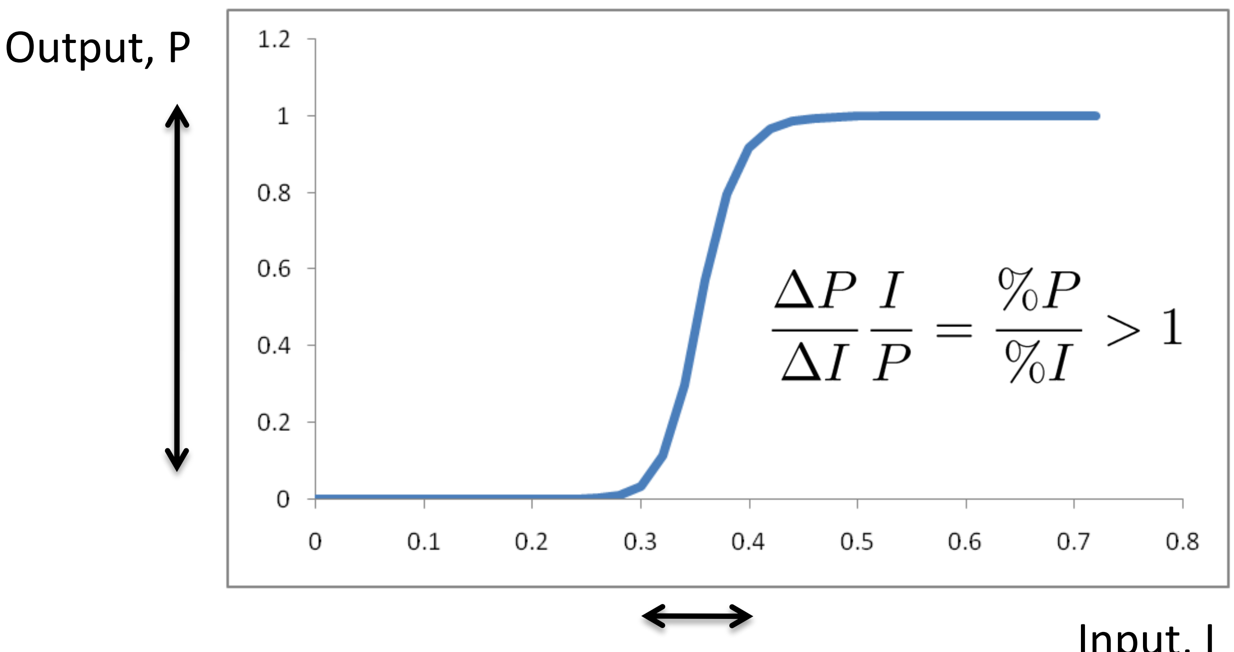
Negative Feedback

```
p = defn NegativeFeedback
     $Xo  -> S;   Xo/(km + S^h);
      S   -> $w;  k1*S;
end;

// initialize
p.h  = 4;   // Hill coefficient
p.k1 = 1;
p.km = 1;
p.S  = 1.5;
p.Xo = 5;
```

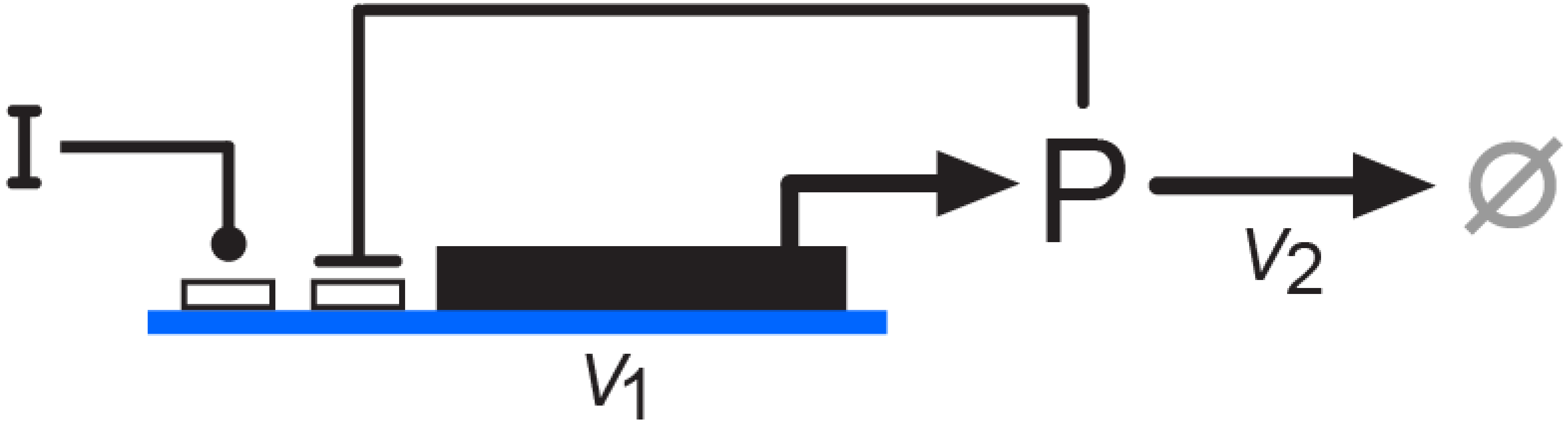
Amplifiers





$$\frac{\Delta P}{\Delta I}\frac{I}{P} = \frac{\%P}{\%I} > 1$$

Amplifiers

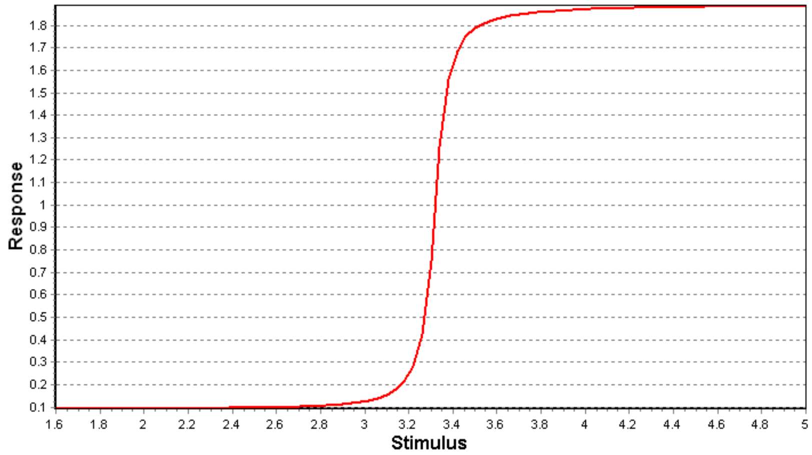


Amplifiers

The Effect of Negative Feedback

No Feedback

Output, P



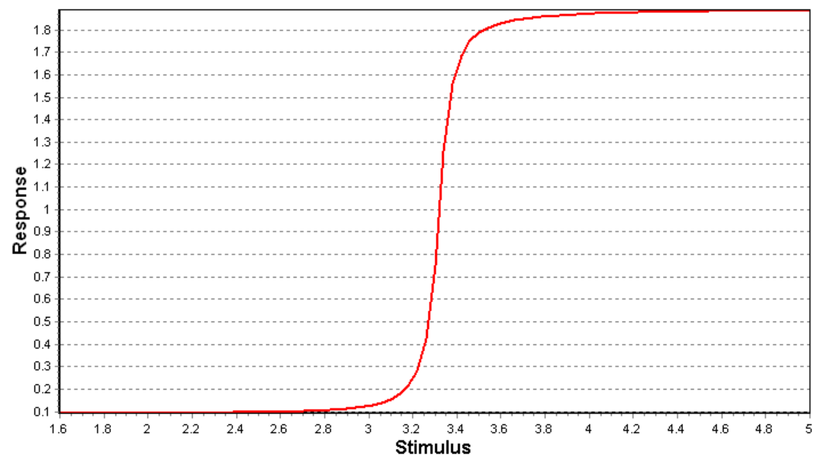
Input, I

Amplifiers

The Effect of Negative Feedback

No Feedback

Output, P

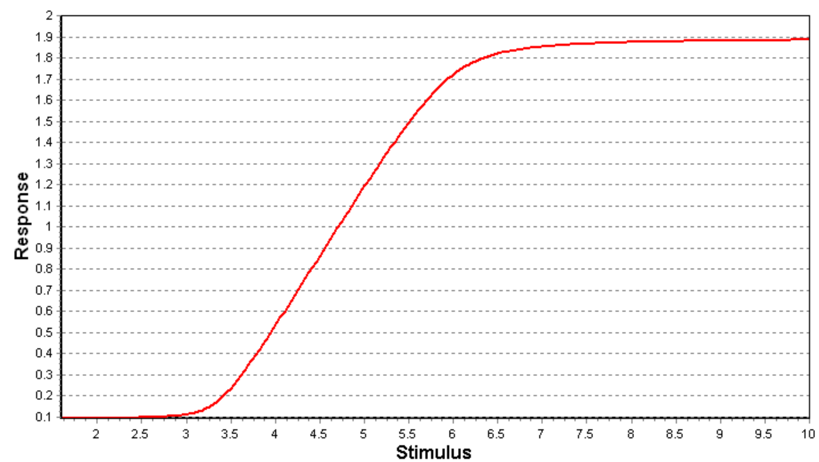


Input, I

Negative Feedback stretches the response and reduces the gain, but what else?

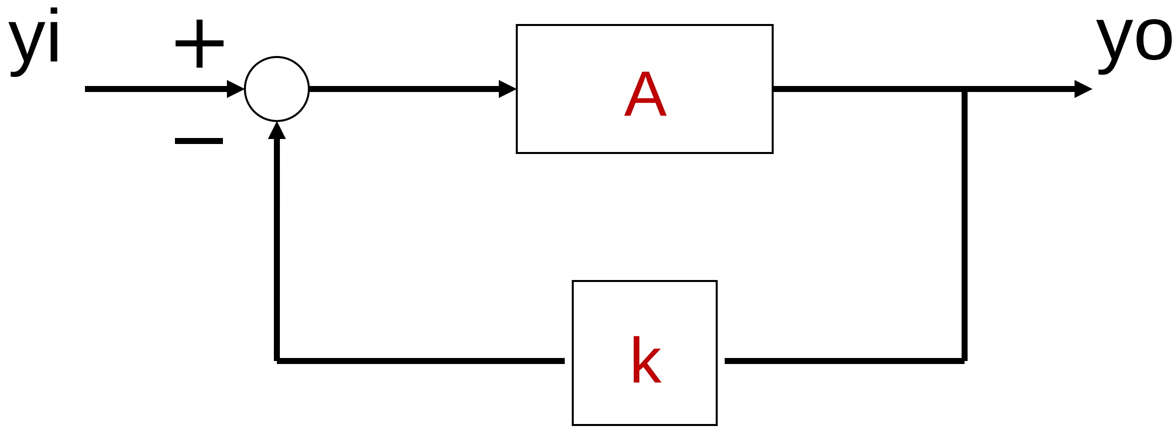
With Feedback

Output, P

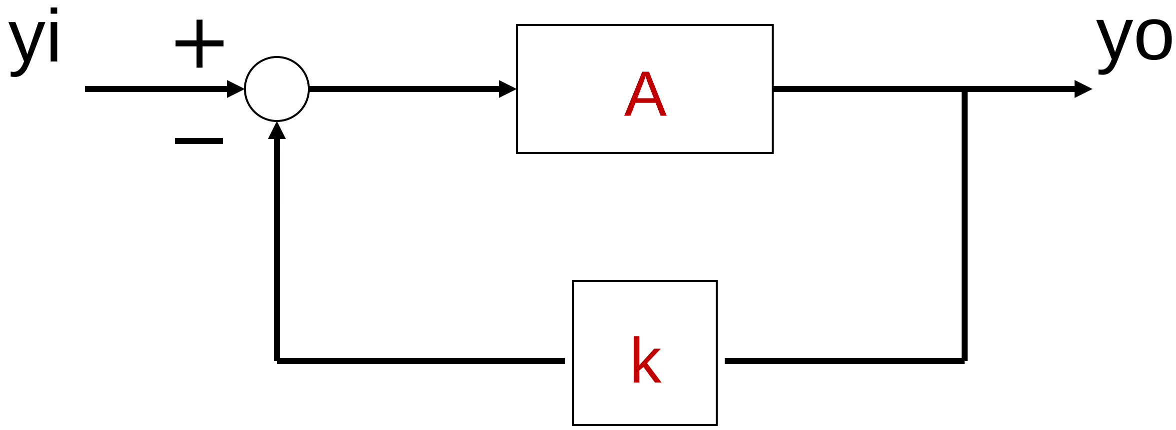


Input, I

Simple Analysis of Feedback



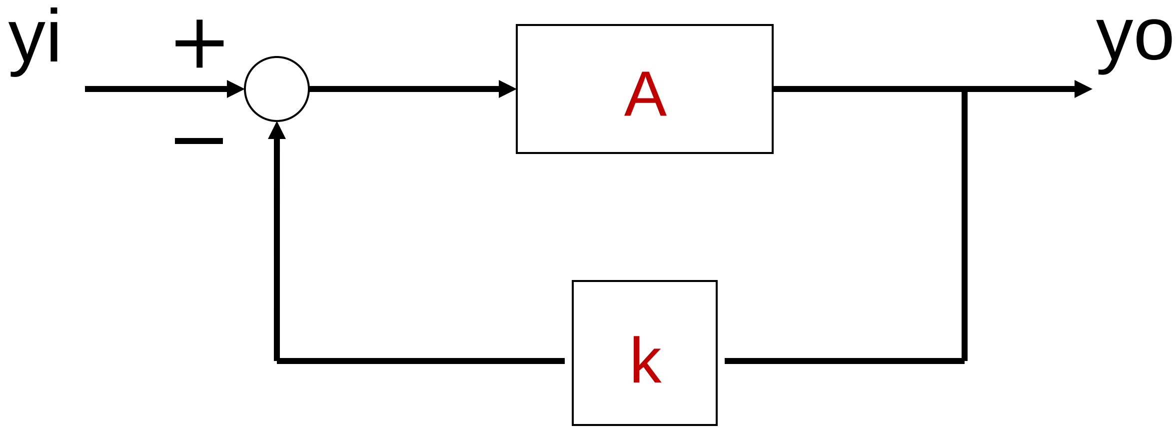
Simple Analysis of Feedback



$$y_o = A(y_i - k y_o)$$

Solve for yo:

Simple Analysis of Feedback



$$y_o = A(y_i - ky_o)$$

Solve for yo:

$$y_o = \frac{Ay_i}{1+Ak}$$

Simple Analysis of Feedback

$$y_o = \frac{Ay_i}{1+Ak}$$

At high amplifier gain (A k > 1):

$$y_o \approx \frac{y_i}{k}$$

In other words, the output is completely independent of the amplifier and is ***linearly*** dependent on the feedback.

Simple Analysis of Feedback

$$y_o = \frac{Ay_i}{1 + Ak}$$

Basic properties of a feedback amplifier:

1. Robust to variation in amplifier characteristics.
2. Linearization of the amplifier response.
3. Reduced gain

The addition of negative feedback to a gene circuit will reduce the level of noise (intrinsic noise) that originates from the gene circuit itself.

Summary of Negative Feedback

1. Noise Suppression
2. Accelerated Response
3. High Fidelity Amplifier
4. Feedback Oscillation