dynamic processes in cells (a systems approach to biology)

jeremy gunawardena
department of systems biology
harvard medical school

lecture 2
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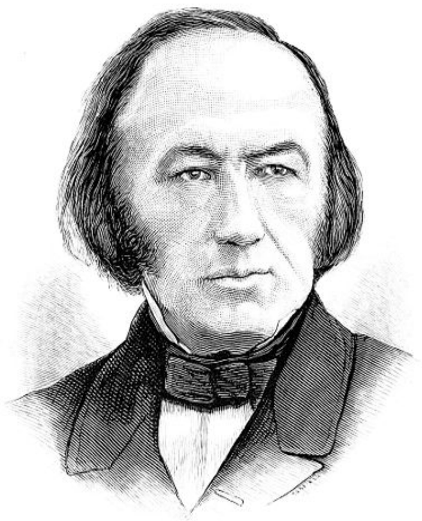
1. homeostasis & microscopic cybernetics

the constancy of the "internal milieu"

"The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and ***equilibrated*** *... All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment ....* ***The stability of the internal environment is the condition for the free and independent life****."* *****



1813-1878

***** Claude Bernard, from **Lectures on the Phenomena Common to Animals and Plants**, 1878. Quoted in C Gross, *"Claude Bernard and the constancy of the internal environment"*, The Neuroscientist, **4**:380-5 1998

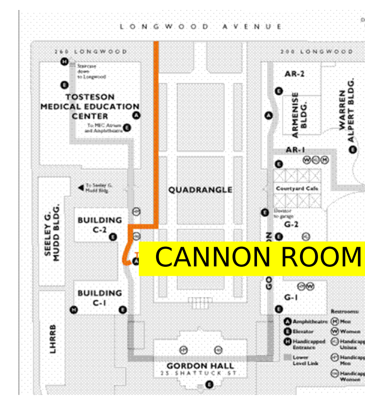
Claude Bernard, **Introduction to the Study of Experimental Medicine**, 1865

homeostasis and negative feedback

“Before those extremes are reached agencies are automatically called into service which act to ***bring back towards the mean position*** *the disturbed state*"*

“Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action and thereby ***wide oscillations are prevented*** *and the internal conditions are held* ***fairly constant****.”**

1871-1945



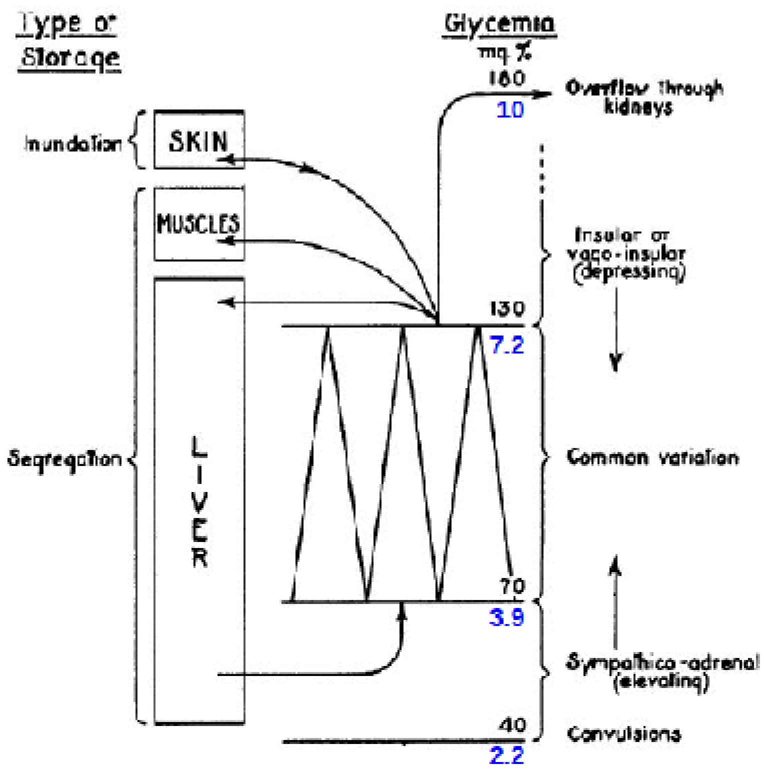
1. “back towards the mean position” – **negative feedback**
2. “wide oscillations are prevented” – **stability**

* Walter B Cannon, *“Organization for physiological homeostasis”*, Physiological Reviews, **9**:399-431, 1929.

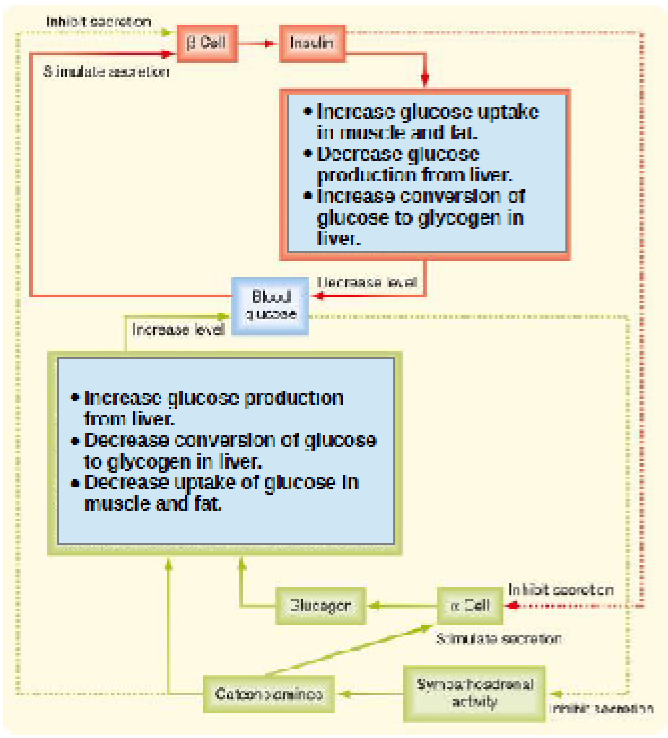
Walter B Cannon, **The Wisdom of the Body**, W W Norton & Co, 1932.

glucose homeostasis

Walter Cannon **(*)**



Berne & Levy **(+)**



mg% is mg per 100 mL or mg/dL. “normal” glucose level is ~100 mg/dL or ~**5mM**

(*) Figure 1 in Walter B Cannon, *“Organization for physiological homeostasis”*, Physiological Reviews, **9**:399-431, 1929.

(+) Figure 38-18 in Koeppen & Stanton, **Berne & Levy Physiology**, Mosby, 6th ed, 2009

teleology vs reductionism

cannon explained how negative feedback achieved homeostasis by attributing it to "*The Wisdom of the Body*" or "the healing power of nature". this is **teleological** thinking:

teleology – the function or purpose of an object is a "final cause", or explanation, of its behaviour

"*Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public.*" **(*)**

aristotle (384-322 BCE) first pointed out that biological organisms exhibit purpose and therefore seem to require teleological explanations

ARISTOTELIAN CAUSES	SYSTEMS BIOLOGY	
material	components	
formal	connections or reactions	**reductionism**
efficient	differential equations	
final		

J H F Bothwell, *"The long past of systems biology"*, New Phytol, **170**:6-10 2006; Armand Leroi, **The Lagoon: How Aristotle Invented Science**, Viking, 2015; **(*)** Cannon, *The Way of an Investigator*, Hafner Publ Co, 1968

glucose homeostasis – with numbers

	rest	40 min
glucose (mM)	4.51 ± 0.13	4.57 ± 0.15
heart rate (beats/min)	53 ± 2	104 ± 6
oxygen intake (ml/min)	279 ± 13	1280 ± 88

Ahlborg, Felig, Hagenfeldt, Hendler, Wahren, *"Substrate turnover during prolonged exercise in man: splanchnic and leg metabolism of glucose, free fatty acids, and amino acids",* J. Clin. Invest., 53:1080-90, 1974

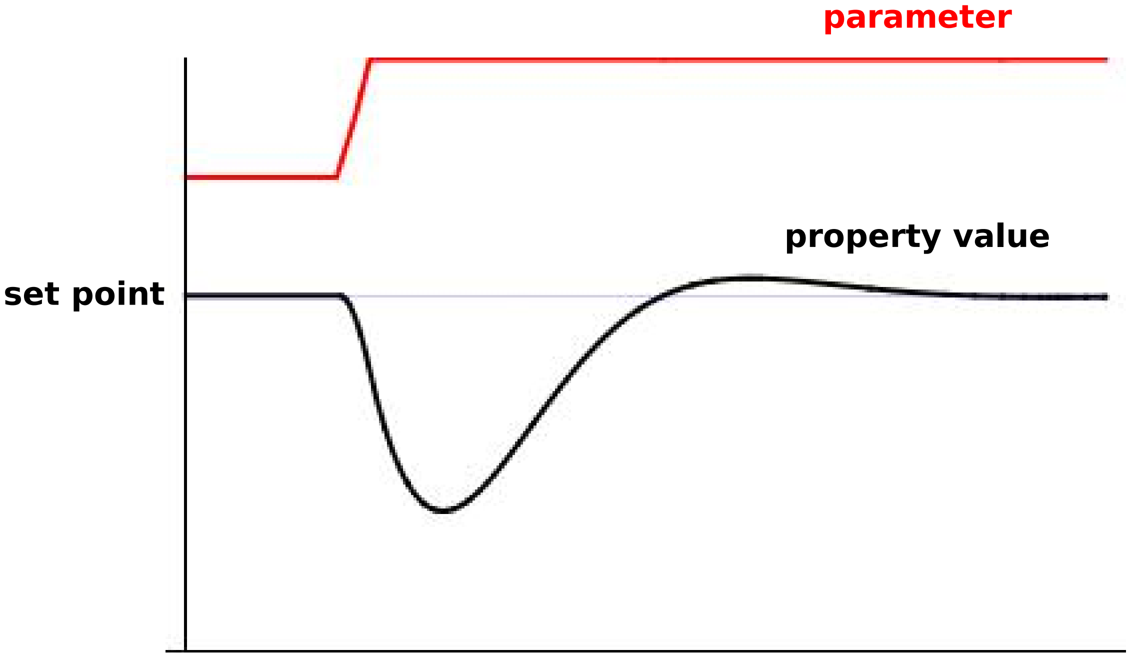
	rest	6 min	10	19	30	46	60
glucose (mM)	4.6	4.4	4.3	4.6	4.7	4.6	4.4

Jeukendrup, Raben, Gijsen, Stegen, Brouns, Saris, Wagenmakers, "*Glucose kinetics during prolonged exercise in highly trained human subjects: effect of glucose ingestion*" J. Physiol, 515:579-89, 1999.

Top, glucose levels of six healthy human male subjects during cycling exercise. The subjects followed a weight-maintaining diet for one week and were then studied after an overnight fast of 12-14 hours. Data are given as means plus or minus standard errors, obtained after a 30 minute period of rest and then after continuous upright cycling for 40 minutes. Glucose was measured enzymatically from arterial blood and pulmonary oxygen intake was estimated from expired air. **Bottom**, glucose levels of six trained cyclists during cycling exercise. The subjects were instructed to keep their diet as constant as possible in the days before the experiment, which was done after an overnight fast. A resting sample was taken and measurements were begun after a five minute cycling warm up. Blood samples were drawn at several time points during continous cycling and glucose levels were measured with an automated spectrophotometric analyser.

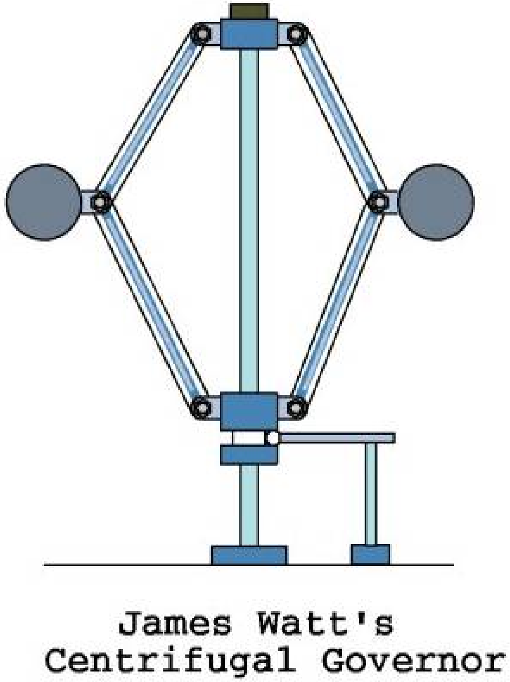
perfect adaptation

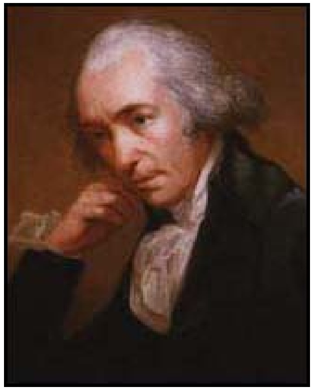
perfect adaptation – a form of homeostasis in which some property, such as glucose concentration, achieves a steady value ("set point") under suitable conditions, such as after an overnight fast, and that same value is eventually recovered despite a sustained change in some parameter, such as exercise rate.



engineers had already worked out homeostasis

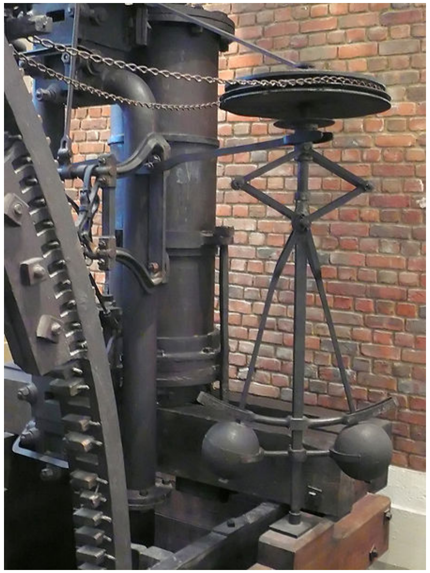
centrifugal governor at a restored windmill in moulton, lincolnshire, UK. design like this date to the 18th century





1736-1819

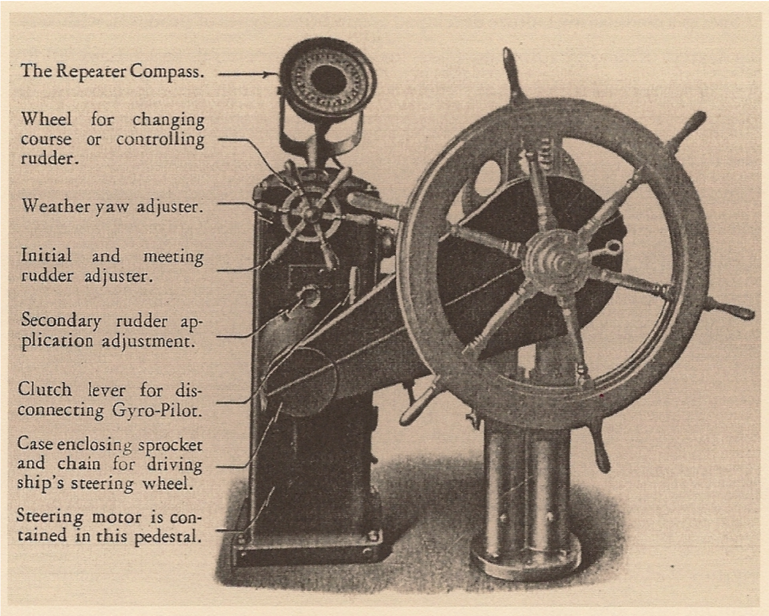
Eric Ravilious, The Brickyard, painted in 1936



Boulton-Watt steam engine with a centrifugal governor

pre-WWII control engineering

maintaining a specified "set point" – perfect adaptation



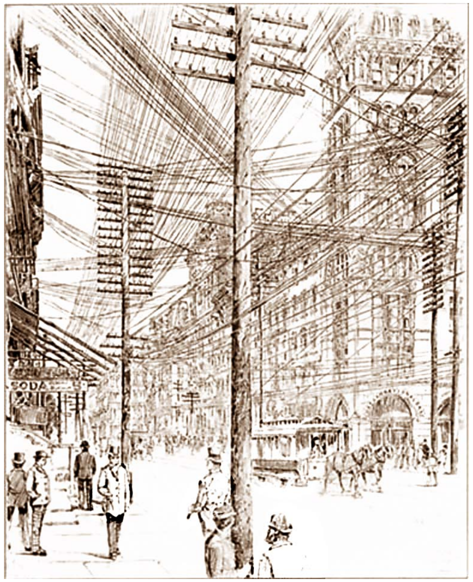
Sperry marine gyropilot - "Metal Mike", 1920s

Sperry aircraft autopilot – Amelia Earhart before her fateful flight in July 1937

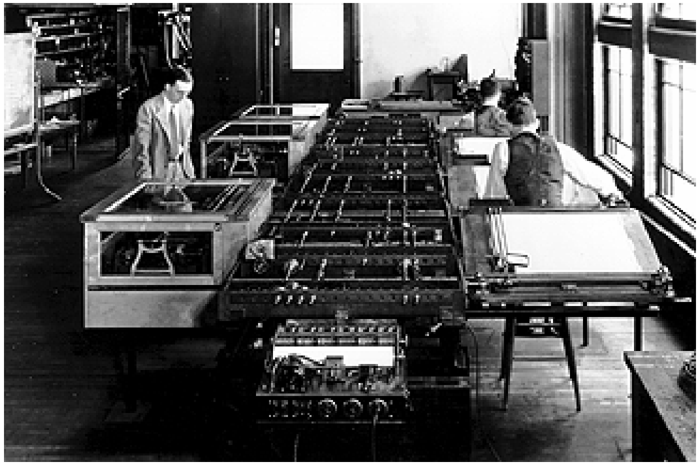
D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002

pre-WWII control engineering

balancing supply against demand in a network



electric light & power network
NY city, 1880s



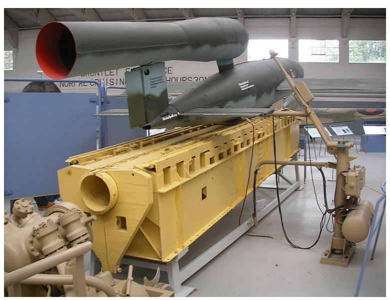
Bush's “differential analyzer”
at MIT

Thomas Hughes, **Networks of Power: Electrification in Western Society, 1880-1930**, Johns Hopkins University Press, 1983

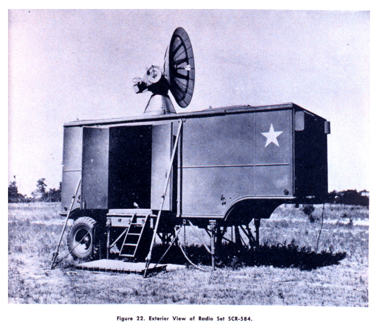
Vannevar Bush, **Operational Circuit Analysis**, John Wiley & Sons, New York, 1929

control engineering at the end of WWII

"pursuit problem" – tracking (and catching) a rapidly moving target



V1 flying bomb



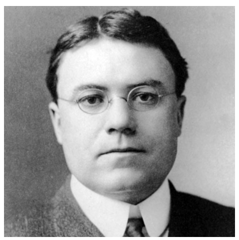
SCR-584 gun control radar

southern England, 1944-45

D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002.

the machine analogy

control problems in physiology are analogous to control problems in engineered systems and may have similar implementations



collaborators

1900-1970

1894-1964

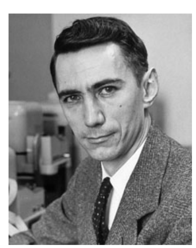
1913-2003

A Rosenblueth, N Wiener, J Bigelow, *"Behavior, purpose and teleology"*, Philos Sci **10**:18-24 1943

brains and minds undertake computation and information processing

1898-1969

1923-1969



1916-2001

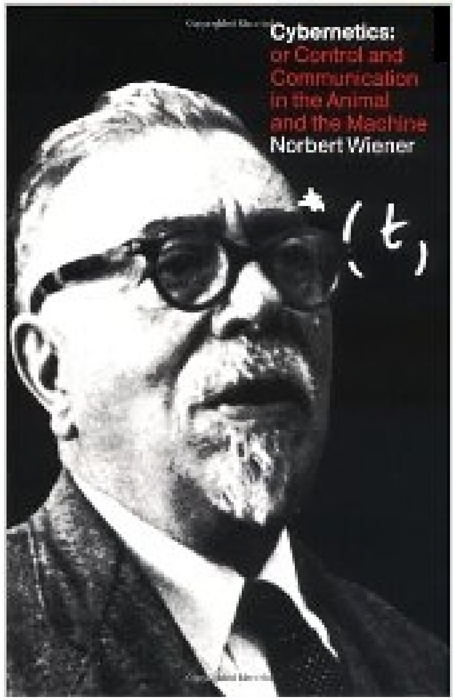
1903-1957

1912-1954

1914-1945

McCulloch, Pitts, *"A logical calculus of the ideas imanent in nervous activity"*, Bull Math Biophys **5**:115-33 1943; Shannon, "*A mathematical theory of communication*", Bell Syst Tech J **27**:623-56 1948; ; von Neumann, **The Computer and the Brain**, Yale Univ Press, 1958; Turing, "*Computing machinery and intelligence*", Mind 59:433-60 1950; Craik, **The Nature of Explanation**, Cambridge Univ Press 1943.

cybernetics



Norbert Wiener, **Cybernetics: or Control and Communication in the Animal and the Machine**, MIT Press, 1948

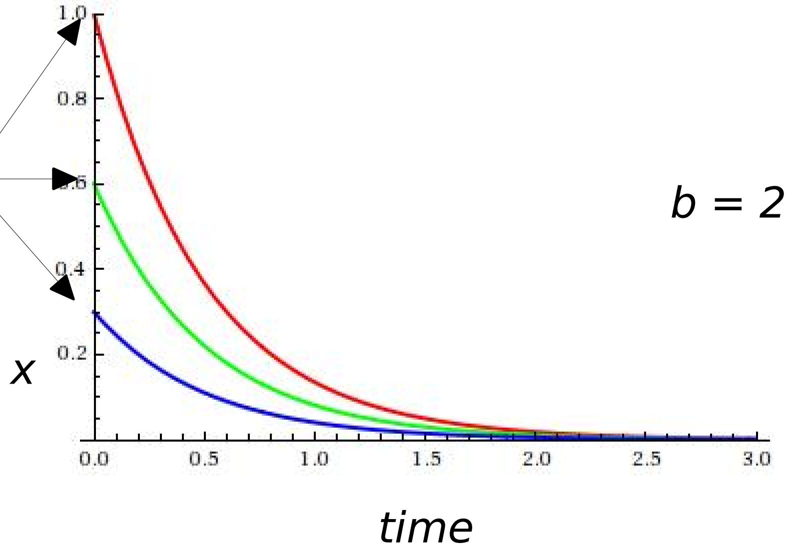
how to control a simple system (at steady state)

$$\boxed{\frac{dx}{dt} = -bx}$$

b > 0

linear, first order system

different choices of
initial condition x(0)



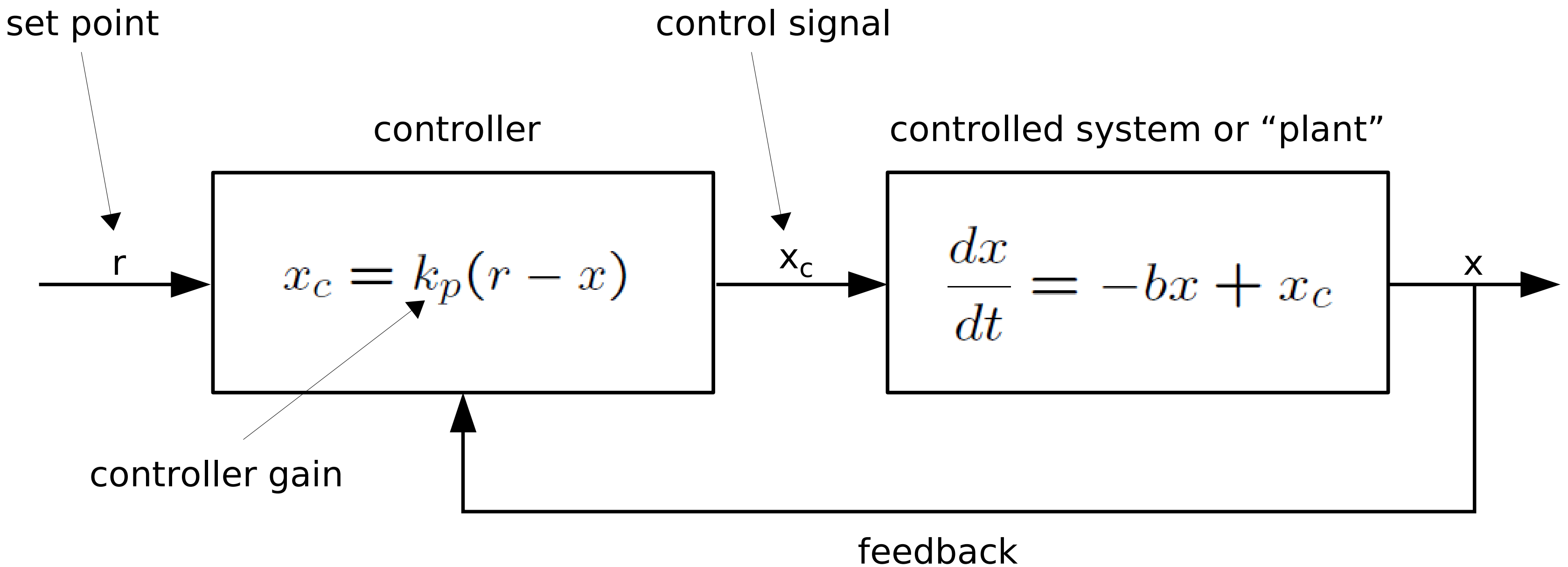
b = 2

at steady state
dx/dt = 0
or, ***x = 0***

proportional control

try to maintain the system at a non-zero “set point”, ***r***

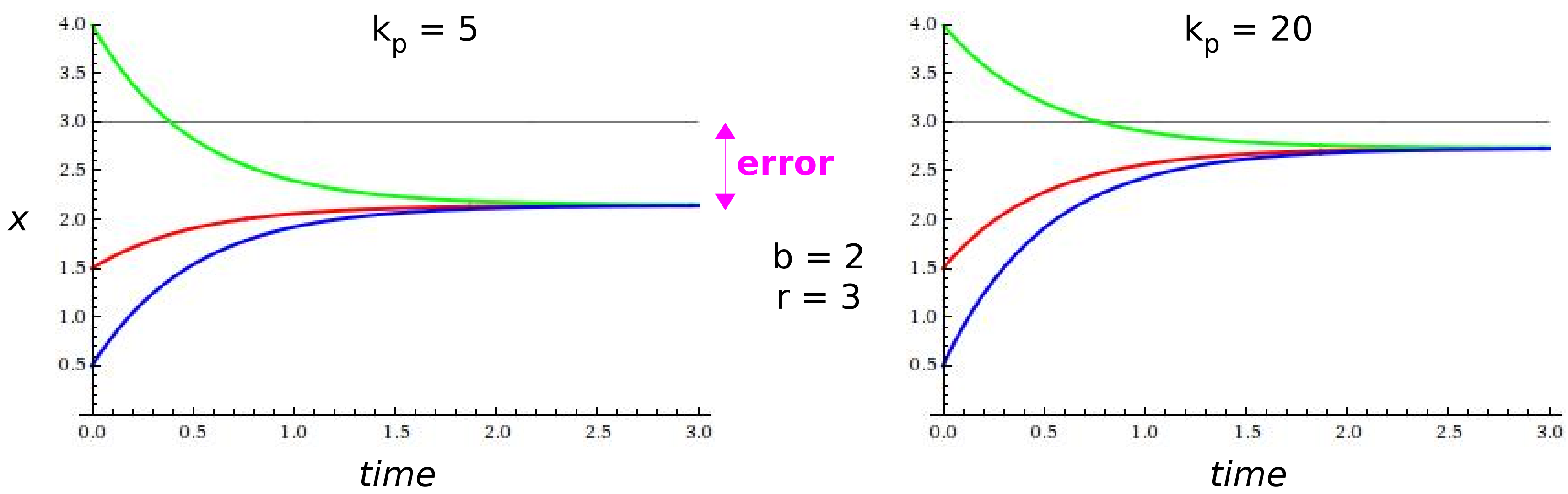
use negative feedback that is proportional to the discrepancy, ***(r - x)***



proportional control

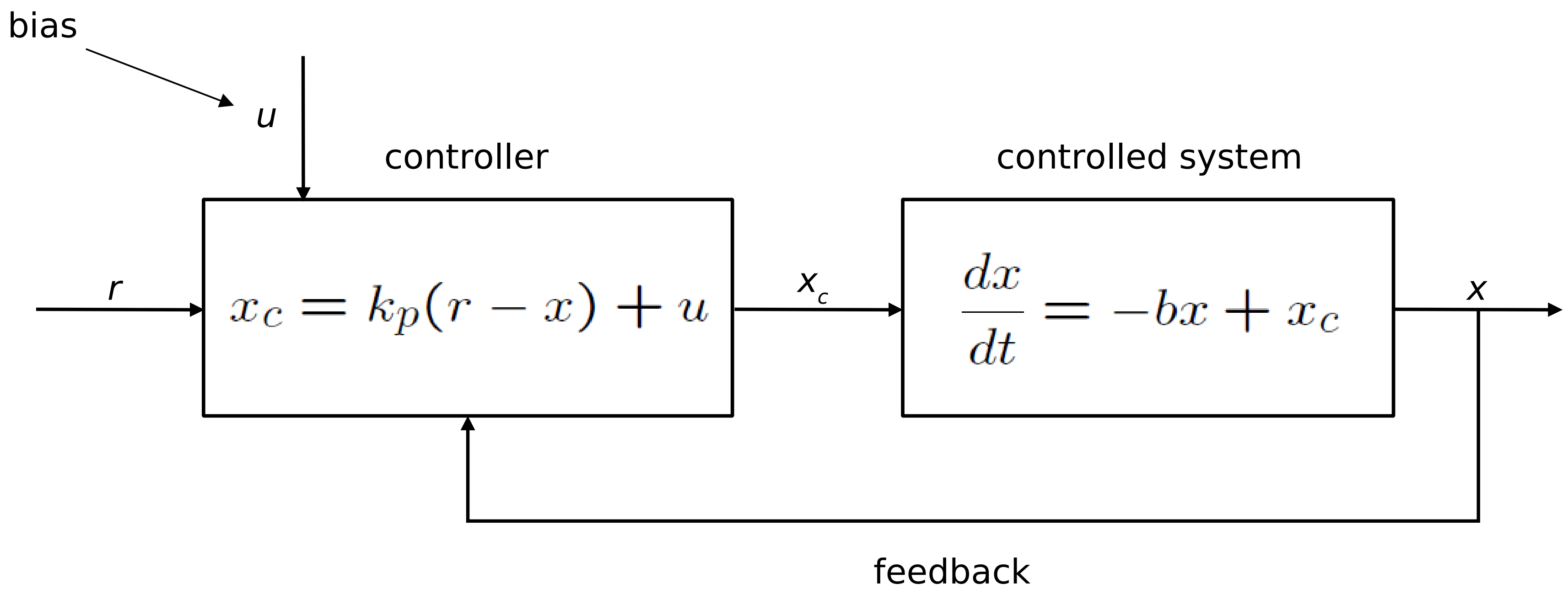
$$\frac{dx}{dt} + (b + k_p)x = k_p r$$

at steady state, ***dx/dt = 0*** $$x = \left(\frac{1}{1 + b/k_p}\right) r$$



proportional control incurs a **steady-state error** and does not adapt perfectly. the error can be reduced by increasing the controller gain.

biased proportional control



biased proportional control

$$\frac{dx}{dt} + (b + k_p)x = k_p r + u$$

at steady state,

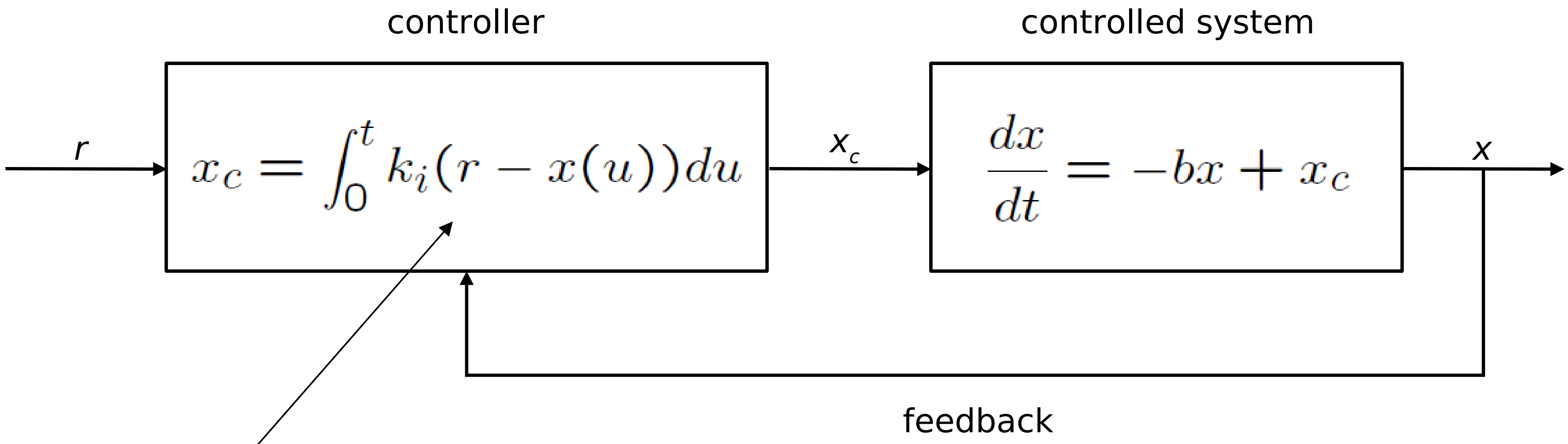
$$x = \left(\frac{k_p}{b + k_p}\right) r + \left(\frac{u}{b + k_p}\right)$$

biased proportional control eliminates steady-state error, and achieves perfect adaptation, if the bias is fine tuned so that ***u = br***

the controller requires knowledge of the parameters of the controlled system, which may alter over time or vary between systems

this solution is **not robust** to changes in parameter values

integral control



the control signal is the time integral of the error

integral control achieves perfect adaptation

$$\frac{d^2x}{dt^2} + b\frac{dx}{dt} + k_i x = k_i r$$

at steady state, $x = r$

integral control eliminates steady-state error robustly with respect to the paramters, at the expense of increasing the order of the system

negative feedback systems do not all behave similarly
their behaviour depends on the feedback mechanism

with integral control, the error signal keeps increasing until the discrepancy changes sign, which tends to cause overshooting and "hunting"

Bennett, *"Nicholas Minorsky and the automatic steering of ships"*, Control Systems Magazine **4**:10-15 1984

evolution has already discovered integral control

Integral Rein Control in Physiology

Peter T. Saunders*‡, Johan H. Koeslag† and Jabus A. Wessels†

Saunders, Koeslag, Wessels, J Theor Biol 194:163-73 1998

Calcium Homeostasis and Parturient Hypocalcemia: An Integral Feedback Perspective

H. El-Samad*, J. P. Goff† and M. Khammash*‡

El-Samad, Goff, Khammash, J Theor Biol 214:17-29 2002

Robust perfect adaptation in bacterial chemotaxis through integral feedback control

Tau-Mu Yi*†, Yun Huang†‡, Melvin I. Simon*§, and John Doyle‡

Yi, Huang, Simon, Doyle, PNAS 97:469-53 2000

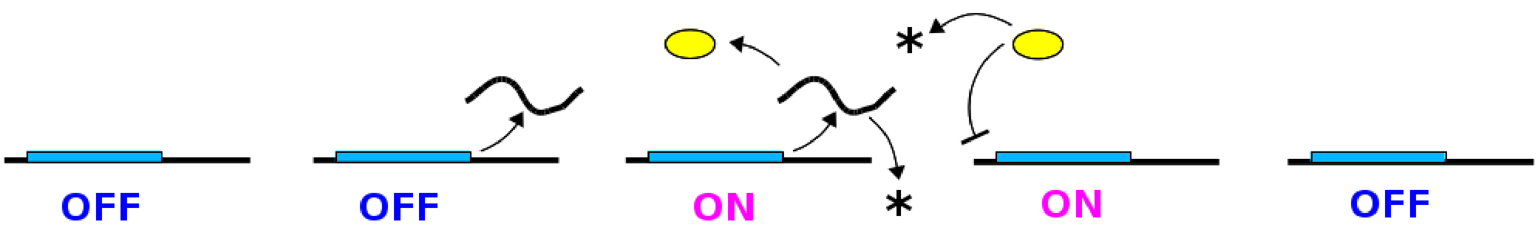
A Systems-Level Analysis of Perfect Adaptation in Yeast Osmoregulation

Dale Muzzey,[1,4,5] Carlos A. Gómez-Uribe,[1,2,5] Jerome T. Mettetal,[1] and Alexander van Oudenaarden[1,3,*]

Muzzey, Gomez-Uribe, Mettetal, van Oudenaarden, Cell 138:160-71 2009

but what about stability?

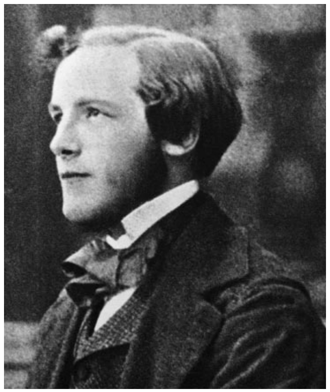
negative feedback can lead to instability and oscillation



James Clerk Maxwell spent sleepless nights worrying about how the Watt governor could remain stable

It will be seen that the motion of a machine with its governor consists in general of a uniform motion, combined with a disturbance which may be expressed as the sum of several component motions. These components may be of four different kinds :-

(1) The disturbance may continually increase.
(2) It may continually diminish.
(3) It may be an oscillation of continually increasing amplitude.
(4) It may be an oscillation of continually decreasing amplitude.



1831-1879

J C Maxwell, *“On governors”*, Proc Roy Soc, **16**:270-83, 1868.

linear equations are “easy” & fundamental

order = n
$$a_n \frac{d^n x}{dt^n} + a_{n-1} \frac{d^{n-1} x}{dt^{n-1}} + \cdots + a_1 \frac{dx}{dt} + a_0 x = 0$$

linear equations have the property that any linear combination of solutions is also a solution (“principle of superposition”).

if $x_1(t)$ and $x_2(t)$ are solutions, then so is $\lambda_1 x_1(t) + \lambda_2 x_2(t)$

nonlinear equations do not satisfy superposition and there is no systematic procedure for solving them.

however, nonlinear ODEs can be approximated by linear ODEs in the vicinity of a steady state. hence, knowledge of linear equations is fundamental for understanding nonlinear equations.

furthermore, biochemical systems conceal a surprising degree of linearity, as we will see when we study the “linear framework”

solving linear ODEs of order 1

the first-order, linear ODE

$$\frac{dx}{dt} = ax$$

has the unique solution

initial condition

$$x(t) = e^{at}x(0)$$

where the exponential function e^t is defined by

$$e^t = 1 + t + \frac{t^2}{2} + \frac{t^3}{3.2} + \cdots + \frac{t^n}{n!} + \cdots$$

(this definition works generally for complex numbers or matrices *)

* see the lecture notes "Matrix algebra for beginners, Part III"