

dynamic processes in cells
(a systems approach to biology)

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lecture 2
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1. homeostasis & microscopic cybernetics

the constancy of the “milieu intérieure”

“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**, 1978. 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" – **perfect adaptation**
2. "wide oscillations are prevented" – **dynamical stability**

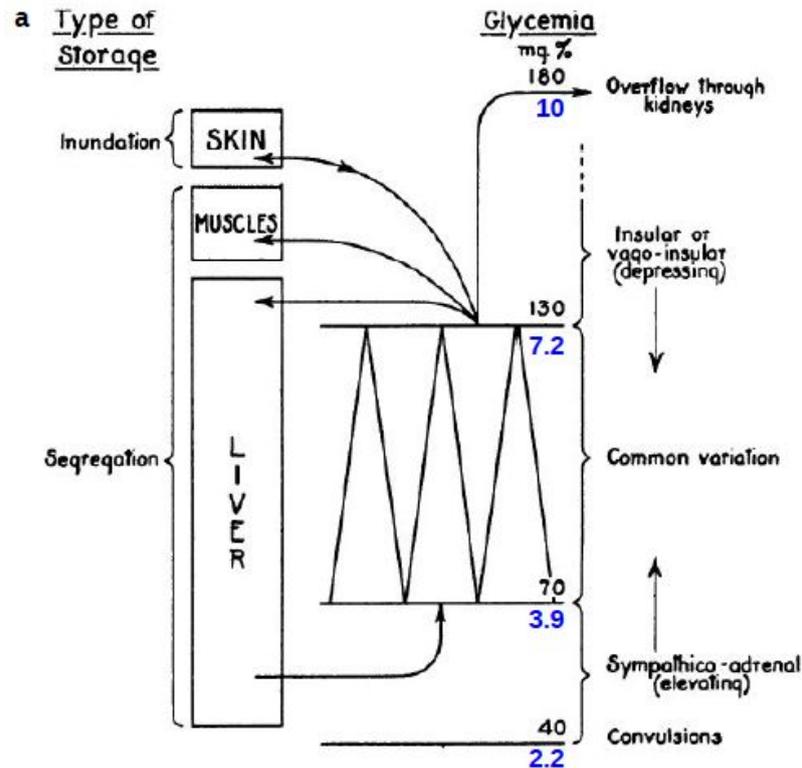


* Walter B Cannon, "Organization for physiological homeostasis", *Physiological Reviews*, **9**:399-431, 1929.

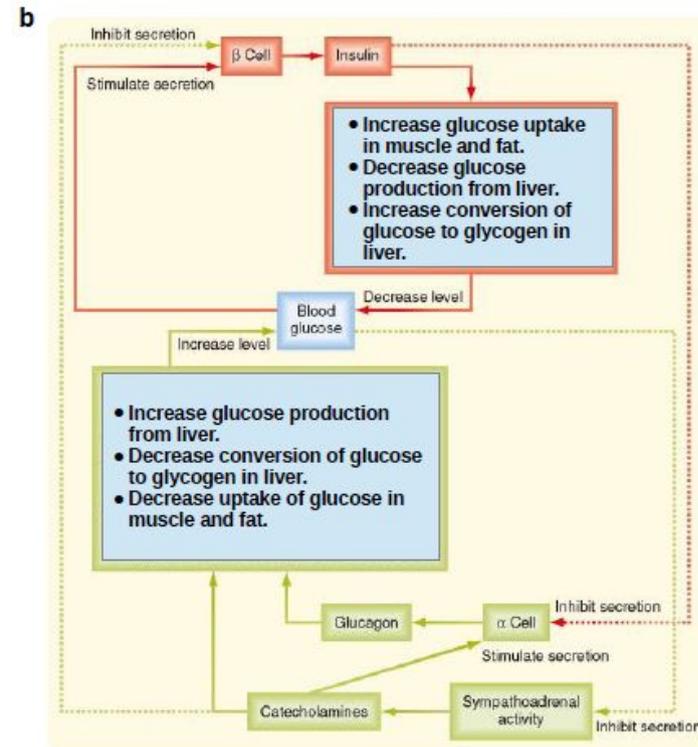
Walter B Cannon, **The Wisdom of the Body**, W W Norton & Co, 1932.

glucose homeostasis

Walter Cannon (*)



Berne & Levy (+)



“mg%” is an old unit meaning “mg per 100 mL”; “mg/dL” is now the preferred notation. normal glucose level is about 100 mg/dL or about **5mM**

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

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

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

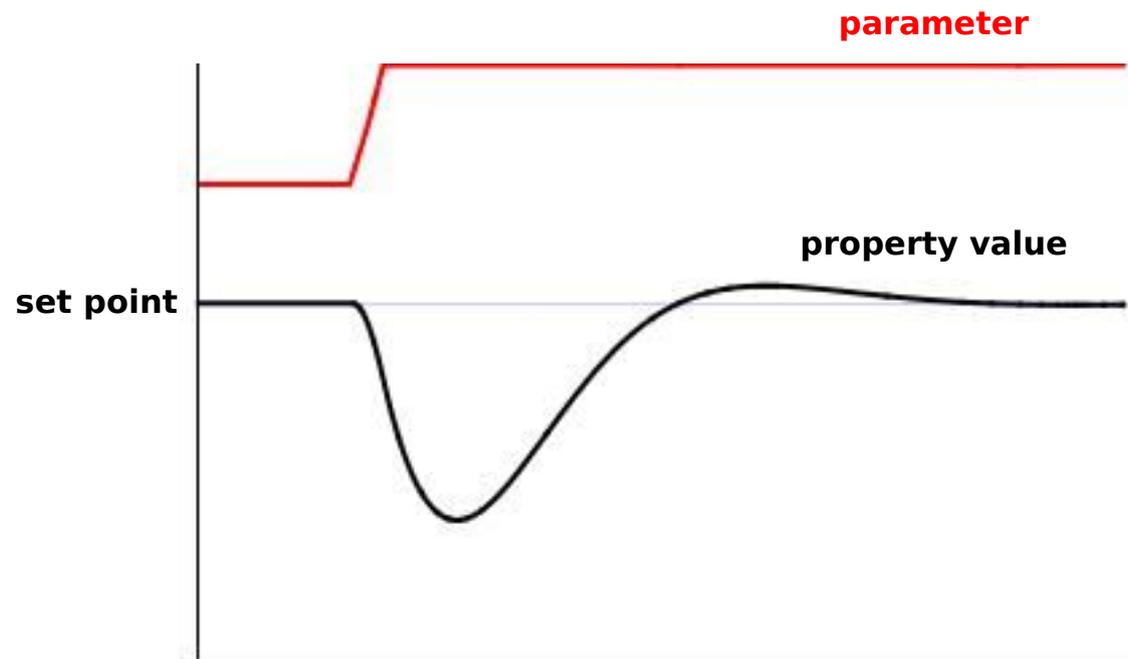
	rest	6 min	10	19	30	46	60
glucose (mM)	4.6	4.4	4.3	4.6	4.7	4.6	4.4

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

Table 1.2: 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 continuous cycling and glucose levels were measured with an automated spectrophotometric analyser. The numerical data were not available from the authors and the time points and average glucose levels were determined by blowing up Figure 1 in GSview 4.9, estimating the coordinates of the plotted points and the unit marks on the axes and calculating the underlying x and y values in minutes and mM, respectively. The error bars could not be feasibly extracted.

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.



teleology vs reductionism

walter cannon did not explain how homeostasis was achieved by negative feedback

he thought it was due 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

aristotle (384-322 BCE), the world's first great biologist, pointed out that biological organisms exhibit purpose and therefore seem to require teleological explanations

ARISTOTELIAN CAUSES

material
formal
efficient

final

SYSTEMS BIOLOGY

components
connections or reactions
differential equations

reductionism

we have been struggling with final causes ever since – “*Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public.*” (*)

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

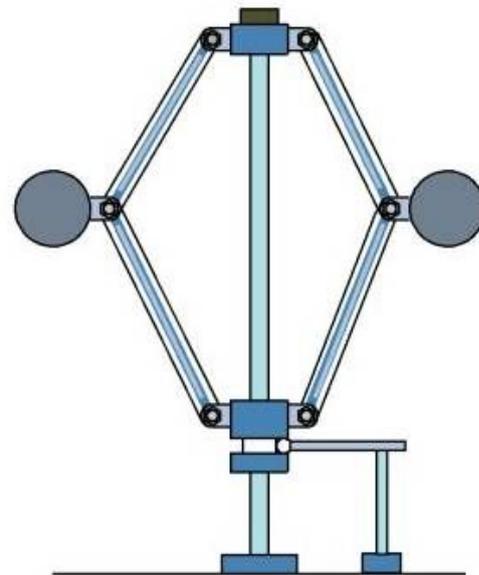
engineers had already worked out homeostasis



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



Eric Ravilious, The Brickyard, painted in 1936



James Watt's
Centrifugal Governor



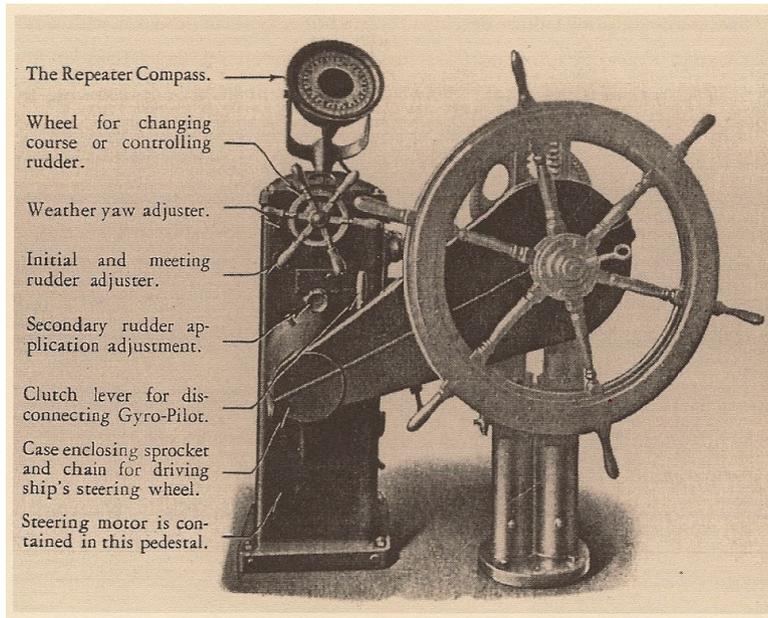
1736-1819



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

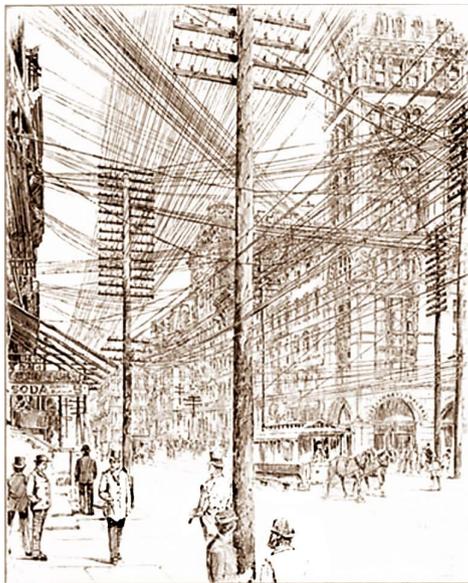


Sperry aircraft autopilot – Amelia Earhart before her fateful flight in July 1937

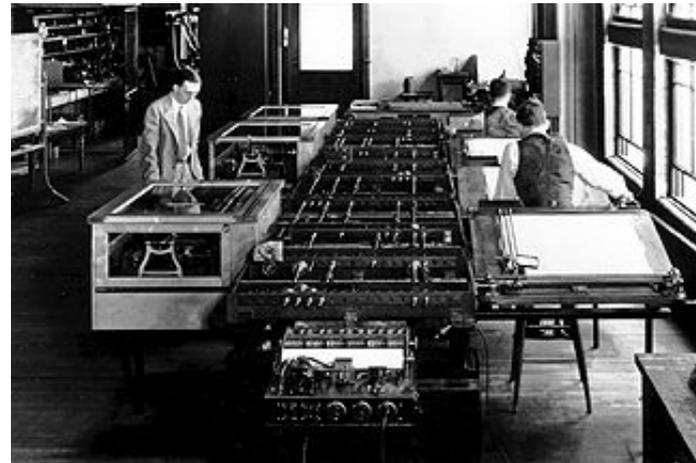
D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002

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, with an appendix by Norbert Wiener.

control problems at the end of WWII

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



V1 flying bomb



SCR-584 gun control radar

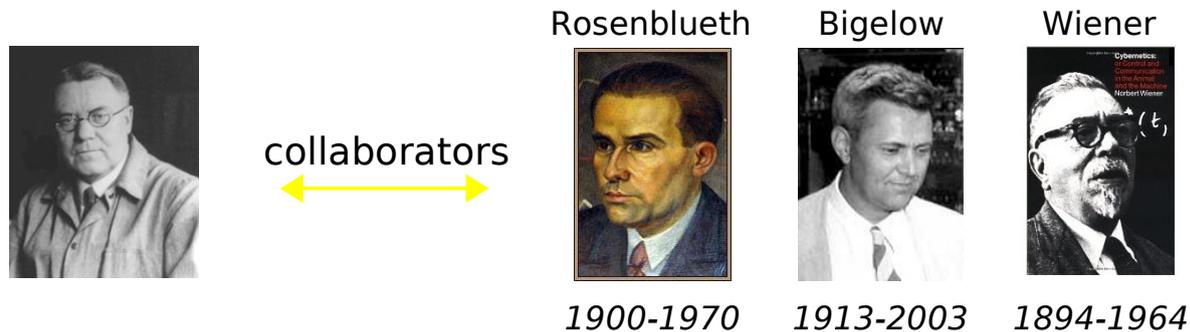


southern England, 1944-45

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

cybernetics - the machine analogy

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



A Rosenblueth, N Wiener, J Bigelow, *“Behavior, purpose and teleology”*, *Philos Sci* **10**:18-24 1943; Wiener, **Cybernetics: or Control and Communication in the Animal and the Machine**, MIT Press, 1948

brains and minds undertake computation and information processing



McCulloch, Pitts, *“A logical calculus of the ideas immanent in nervous activity”*, *Bull Math Biophys* **5**:115-33 1943; Lettvin, Maturana, McCulloch, Pitts, *“What the frog's eye tells the frog's brain”*, *Proc IRE* 47:1940-51 1959; von Neumann, **The Computer and the Brain**, Yale Univ Press, 1958; Craik, **The Nature of Explanation**, Cambridge Univ Press 1943.

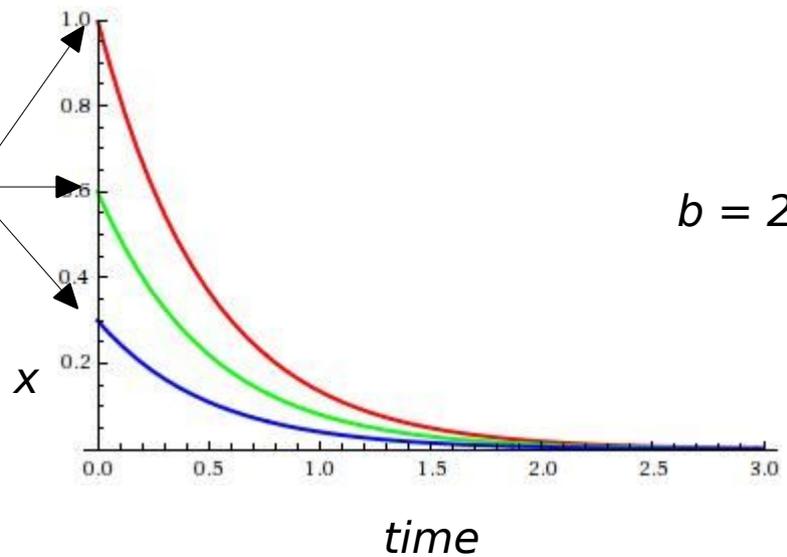
how to control a simple system (at steady state)

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

$$b > 0$$

linear, first order system

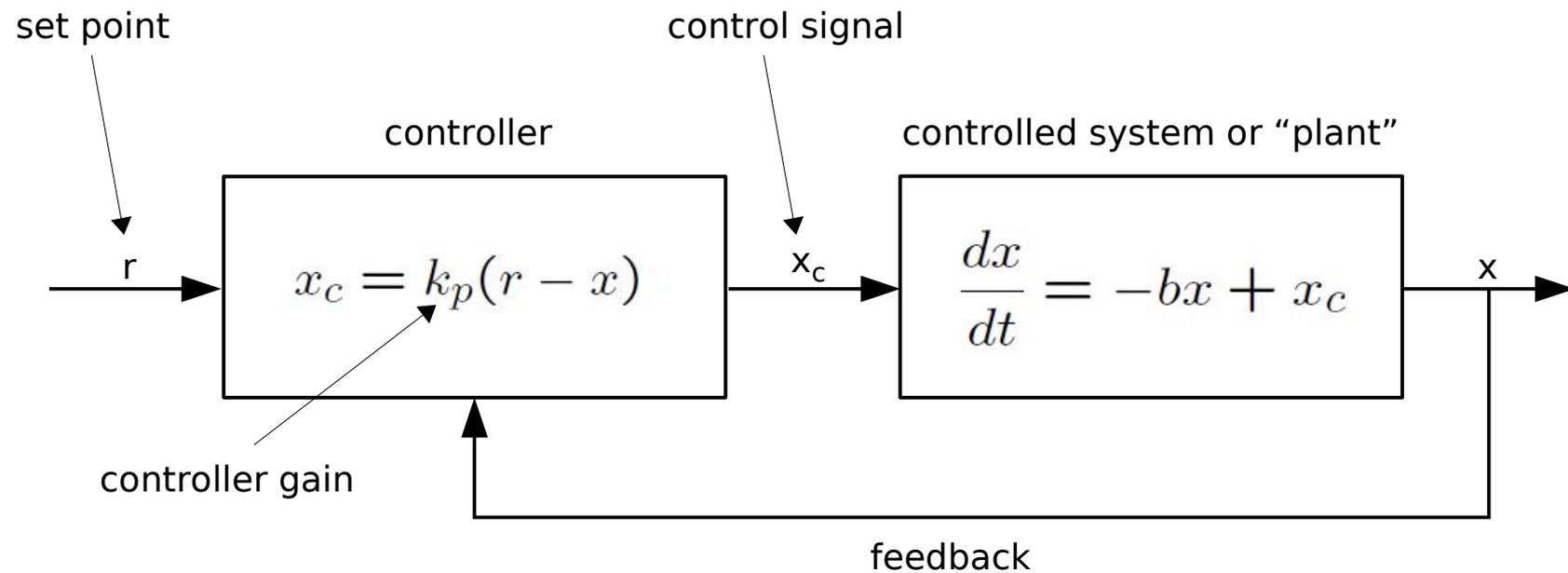
different choices of
initial condition $x(0)$



proportional control

try to maintain the system at a set point “r”

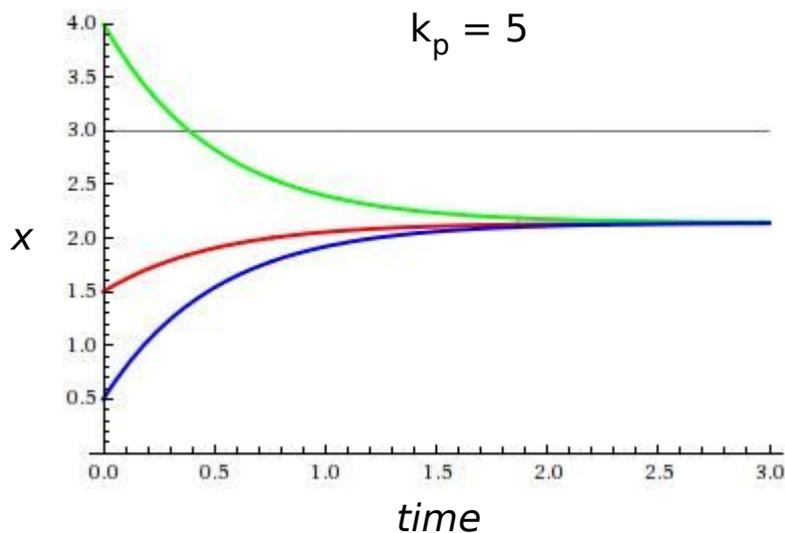
use negative feedback that is proportional to the discrepancy (r - x)



proportional control

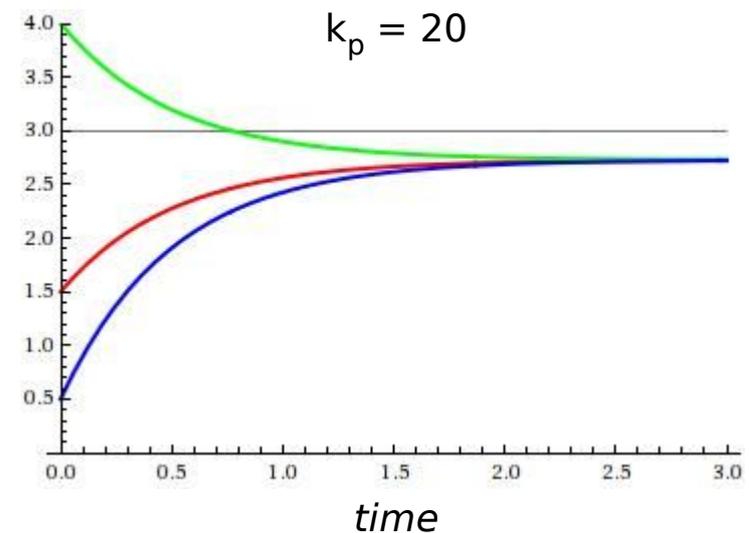
$$\frac{dx}{dt} + (b + k_p)x = k_p r$$

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



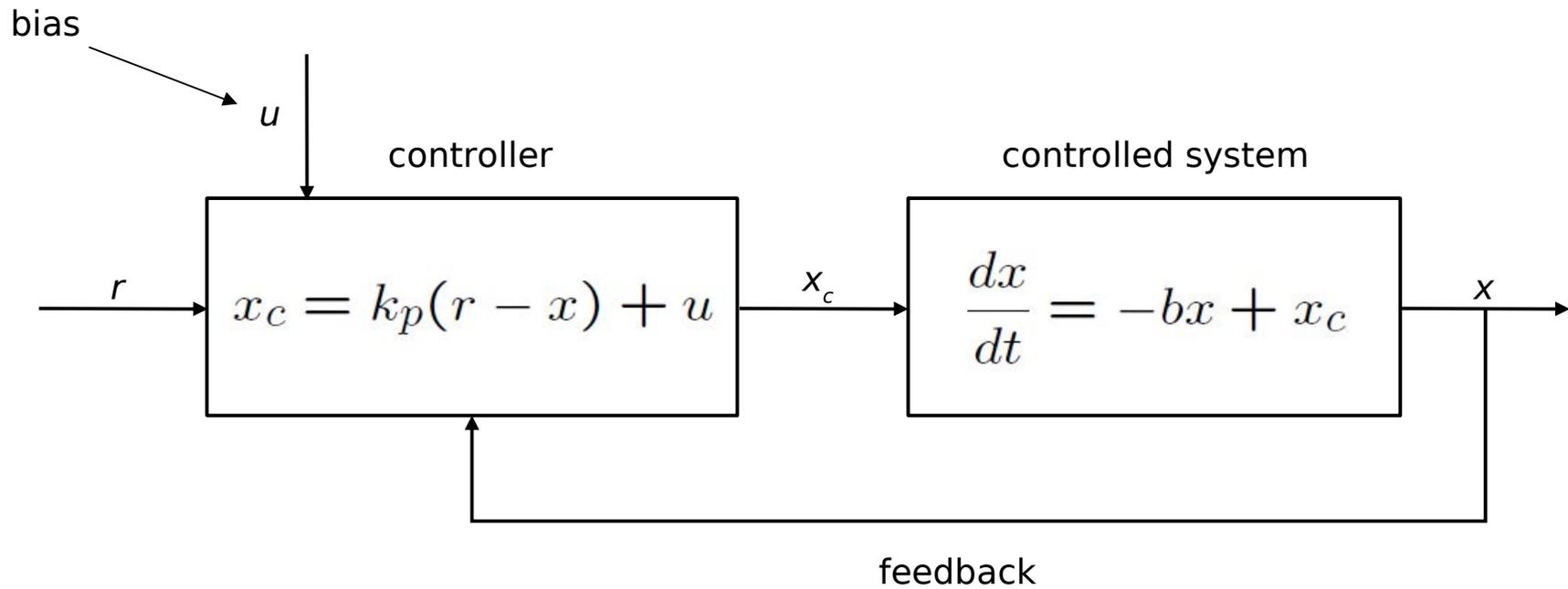
error

$$b = 2$$
$$r = 3$$



proportional control incurs a **steady-state error** that 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,

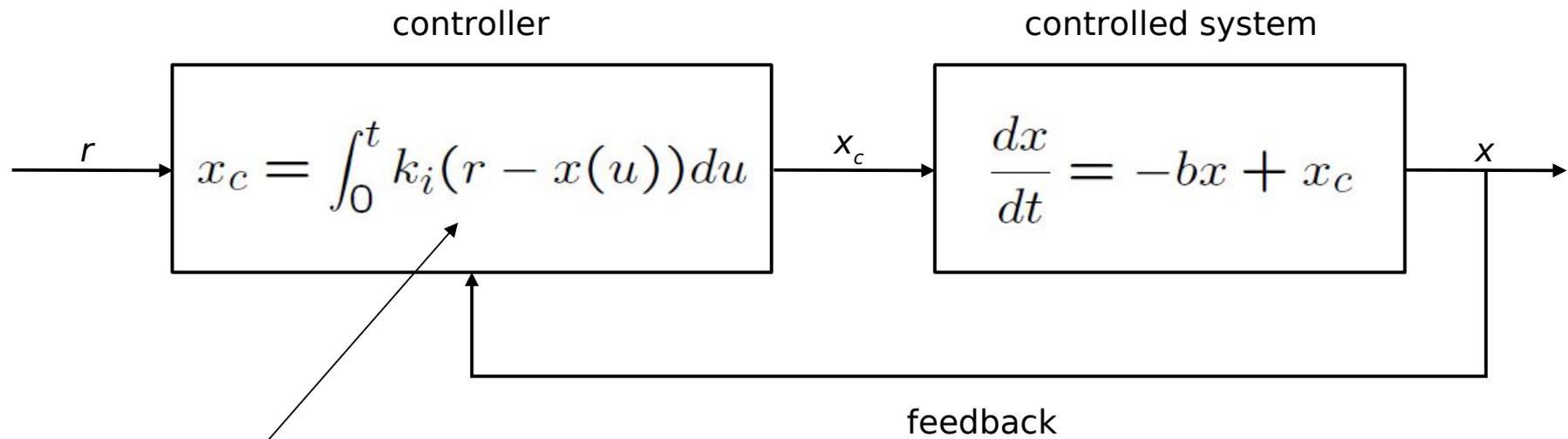
$$x = \left(\frac{k_p}{b + k_p} \right) r + \left(\frac{u}{b + k_p} \right)$$

biased proportional control eliminates steady-state error 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 is not a robust solution

integral control



the control signal is the time integral of the error

integral control achieves perfect adaptation

$$\frac{d^2x}{dt^2} + b\frac{dx}{dt} + k_ix = k_ir$$

at steady state, $x = r$

integral control eliminates steady-state error robustly with respect to the parameters

at the expense of increasing the order of the system (and potentially introducing instability)

integral control can be combined with **proportional** control and **derivative** control (PID control), to enhance stability and the transient response - multiple control mechanisms are needed to shape the overall behaviour of a controller

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

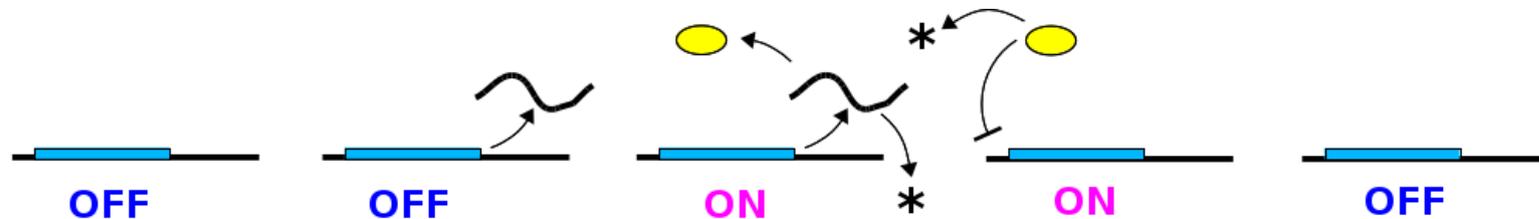
A Systems-Level Analysis of Perfect Adaptation in Yeast Osmoregulation

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 dynamical stability?

engineers know that negative feedback can lead to oscillation and instability -



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.

Maxwell



1831-1879

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

mention initial conditions!!

linear equations are “easy” & fundamental

order = n

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

linear problems can be solved analytically

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 (next lecture). 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 (lecture 6).

solving linear ODEs of order 1

the first-order, linear ODE $\frac{dx}{dt} = ax$

has the unique solution $x(t) = e^{at}x(0)$

initial condition
↓

where the exponential function e^t is defined by

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

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

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

solving linear ODEs of order 2

the second-order, linear ODE $\frac{d^2x}{dt^2} = -ax \quad a > 0$

has solutions $\cos(\sqrt{at})$ and $\sin(\sqrt{at})$

but trigonometric functions are really exponential functions in disguise, over the complex numbers

$$e^{it} = \cos(t) + i \sin(t) \longleftarrow \text{Euler's formula}$$

$$\cos(t) = \frac{e^{it} + e^{-it}}{2} \quad \sin(t) = \frac{e^{it} - e^{-it}}{2i}$$



1707-1783

we only need the exponential function (over the complex numbers) to solve ODEs of order 1 and 2