dynamic processes in cells (a systems approach to biology)

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lecture 2
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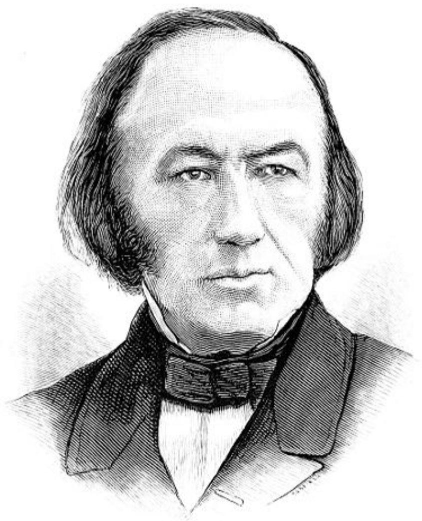
1. homeostasis & microscopic cybernetics

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

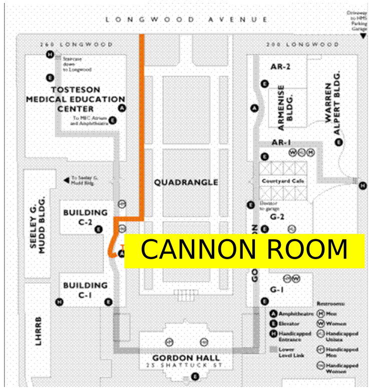
Claude Bernard, **Introduction to the Study of Experimental Medicine**, 1865

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

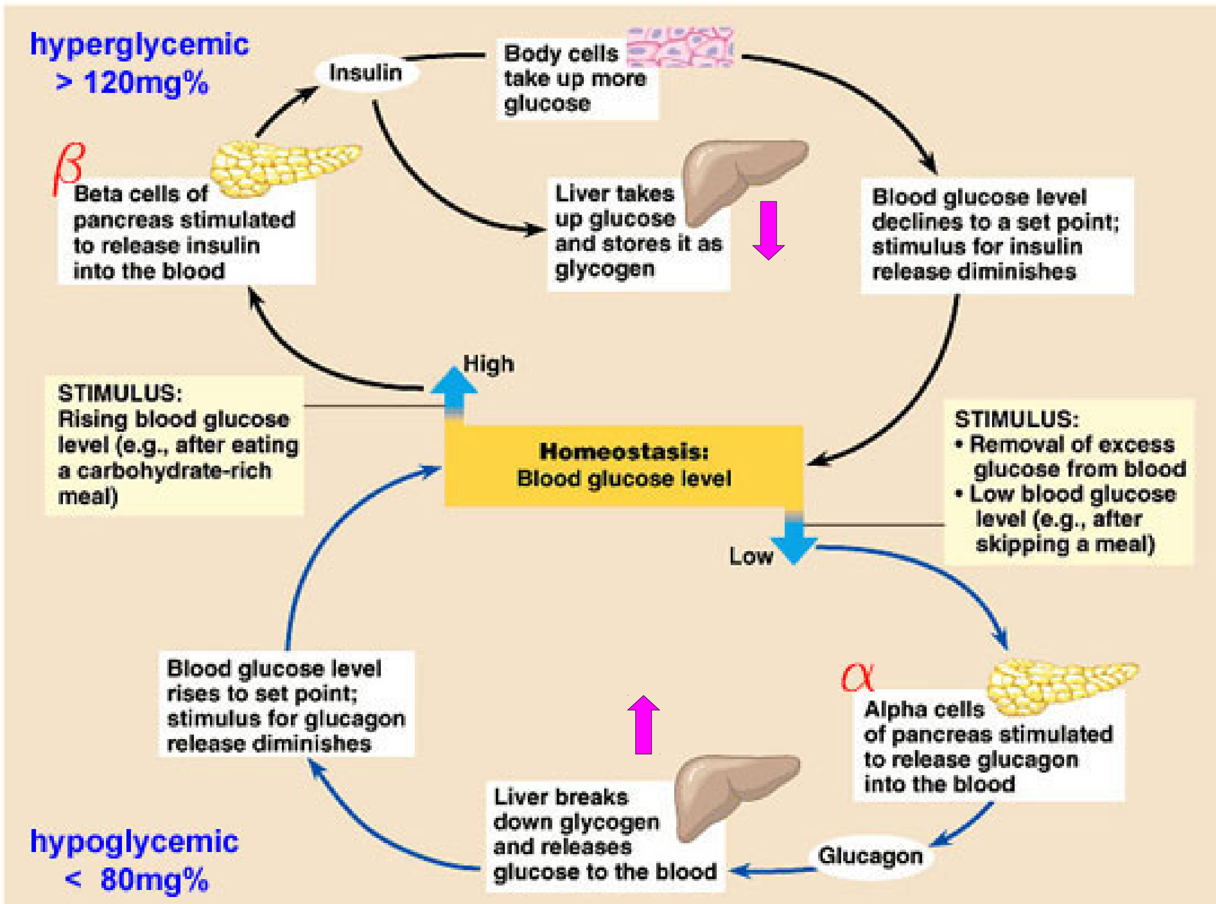


1. "back towards the mean position" – **perfect adaptation**
2. "wide oscillations are prevented" – **dynamical stability**

***** 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.

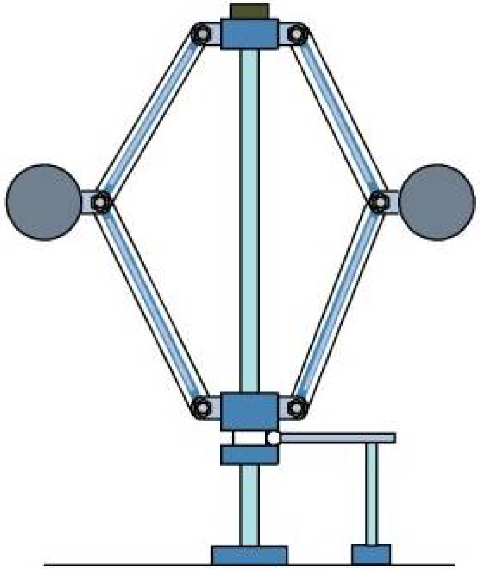
homeostasis of blood glucose



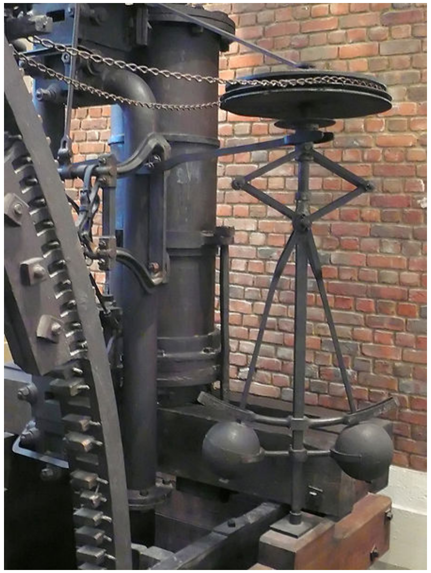
“mg%” is an old unit meaning “mg per 100 mL”; “mg/dL” is now used
normal glucose level is about 100 mg/dL or about 5mM

the engineers had already worked it out

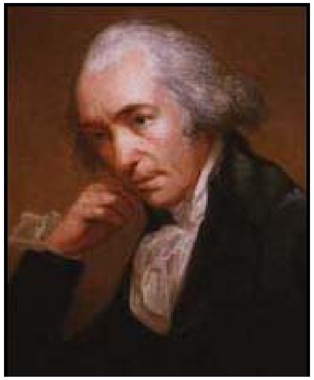
centrifugal governor at a restored windmill in moulton, lincolnshire, UK, dating from the 1820s



James Watt's
Centrifugal Governor



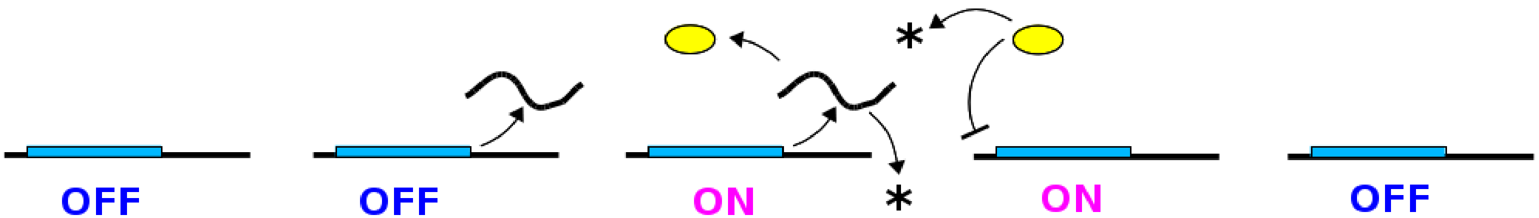
Boulton-Watt steam engine with a centrifugal governor



1736-1819

negative feedback can lead to instability

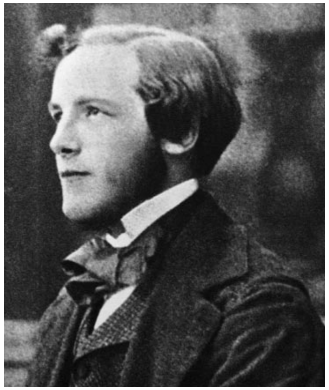
delay can lead to oscillation – (see lecture 9 for this example)



James Clerk Maxwell spend 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.

teleology

Walter Cannon did not explain how stability was achieved by negative feedback

he seemed to think 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

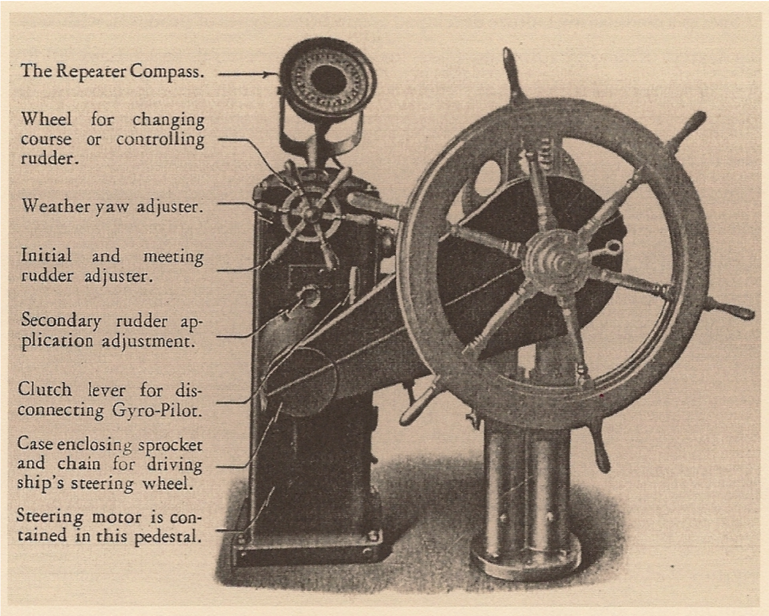
ARISTOTELIAN CAUSES	**SYSTEMS BIOLOGY**
material	components
formal	connections or reactions
efficient	differential equations
final	

we now believe that purposeful behaviour in living organisms can be explained by material, formal and efficient causes, without invoking final causes

J H F Bothwell, *“The long past of systems biology”*, New Phytol, **170**:6-10 2006.

pre-WWII control engineering

maintaining a specified "set point"



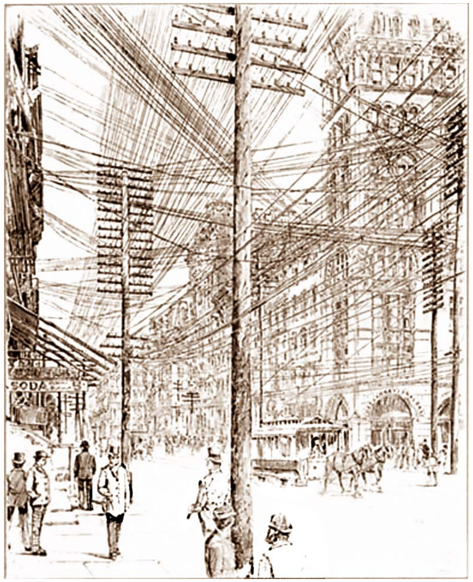
Sperry marine gyropilot - "Metal Mike", 1920s

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

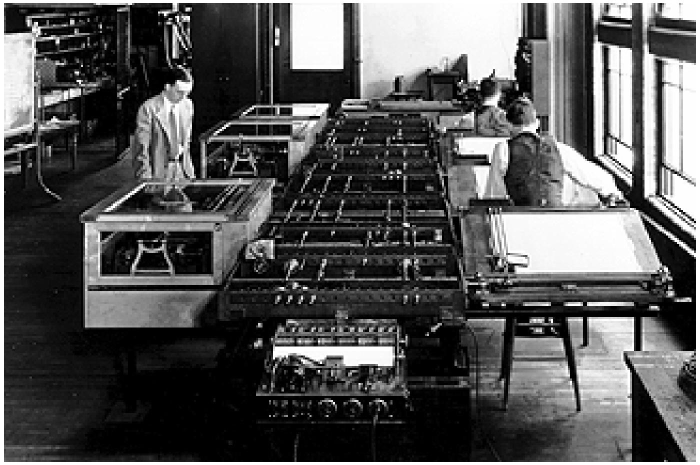
D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002

pre-WWII control engineering

balancing supply against demand in a network



electric light & power network
NY city, 1880s



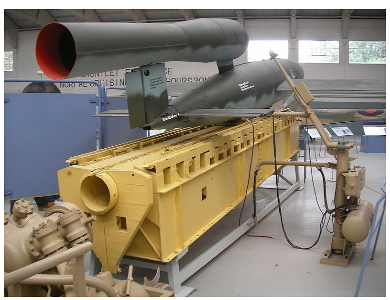
Bush's “differential analyzer”
at MIT

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

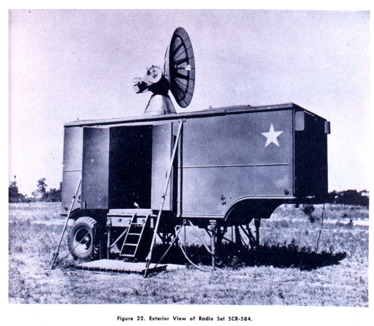
Vannevar Bush, **Operational Circuit Analysis**, John Wiley & Sons, New York, 1929, with an appendix by Norbert Weiner.

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.

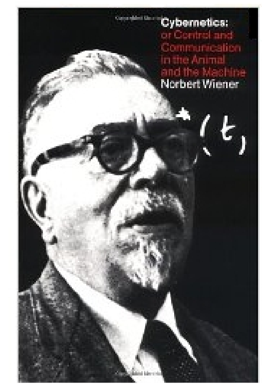
cybernetics – biology catches up with engineering

control problems in organisms, such as homeostasis, are analogous to control problems in engineered systems and may have similar implementations

collaborators

1900-1970

1913-2003



1894-1964

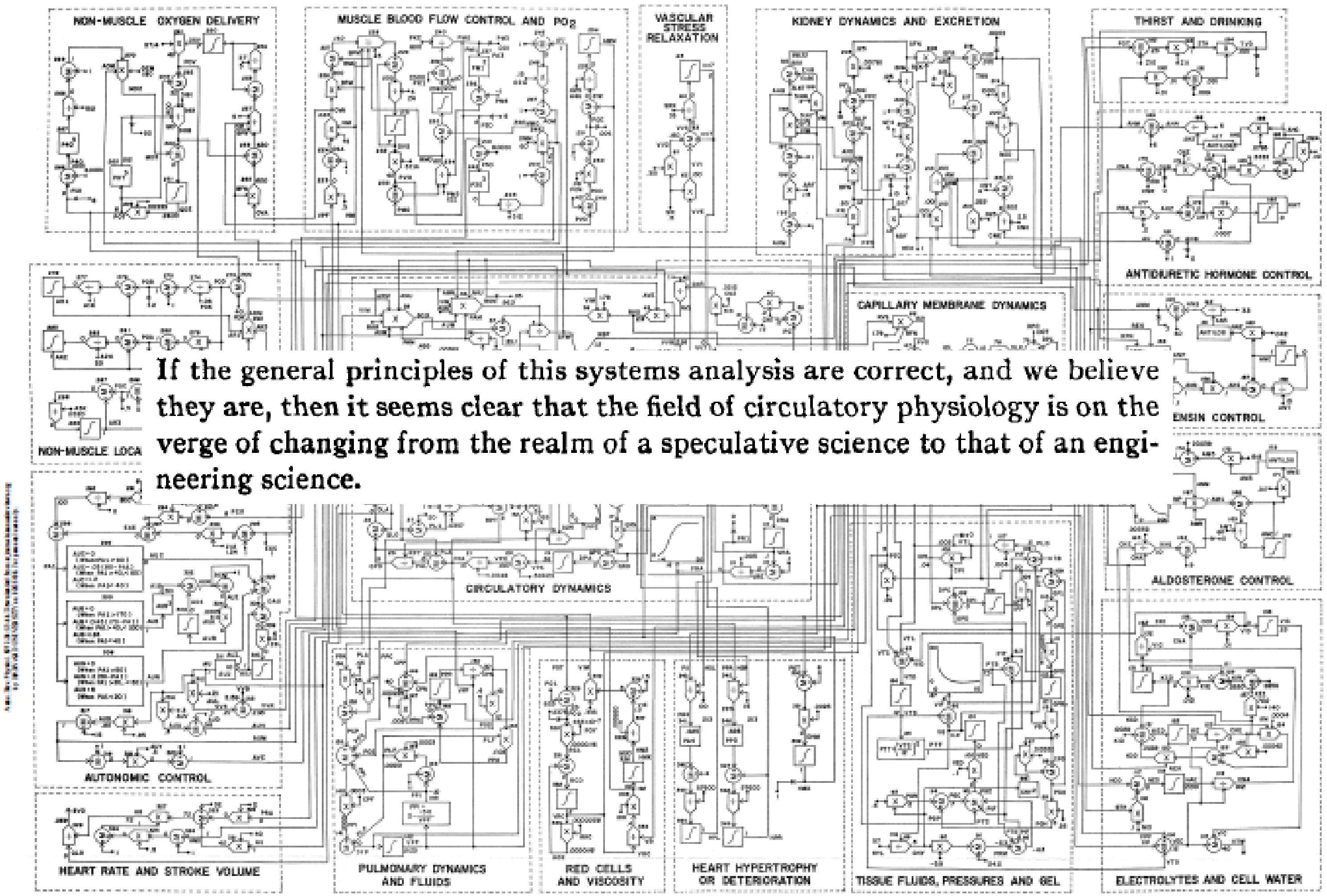
homeostasis can be explained using material, formal and efficient causes, without invoking teleology

A Rosenblueth, N Wiener, J Bigelow, *“Behavior, purpose and teleology”*, Philosophy of Science **10**:18-24 1943

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

post-WWII physiological cybernetics

Arthur Guyton's model of human blood circulation



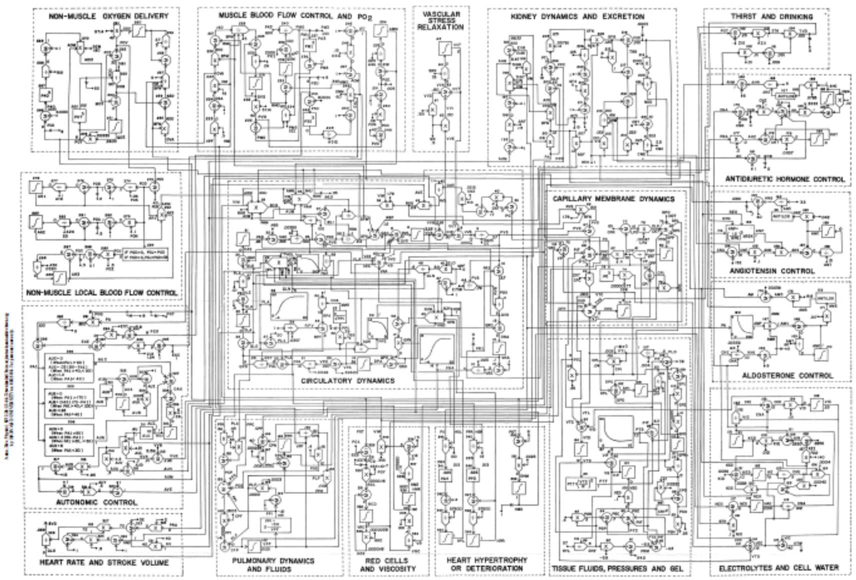
If the general principles of this systems analysis are correct, and we believe they are, then it seems clear that the field of circulatory physiology is on the verge of changing from the realm of a speculative science to that of an engineering science.

1919-2003

Guyton, Coleman, Granger, *“Circulation: overall regulation”*, Annu Rev Physiol **32**:13-44 1972

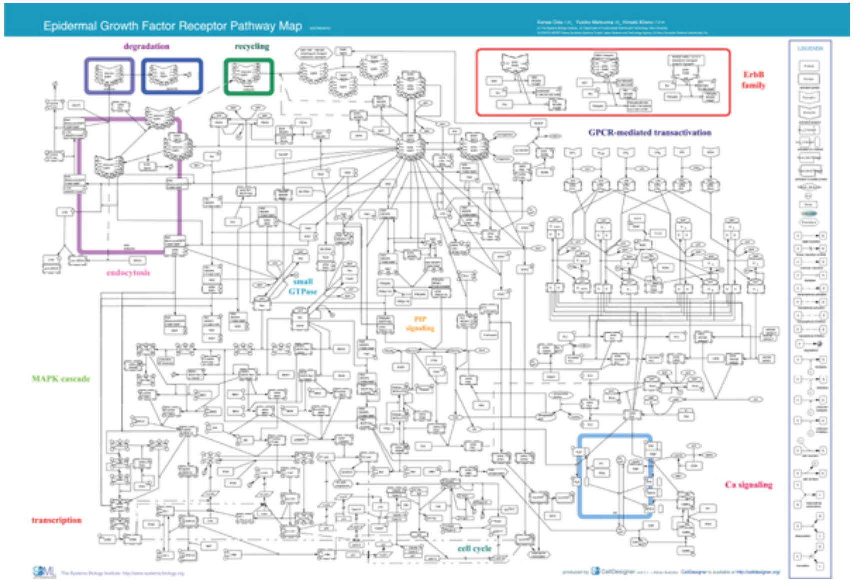
the molecular revolution

1970



a systems understanding
but no molecules

2014



many molecules but no systems
understanding

the challenge is to integrate the two, which is systems biology

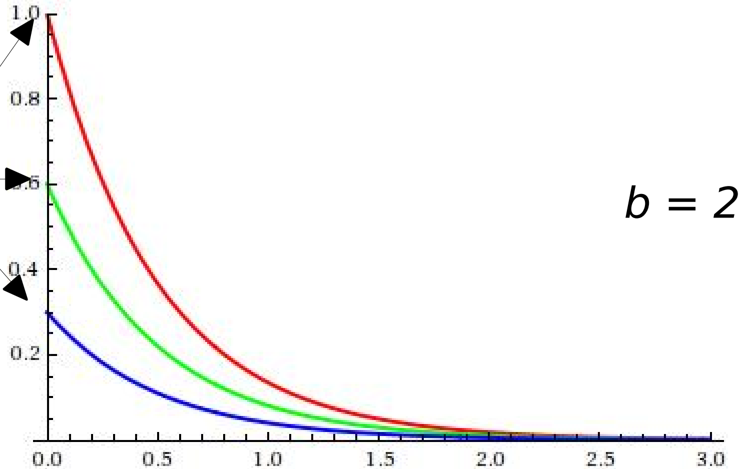
how to control a simple system (at steady state)

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

b > 0

linear, first order system

different choices of
initial condition x(0)



x

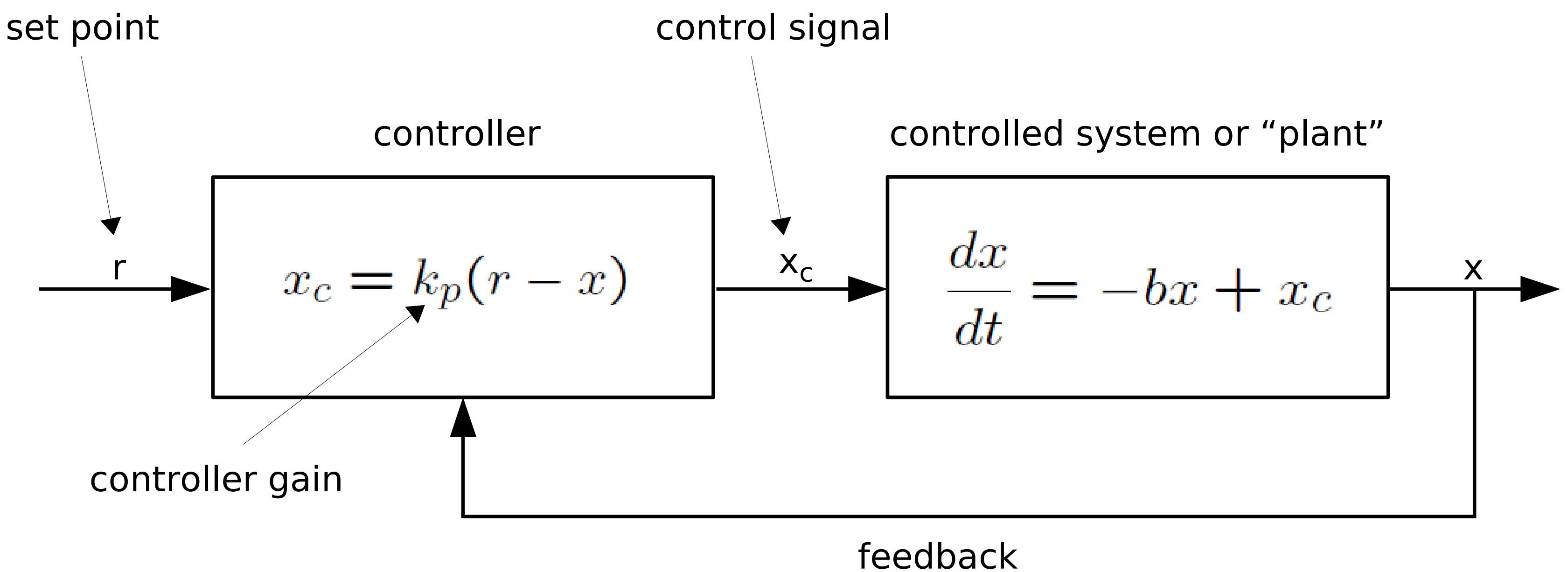
b = 2

time

proportional control

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

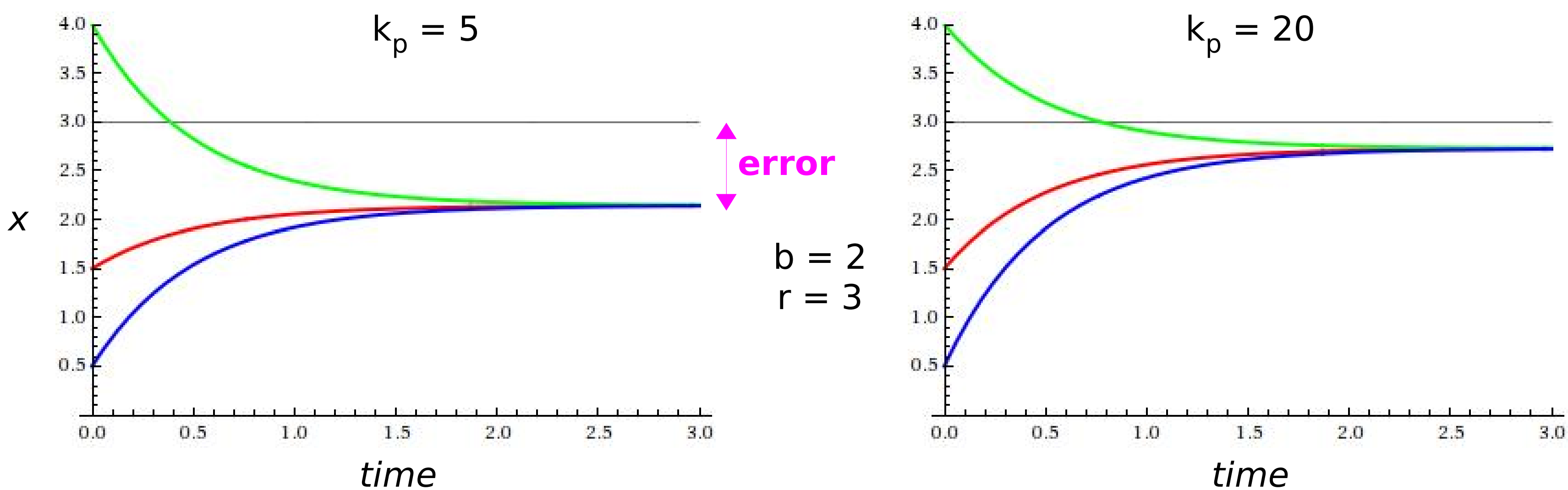
use negative feedback that is proportional to the discrepancy (r - x)



proportional control

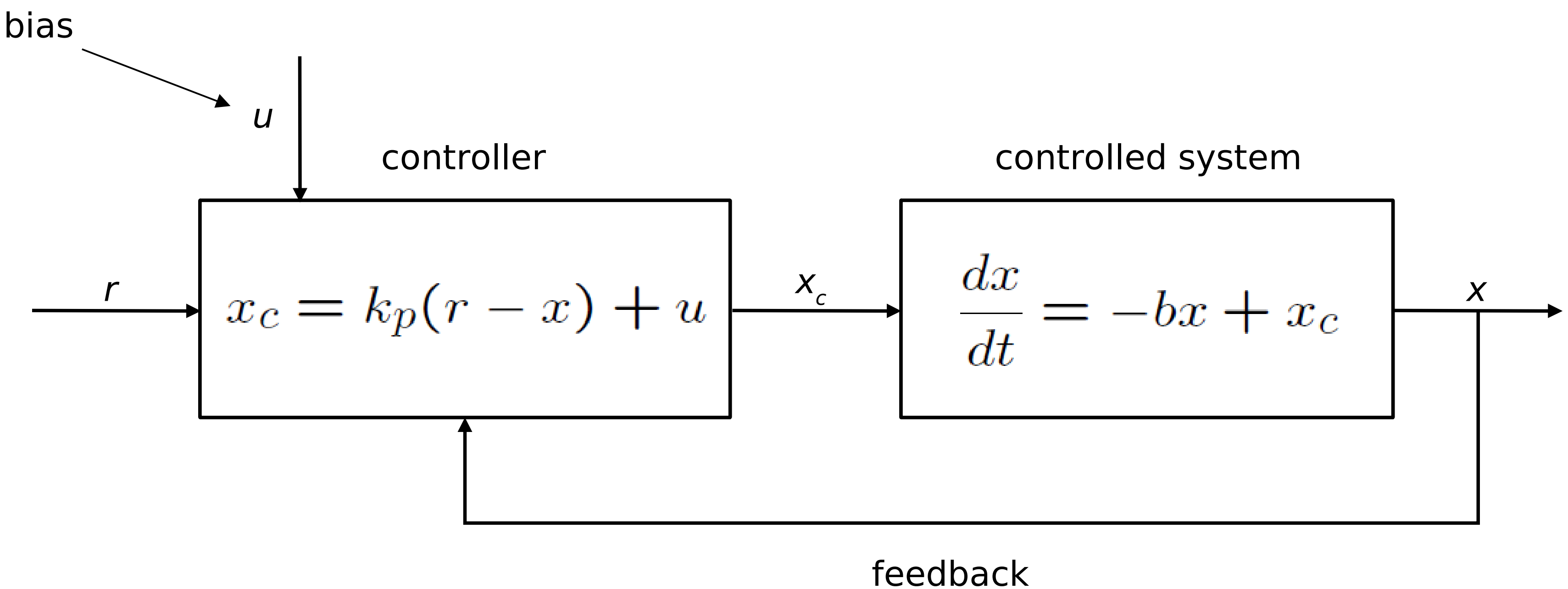
$$\frac{dx}{dt} + (b + k_p)x = k_p r$$

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



proportional control incurs a **steady-state error** that can be reduced by increasing the controller gain

biased proportional control



biased proportional control

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

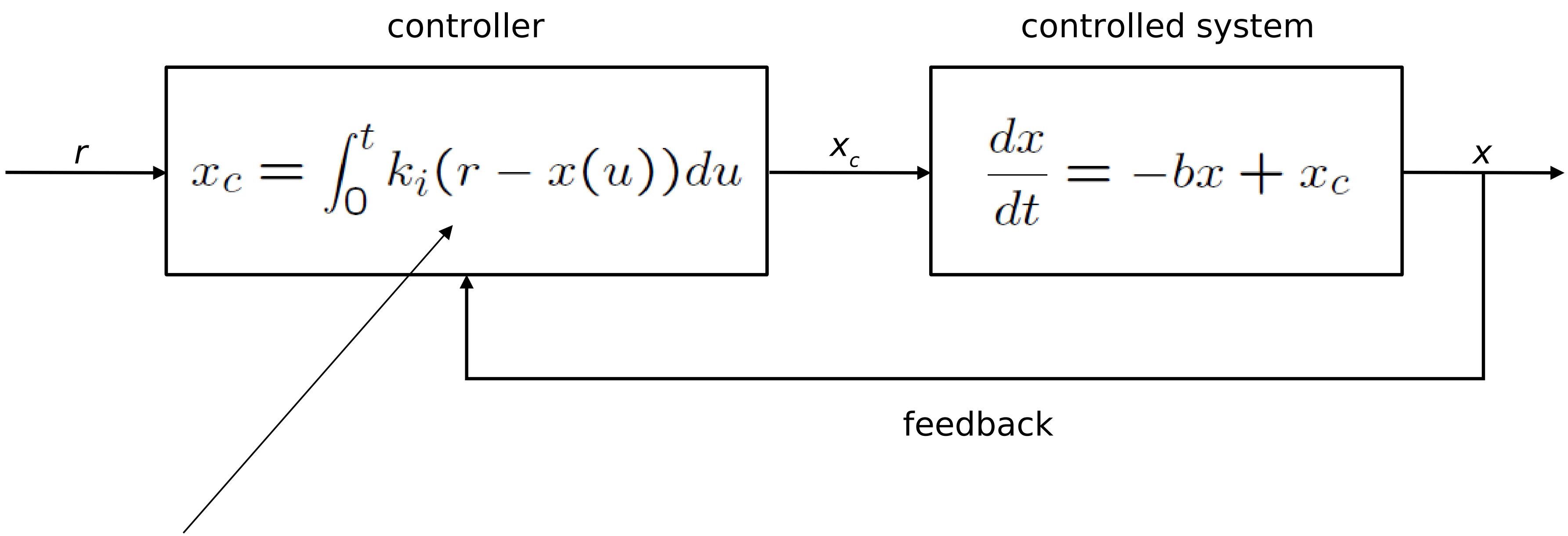
at steady state, $$x = \left(\frac{k_p}{b + k_p}\right) r + \left(\frac{u}{b + k_p}\right)$$

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

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

at steady state, $x = r$

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

at the expense of <u>increasing the order</u> of the system (and potentially <u>introducing instability</u>)

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?

systems must not only reach steady state but do so in an efficient, stable way.

to analyse this, we need to find the solution of the equations as a function of time

the systems are described by **LINEAR ORDINARY DIFFERENTIAL EQUATIONS**

order = n

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

with constant (ie: not varying over time) coefficients

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”

solving linear ODEs of order 2

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

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

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

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

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

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

solving linear ODEs of order n

THAT IS ALL YOU NEED (WELL, NEARLY*)

once you have exponential functions and complex numbers, any linear ODE, no matter what its order, can be solved in terms of them (nearly*)

we will see that this is a consequence of the Fundamental Theorem of Algebra

* you also need powers of t (which arise because of repeated roots)

$$t^j \sin(at) \qquad t^k \cos(bt)$$

the solution of any linear ODE is a linear combination of such functions