lecture 2
homeostasis of the organism

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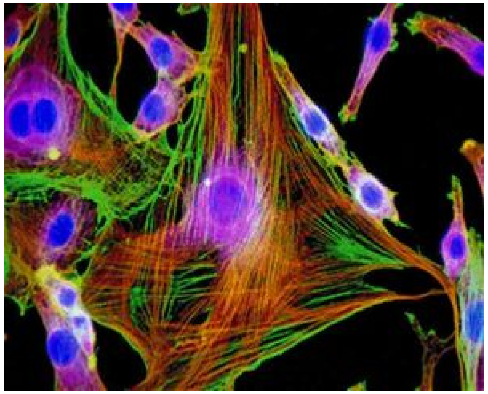
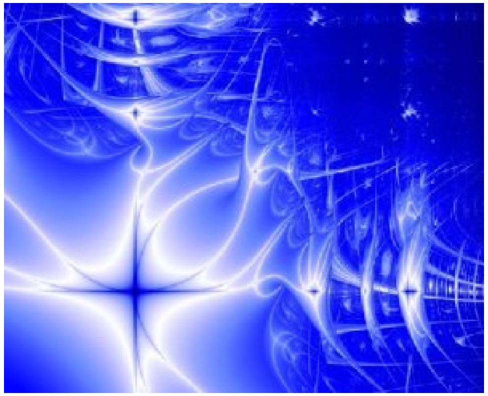




"A Systems Approach to Biology", UBA Buenos Aires, 11-22 June 2018

the origins of this course

lectures in cambridge & cambridge

Autumn 2016 SB 200 - Dynamic Processes in Cells (also known as A Systems Approach to Biology)

Co-taught with Johan Paulsson.

This is a completely revised course, that tries to develop a more conceptual basis for systems biology. It was started in 2010 and evolved further in Cambridge, UK in Spring 2011 (for which, see below).

Lectures:
- Introduction: why mathematics? – 16-1
- Homeostasis & microscopic cybernetics – 16-2, 16-3, 16-4
- Evolution, modularity & weak linkage – 16-5, 16-6
- Time-scale separation & the linear framework – 16-7
- Cellular identity & gene regulatory networks– 16-8, 16-9, 16-10
- Information processing in signal transduction – 16-11, 16-12
- Metabolic economics (from 2011) – 11-7, 11-8, 11-9

Nullcline theorem handout.
Matrix algebra for beginners: 1, 2, 3.

Spring 2011 Six Lectures on Systems Biology

Delivered in the Department of Genetics, University of Cambridge, as part of the Physics of Medicine initative.

This series covers a mixture of topics from SB200 below and from work in my own lab, loosely following three themes: (1) post-translational modification, (2) microscopic cybernetics, (3) modularity and evolution.

Lectures: 1, 2, 3, 4, 5, 6.

book in preparation

Molecules into Life: A Conceptual Introduction to Systems Biology

http://vcp.med.harvard.edu/teaching.html

syllabus

1. the role of mathematics in biology
2. $\boxed{\text{2. homeostasis of the organism}}$
3. the complexity of evolution
4. weak linkage and learning
5. timescale separation and the linear framework

homeostasis and systems biology

systems biology

how do we get from dead molecules to living organisms?

how do the collective interactions of molecular components give rise to the phenotype of the organism?

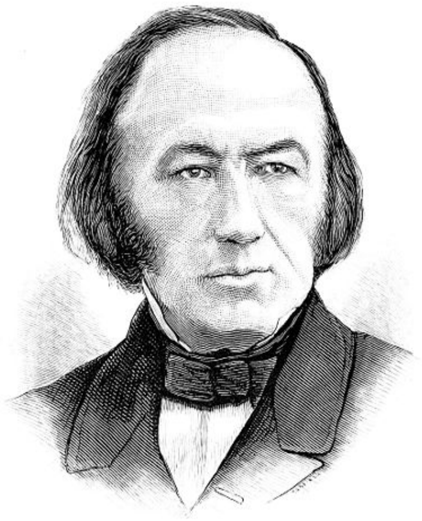
homeostasis is the first systems property to be defined in biology

by starting there, we can try and understand some of the requirements which systems behaviour imposes on the mechanisms of molecules, cells and organs

1. the internal milieu & glucose regulation

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

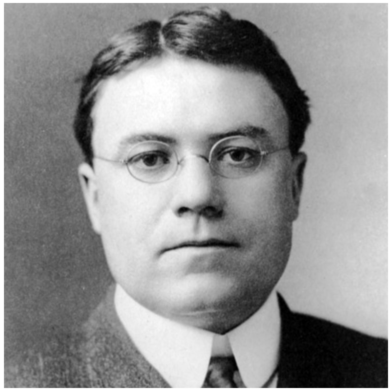
***** Claude Bernard, from **Lectures on the Phenomena Common to Animals and Plants**, 1878. Quoted in C Gross, *"Claude Bernard and the constancy of the internal environment"*, The Neuroscientist, **4**:380-5 1998

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

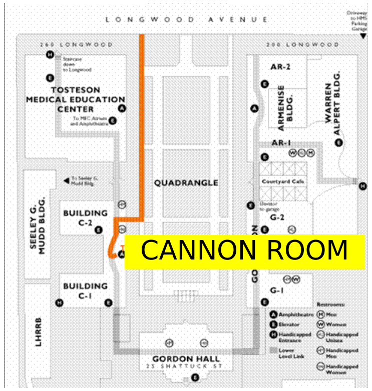
homeostasis and negative feedback

*“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

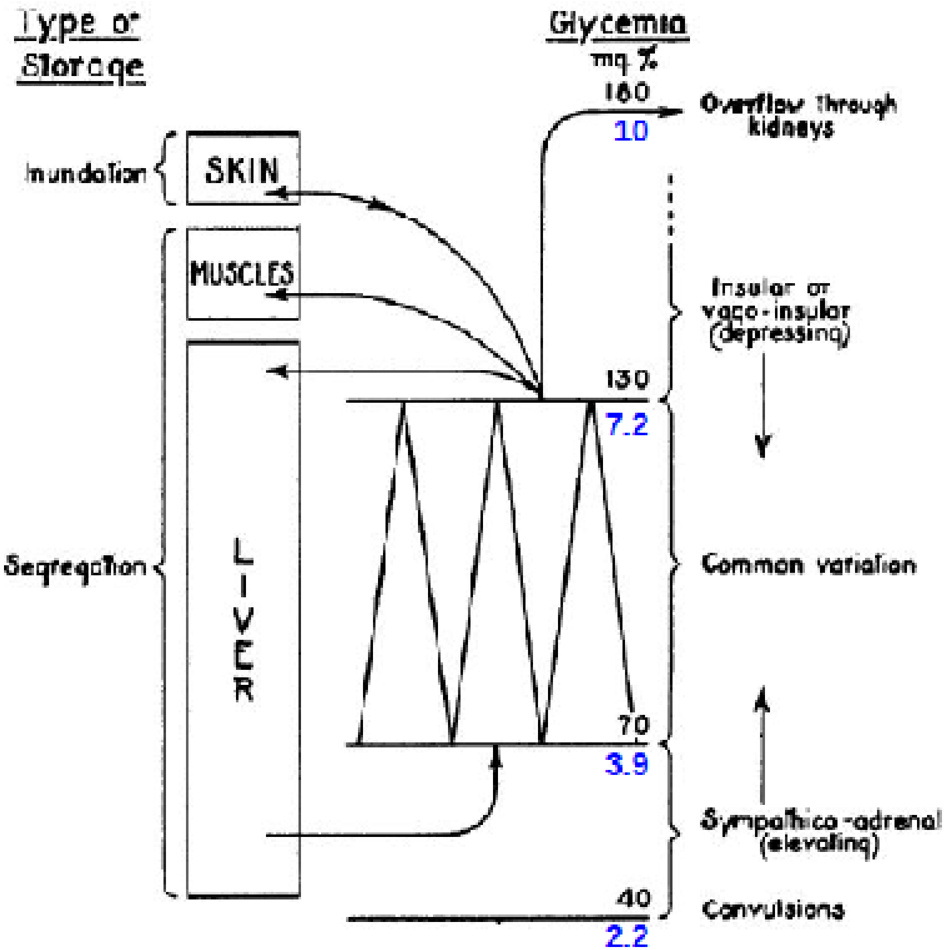


1. “back towards the mean position” – **negative feedback**
2. “wide oscillations are prevented” – **stability**

***** 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.

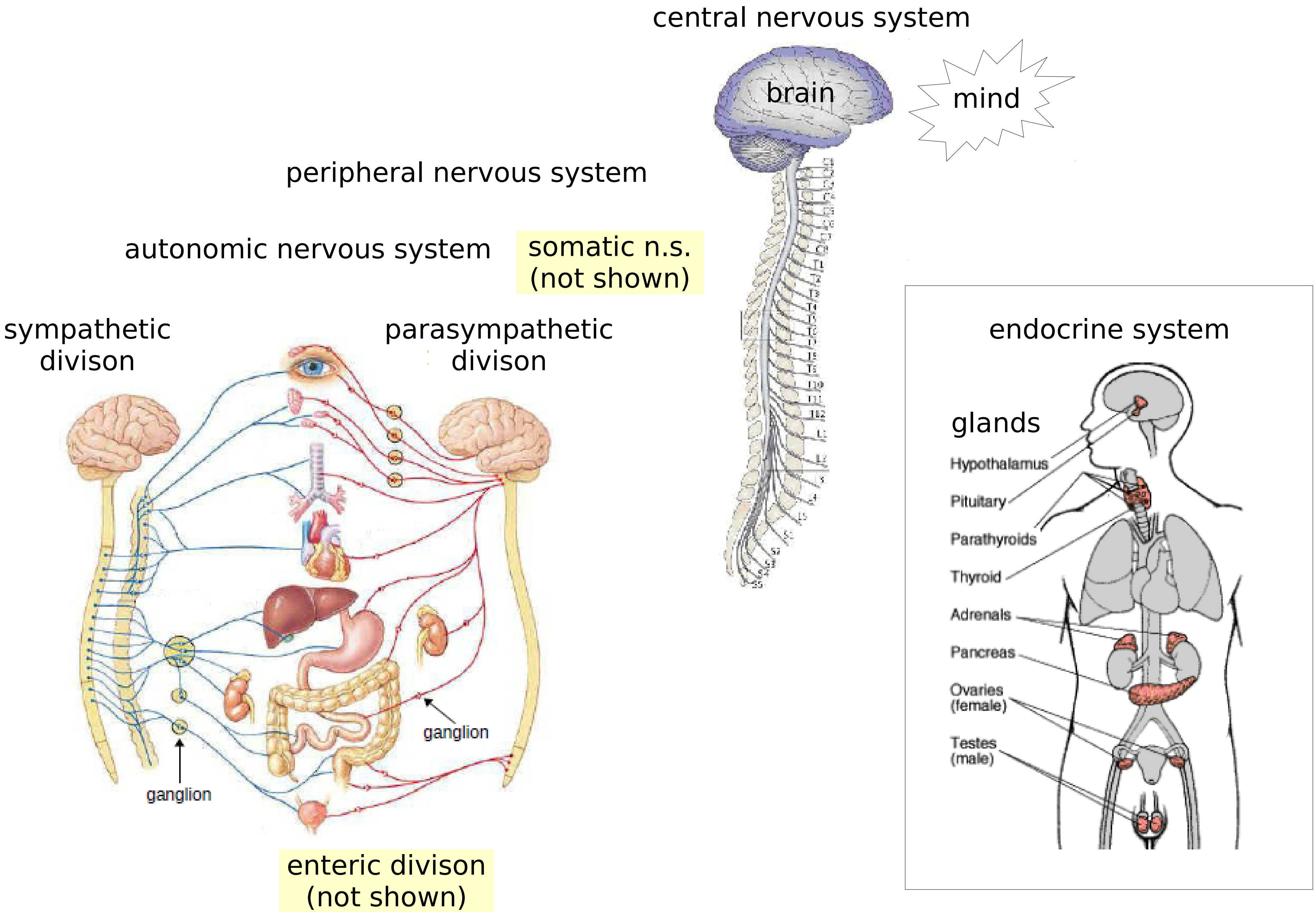
glucose homeostasis by cannon



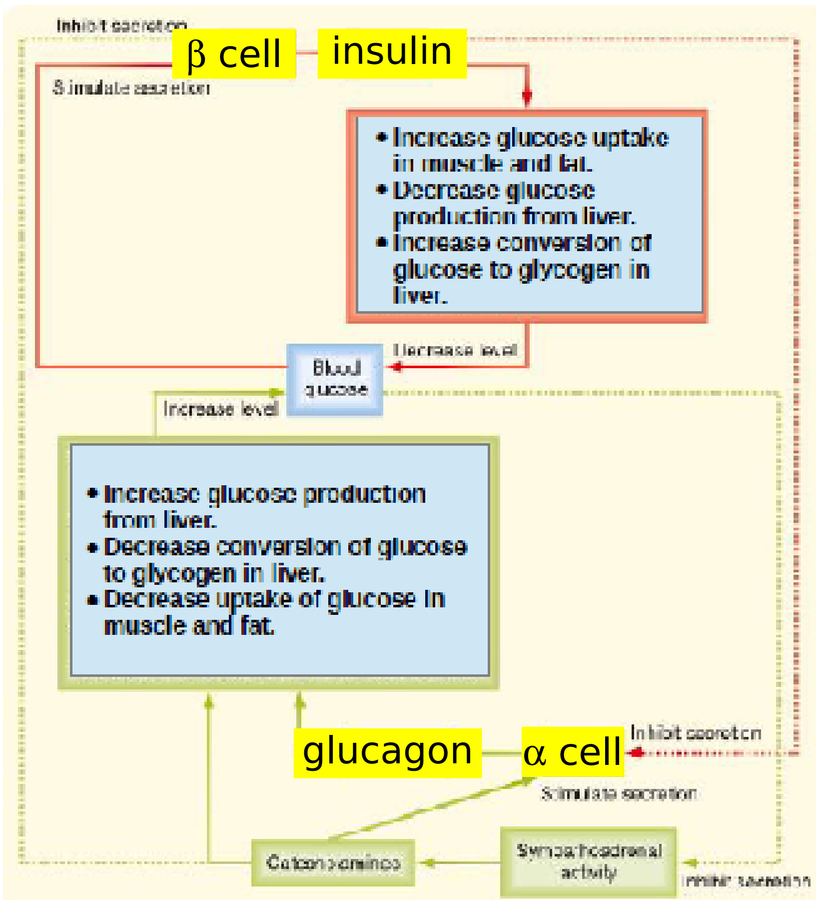
mg% is mg per 100 mL or mg/dL. “normal” glucose level is ~100 mg/dL or ~**5mM**

Figure 1 in Walter B Cannon, *“Organization for physiological homeostasis”*, Physiol Rev, **9**:399-431, 1929.

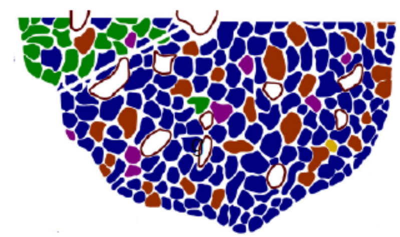
physiological regulatory systems



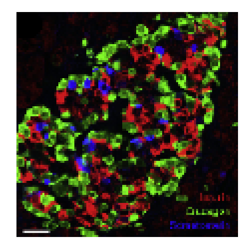
endocrine feedback in glucose homeostasis



pancreatic islet



alpha
beta



alpha
beta

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

Suckale, Solimena, *"Pancreatic islets in metabolis signaling – focus on the beta cell"*, Front Biosci **13**:7156-71 2008; .

glucose homeostasis with the 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

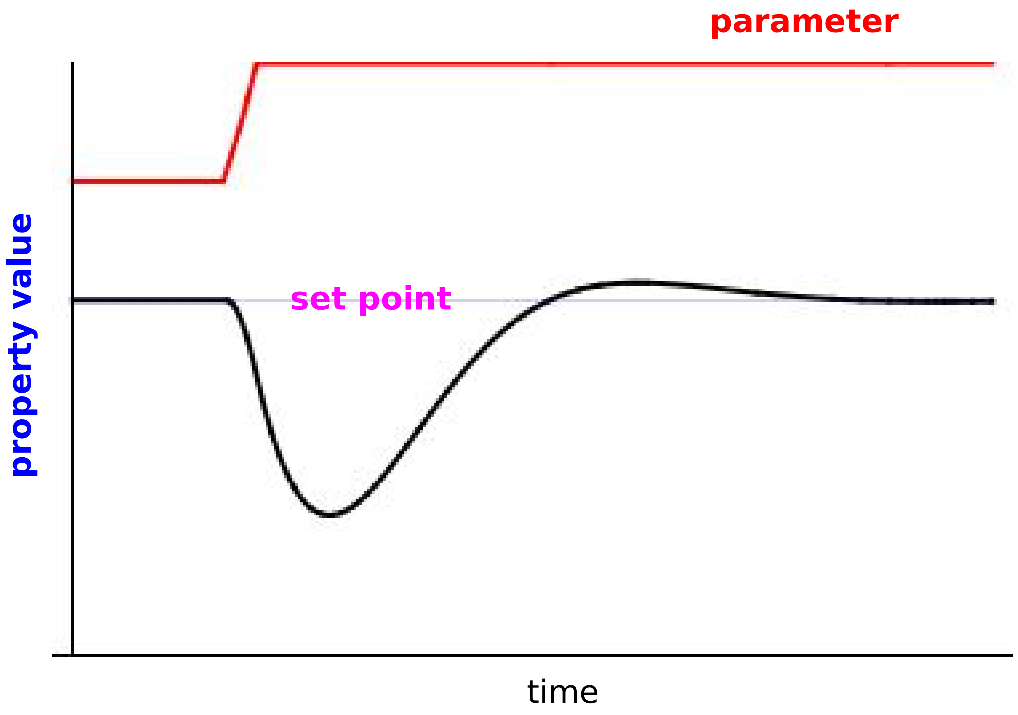
	rest	6 min	10	19	30	46	60
glucose (mM)	4.6	4.4	4.3	4.6	4.7	4.6	4.4

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.

zero steady-state error

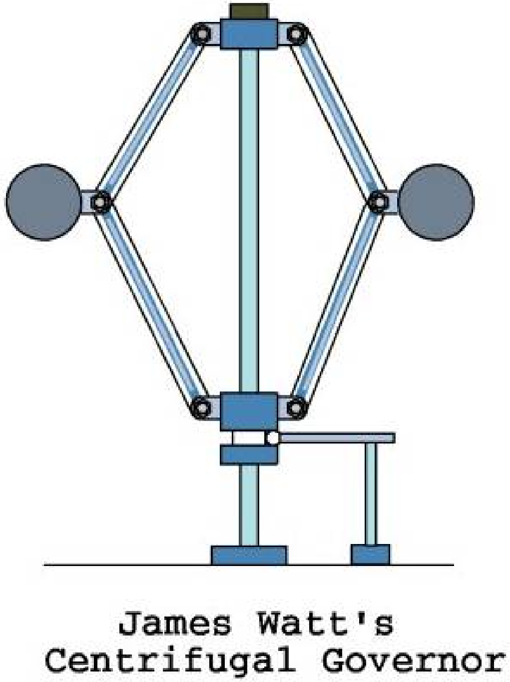
zero steady-state error – a form of homeostasis in which some **property**, such as glucose concentration, achieves a steady value ("**set point**") under suitable conditions and that same value is eventually recovered despite a sustained change in some **parameter**, such as exercise rate.

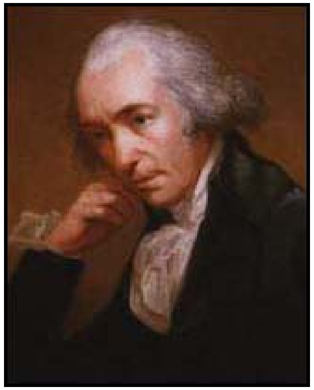


2. cybernetics

engineers already understood negative feedback

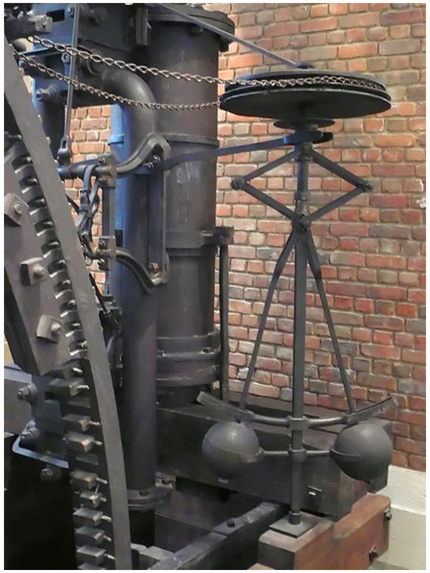
centrifugal governor at a restored windmill in moulton, lincolnshire, UK. design like this date to the 18th century





1736-1819

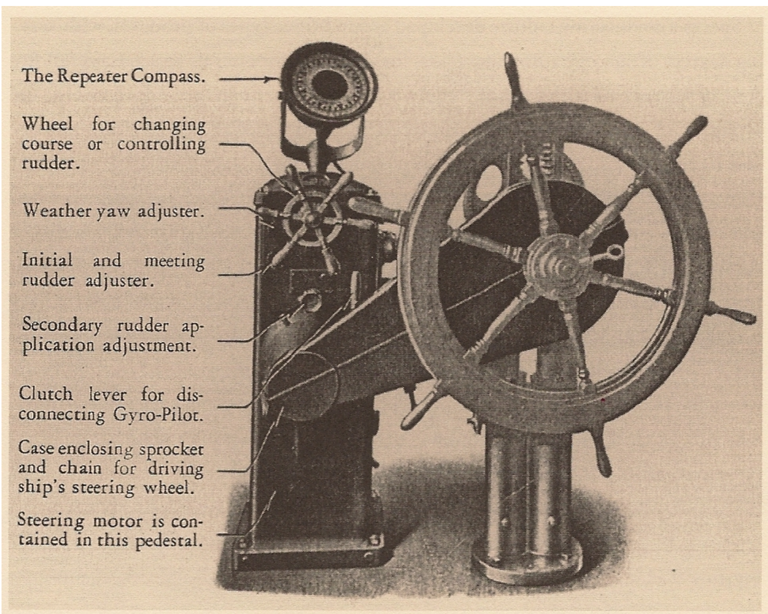
Eric Ravilious, The Brickyard, painted in 1936



Boulton-Watt steam engine with a centrifugal governor

pre-WWII control engineering

maintaining a specified "set point" – zero steady-state error



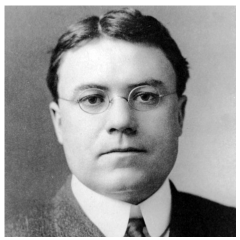
Sperry marine gyropilot - "Metal Mike", 1920s

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

cybernetics – the machine analogy

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

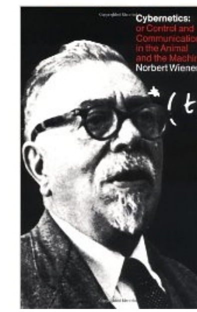


collaborators

1900-1970

1894-1964

1913-2003

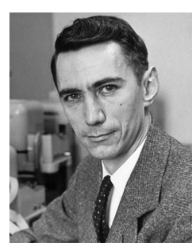


Rosenblueth, Wiener, Bigelow, *"Behavior, purpose and teleology"*, Philos Sci **10**:18-24 1943; Wiener, **Cybernetics: or Control and Communication in the Animal and the Machine**, MIT Press, 1948

brains and minds undertake computation and information processing

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.

3. integral control

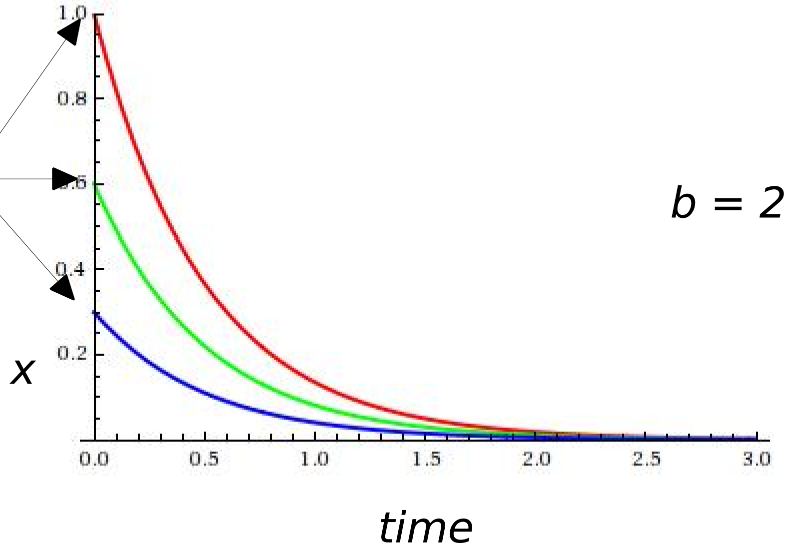
how to control a simple dynamical system

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

b > 0

linear, first order system

different choices of
initial condition x(0)



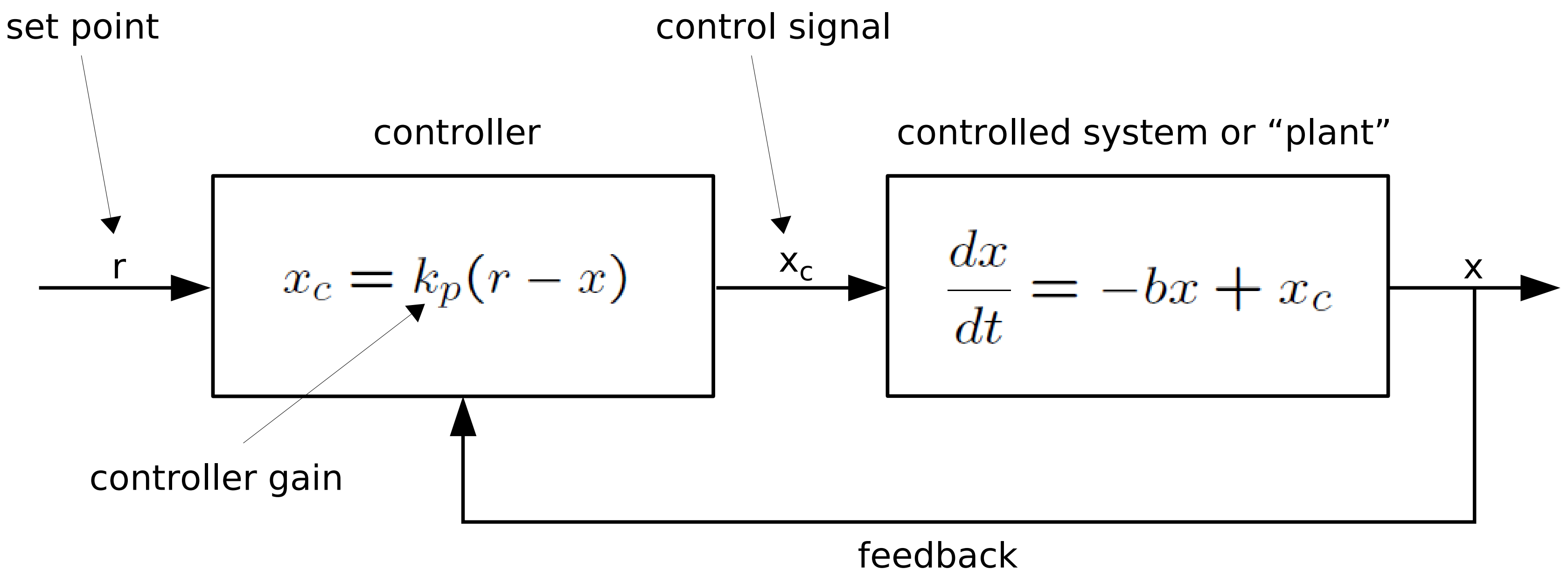
b = 2

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)***

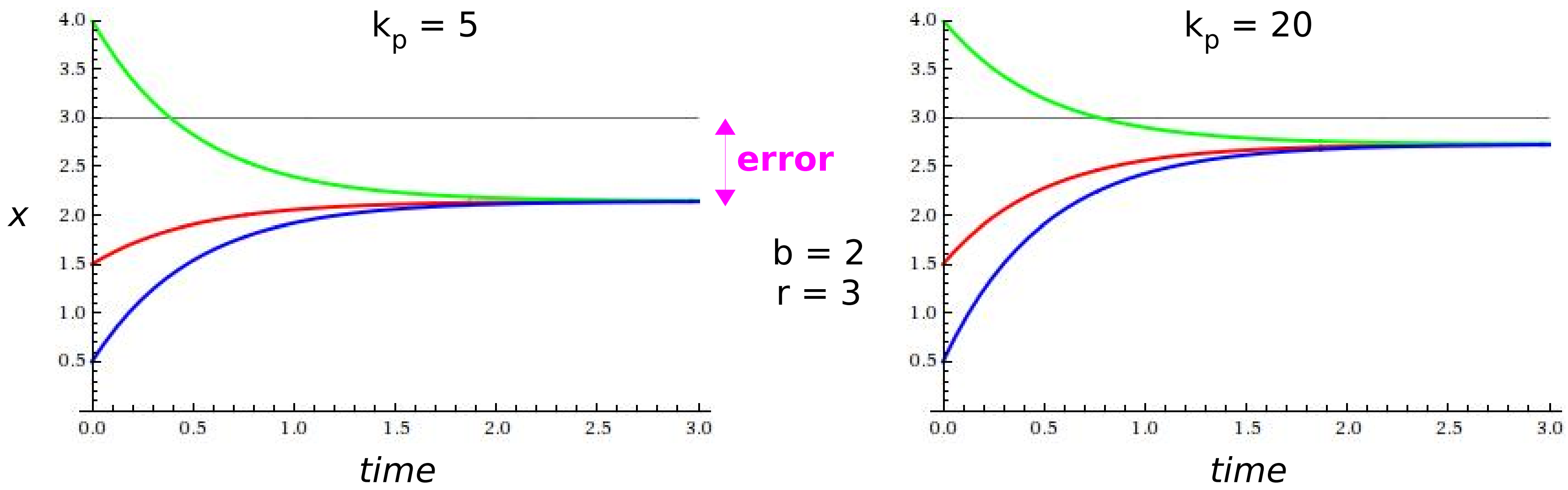


proportional control exhibits steady-state error

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

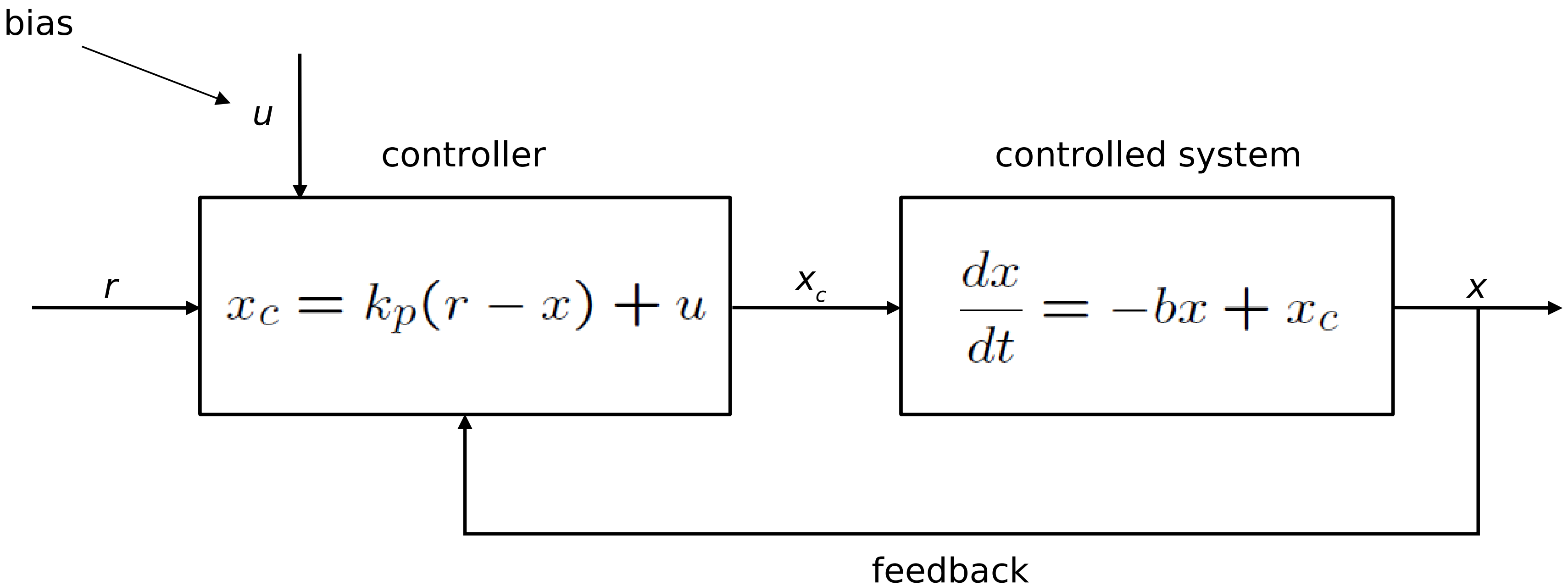
at steady state, ***dx/dt = 0***

$$x = \left(\frac{1}{1 + b/k_p}\right) r$$



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

biased proportional control



biased proportional control is not robust

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

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

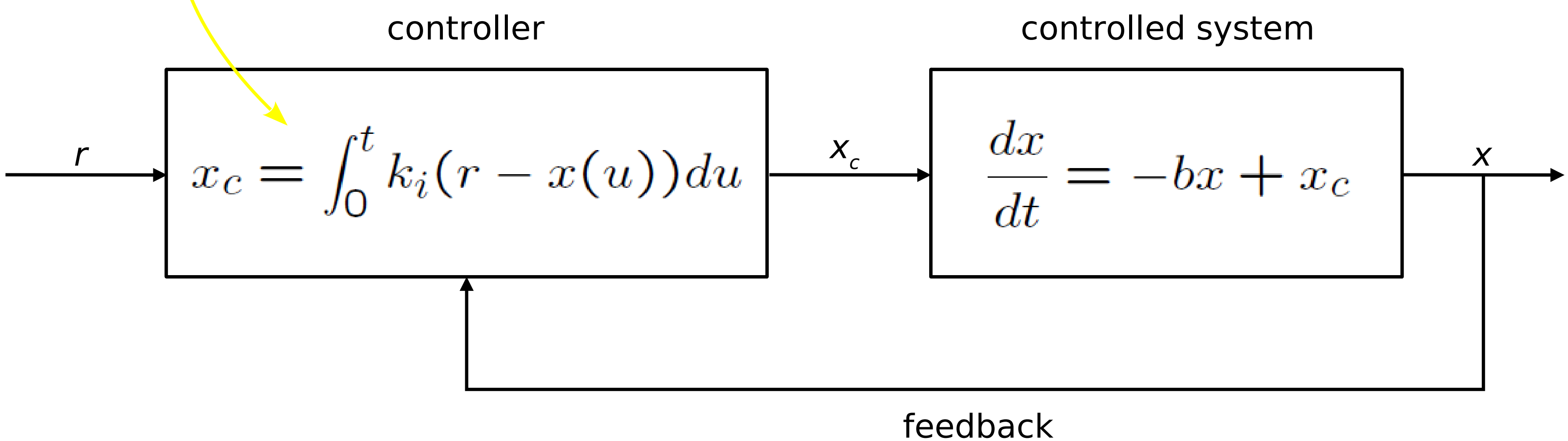
this solution is **not robust** to changes in parameter values

integral control

suppose the control signal reaches steady state when the error is zero

$$\frac{dx_c}{dt} = k_i(r - x)$$

then there should be zero steady-state error ...



integral control achieves zero s.s. error robustly

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

at steady state, $x = r$

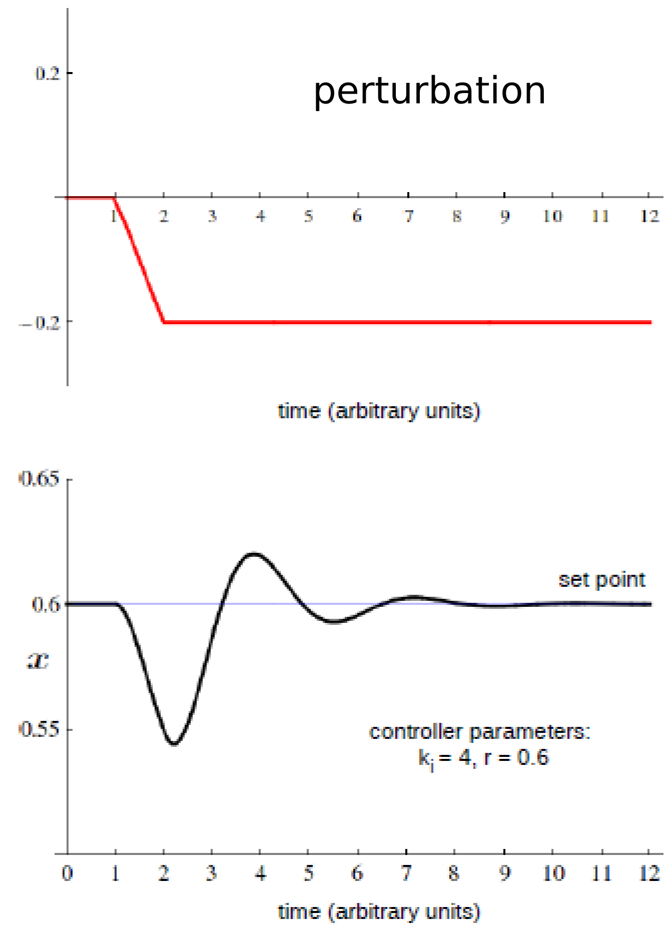
integral control eliminates steady-state error robustly with respect to the controlled system's paramters, at the expense of increasing the order of the overall system

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

but can be prone to transient oscillations

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

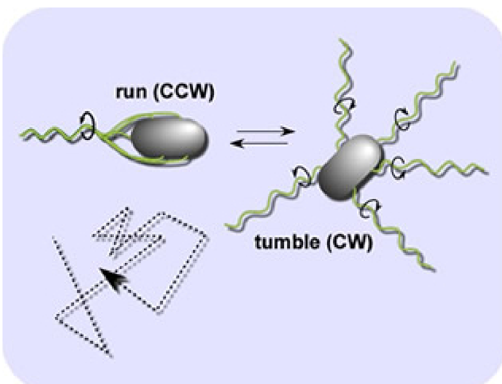
in engineering practice, integral control (I) is usually combined with proportional (P) and derivative (D) control to provide better transient behaviour (PID control)



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

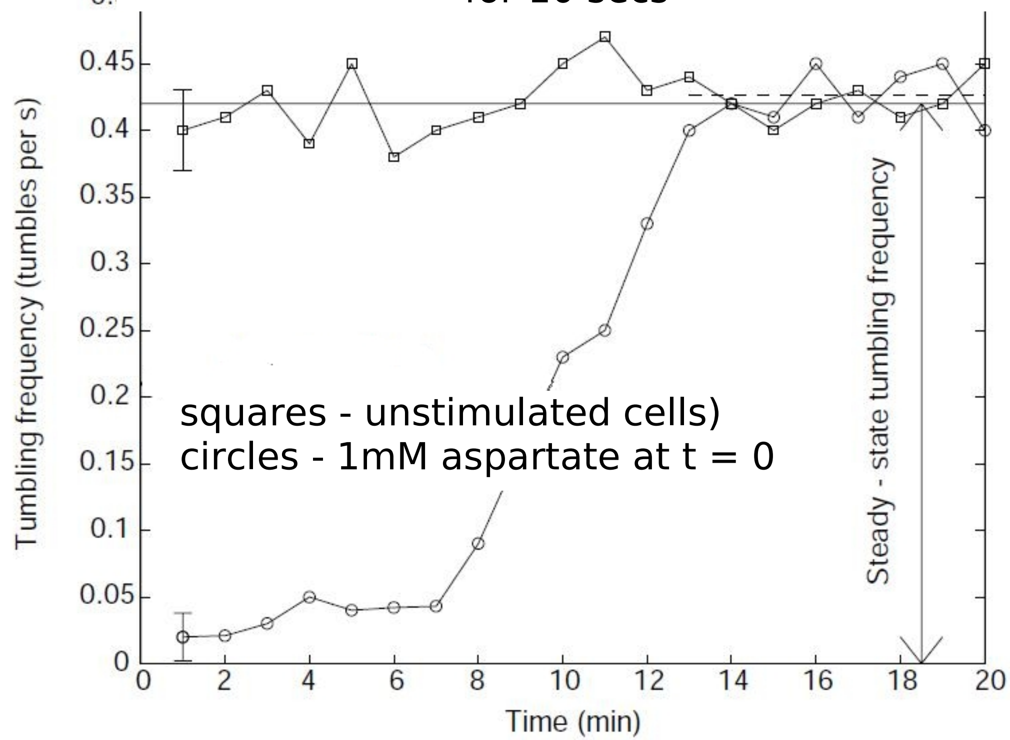
4. evidence for integral control

E coli chemotaxis – tumbling frequency



E coli RP437 strain

each data point averaged over 100-400 cells
for 10 secs

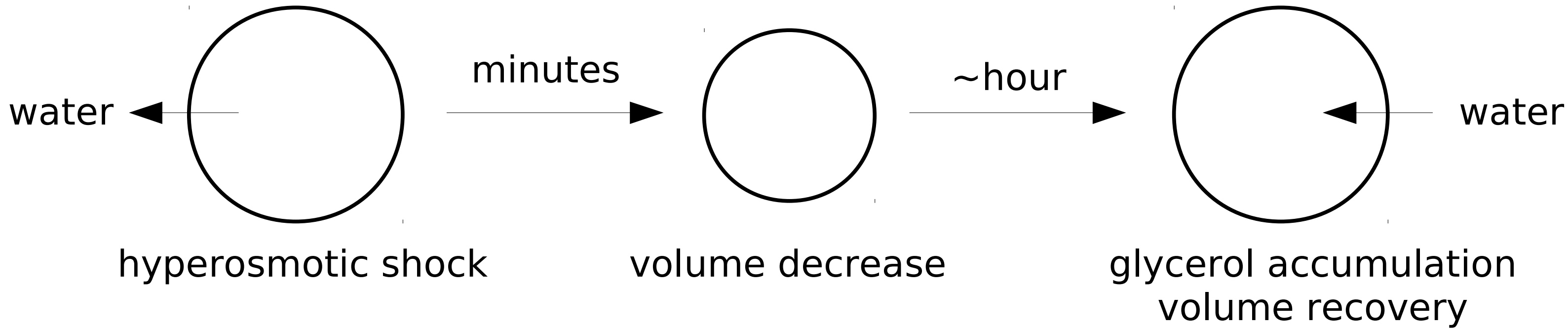


population average returns to its set point

U Alon, M G Surette, N Barkai, S Leibler, *"Robustness in bacterial chemotaxis"*, Nature **397**:168-71 1999

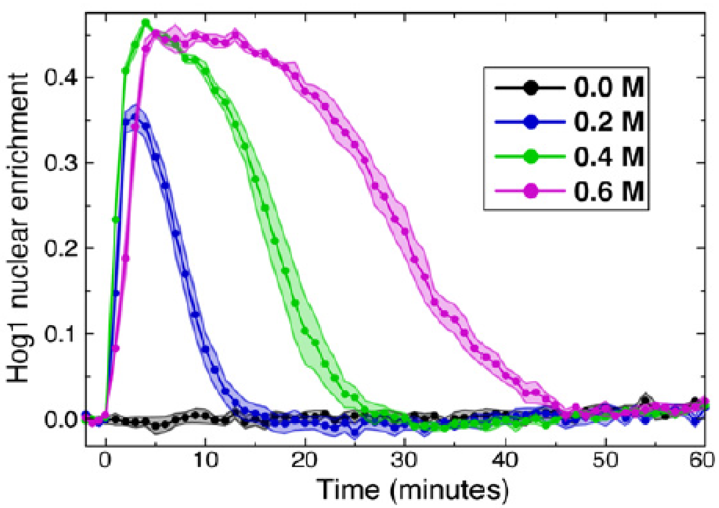
T-M Yi, Y Huang, M I Simon, J Doyle, *"Robust perfect adaptation in bacterial chemotaxis through integral feedback control"*, PNAS **97**:4649-53 2000

S cerevisiae osmolarity – Hog1 nuclear enrichment



in haploid SHO1- cells, sustained increase in external NaCl leads to transient nuclear accumulation of the activated MAP kinase Hog1, measured by Hog1-YFP "nuclear enrichment"

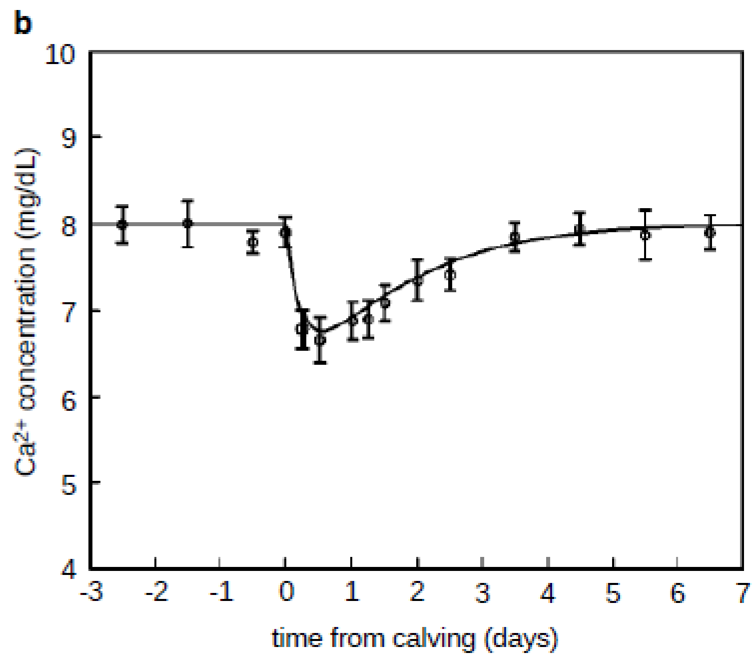
SHO1 deletion disables one of the two pathways of Hog1 activation



population average returns to its set point
no steady-state error

D Muzzey, C Gomez-Uribe, J T Mettetal, A van Oudenaarden, "*A systems-level analysis of perfect adaptation in yeast osmoregulation*", Cell **138**:160-71 2009

calcium levels after calving in cows



b. Experimental data showing the change in calcium levels in Jersey cows around the time of calving (day 0), adapted from [60, Figure 4], which should be consulted for more details. The data points are given as the mean, plus/minus the standard error of the mean, of total plasma calcium measured from blood samples taken from 18 cows at the indicated time point. The black curve is a fit to a mathematical model that is discussed in [60].

El Samad, Goff, Khammash, "*Calcium homeostasis and parturient hypocalcemia: an integral feedback perspective*", J Theor Biol **214**:17-29 2002

eye movement control

INTEGRATING WITH NEURONS

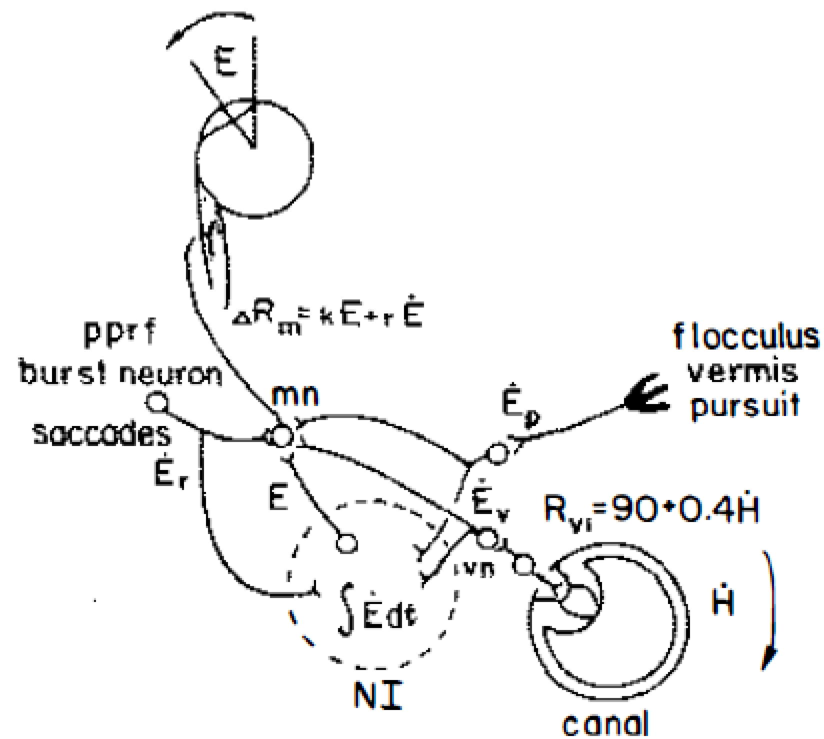
D. A. Robinson

Ann. Rev. Neurosci. 1989. 12 : 33–45

Department of Ophthalmology and Biomedical Engineering, The Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205

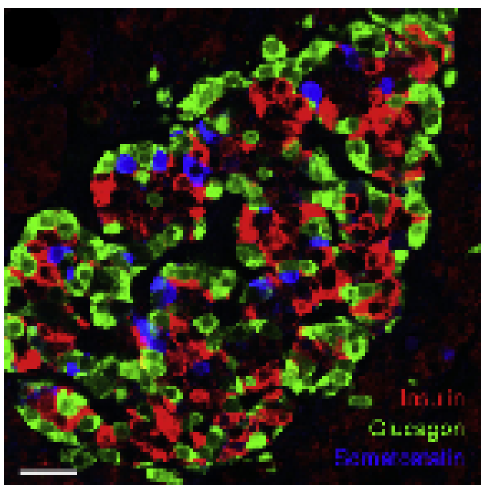
1924-2016

"The retina sense the error between the eye (fovea) and the target and the system turns the eye until the error is zero – a simple negative feedback scheme. Moreover, when the goal is reached, a constant eye deviation (output) is maintained while the ***error (input) is zero.*** *But that is just whan an integrator does."*



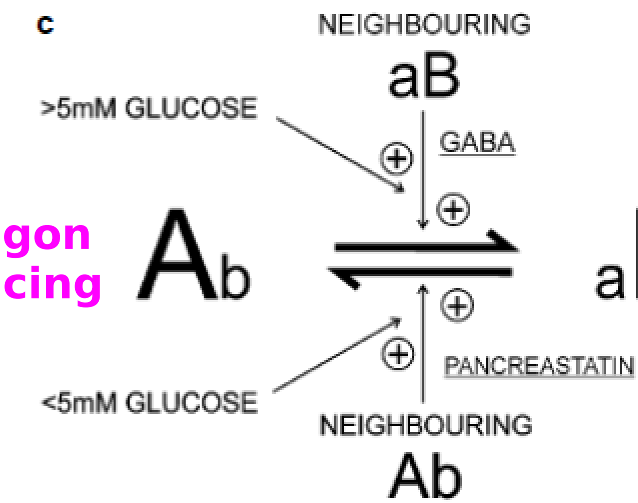
integral rein control for glucose homeostasis

two opposing integral controllers ("rein control") can exhibit zero steady-state error, provided they mutually inhibit each other



alpha
beta

glucagon producing



insulin producing

Koeslag, Saunders, Terblanche, *"A reappraisal of the blood glucose homeostat which comprehensively explains the type 2 diabetes mellitus-syndrome X complex"*, J Physiol **549**:333-46 2003

insulin & glucagon response under fixed error

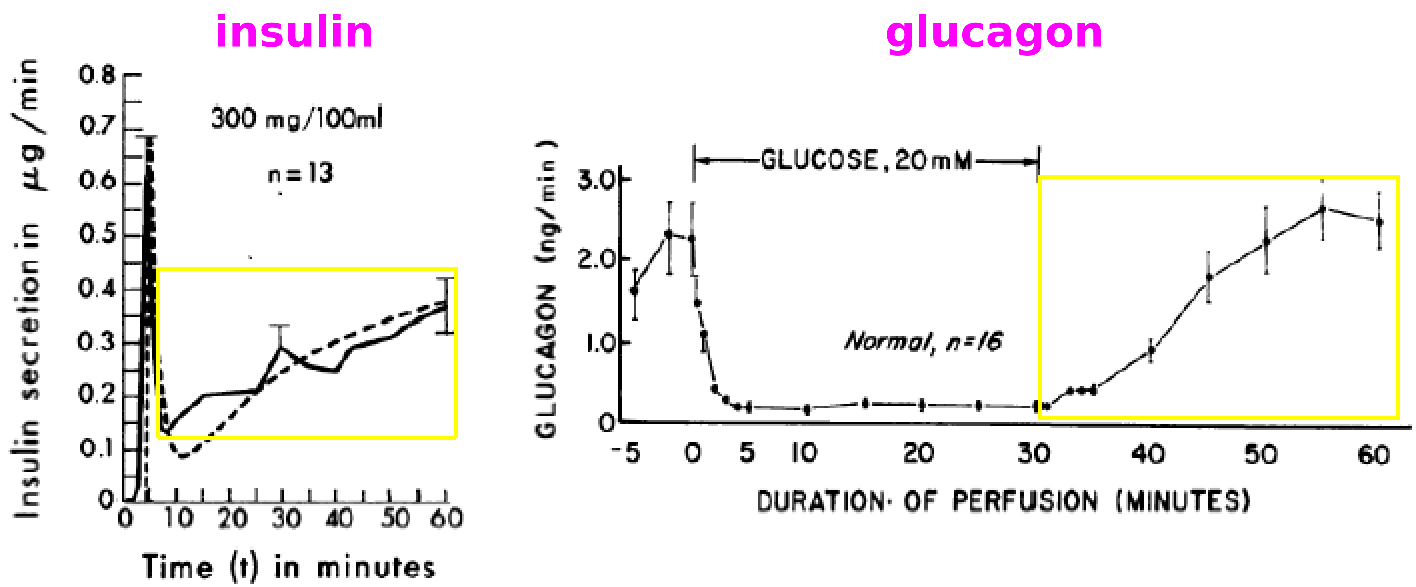


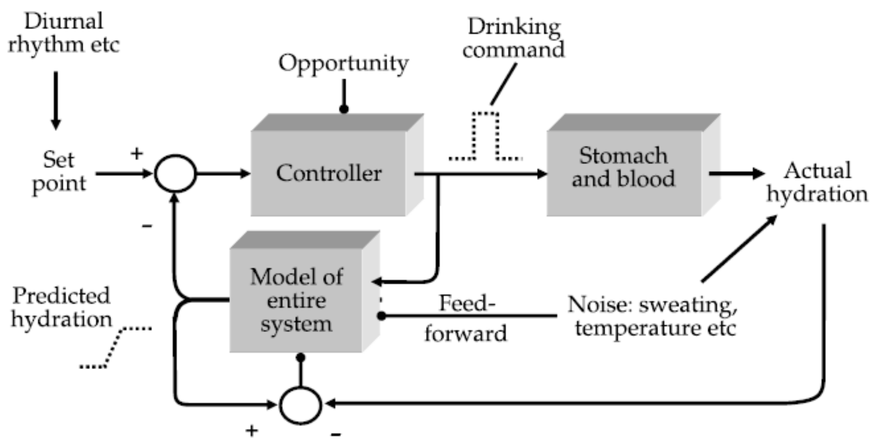
Figure 4.7: Evidence for integral control in glucose homeostasis, with the relevant data in the yellow boxes. a. Rate of insulin secretion, measured in μg/min, of an isolated rat pancreas continuously perfused with buffer containing 300 mg/dL = 16.7mM glucose (§1.6). Data points are mean $\pm$ the standard error of the mean from 13 normal rats. The dashed line shows the results of a simulation that is not discussed here. Adapted from [83, Figure 2]. b Rate of glucagon secretion, measured in ng/min, of an isolated rat pancreas continuously perfused with buffer containing no glucose. Glucose at 20mM was added to the buffer as shown from 0 to 30 minutes. Data points are mean $\pm$ the standard error of the mean from 16 normal rats. Adapted from [155, Figure 5].

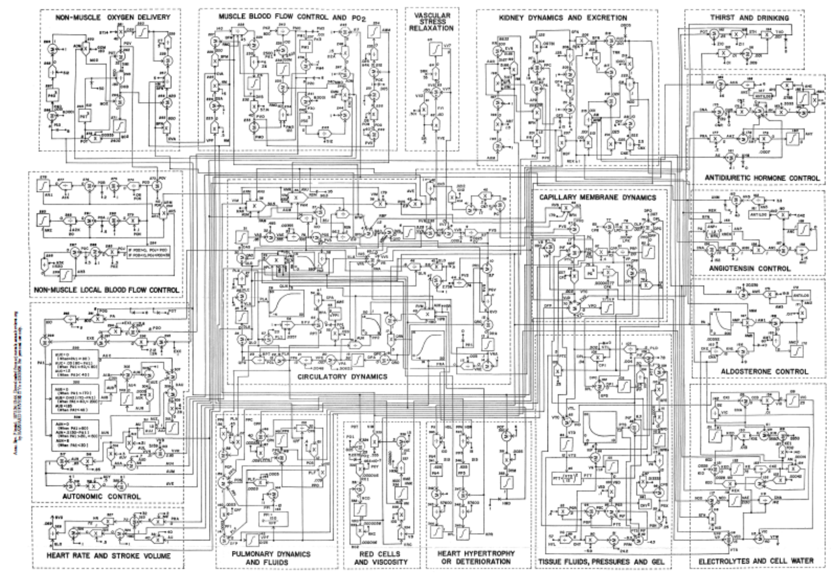
Grodsky, *"A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling"*, J Clin Invest **51**:2047-59 1972

Pagliara, ..., Matschinsky, *"Insulin and glucose as modulators of the amino acid-induced glucagon release in the isolated pancreas of alloxan and streptozotocin diabetic rats"*, J Clin Invest **55**:244-55 1975

control theory as a foundation for homeostasis

control engineering provides mathematical formulations for more complex forms of regulation than integral control





"Accompanying the progressive erosion of a coherent sense of physiology as an intellectual discipline, there has been a tendency to lose sight of the homeostatic principles that underpin physiological science, and to teach them in an oversimplified form. When (as is increasingly the case) these principles are rediscovered, they are often treated as something both novel and distinct from homeostasis, fragmenting what is best understood and taught as a unified whole. This article urges a more unitary approach to homeostasis, and attempts to show how such an approach can be presented."

Carpenter, "Homeostasis: a plea for a unified approach", Adv Physiol Edu **28**:S180-7 2004

Guyton, Coleman, Granger, *"Circulation: overall regulation"*, Annu Rev Physiol **34**:13-44 1972

4. challenges

“The guiding motto in the life of every natural philosopher should be, "Seek simplicity and distrust it."

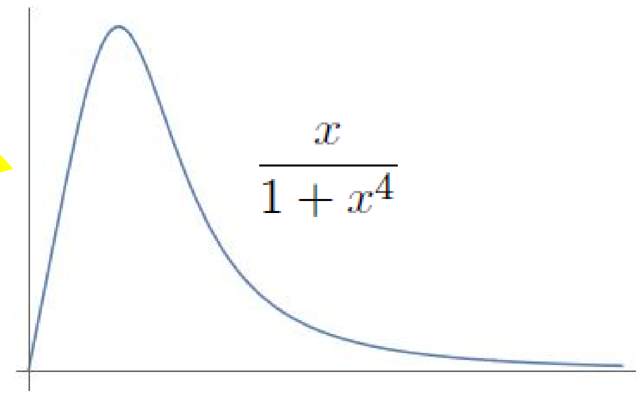
delays can cause chaos

physiological systems always exhibit time delays

Mackey-Glass equation

$$\frac{dx}{dt} = \frac{\beta x(t-\tau)}{1 + x(t-\tau)^n} - \gamma x$$

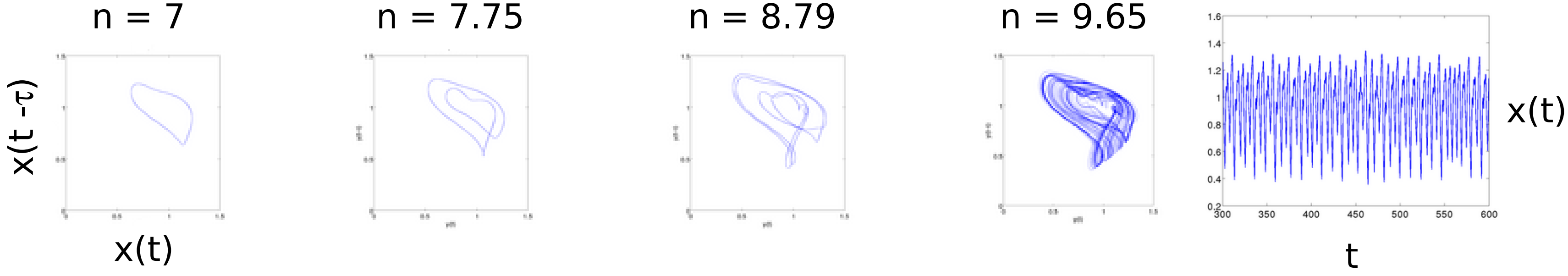
nonlinear
differential-delay equation



nonmonotonic feedback

$\beta = 2\,,\ \gamma = 1\,,\ \tau = 2$

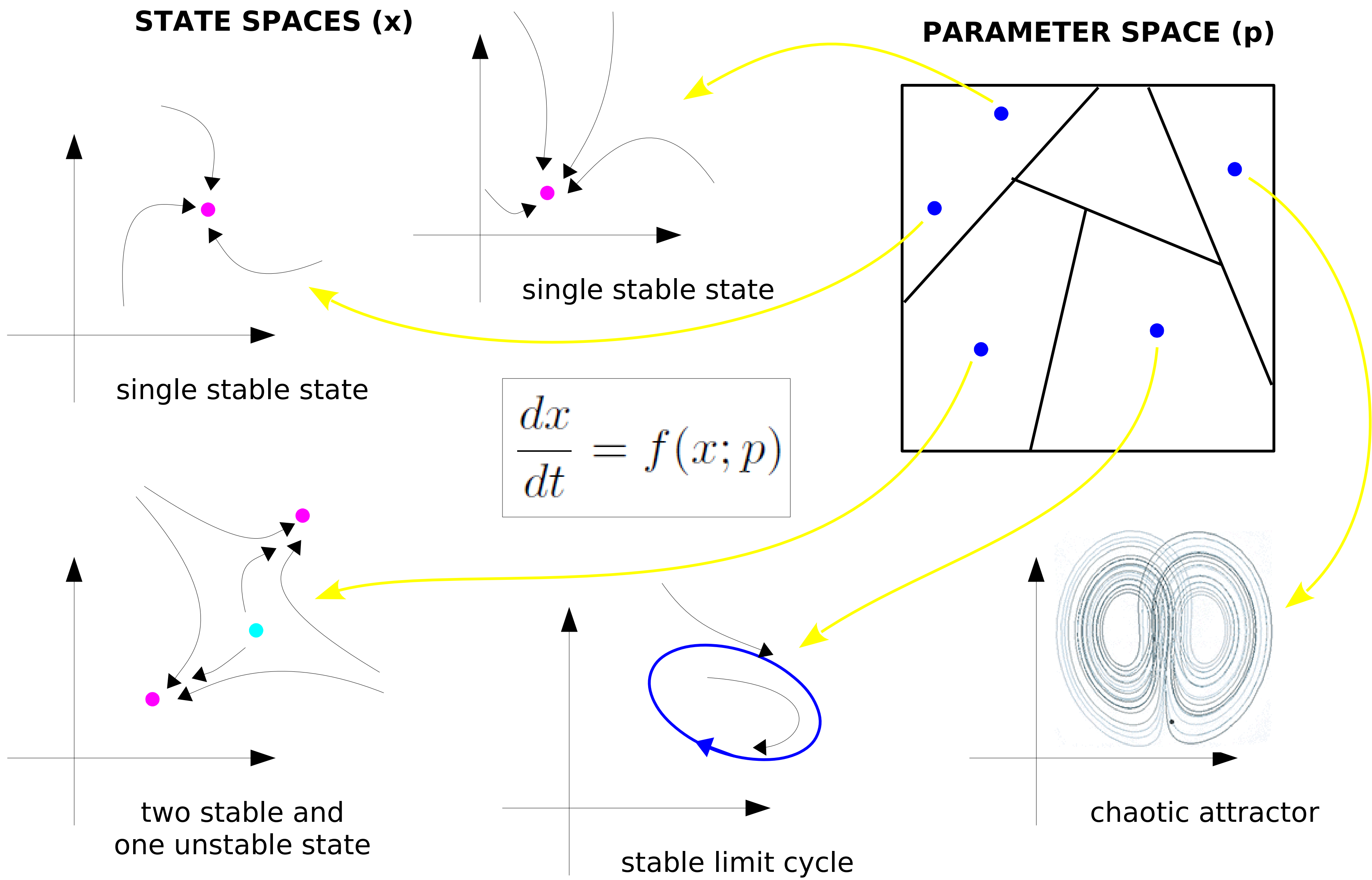
n = 7 n = 7.75 n = 8.79 n = 9.65



exponential sensitivity to initial conditions = chaos

Mackey, Glass,*"Oscillation and chaos in physiological control systems"*, Science **197**:287-9 1977
http://www.scholarpedia.org/article/Mackey-Glass_equation

dynamical systems

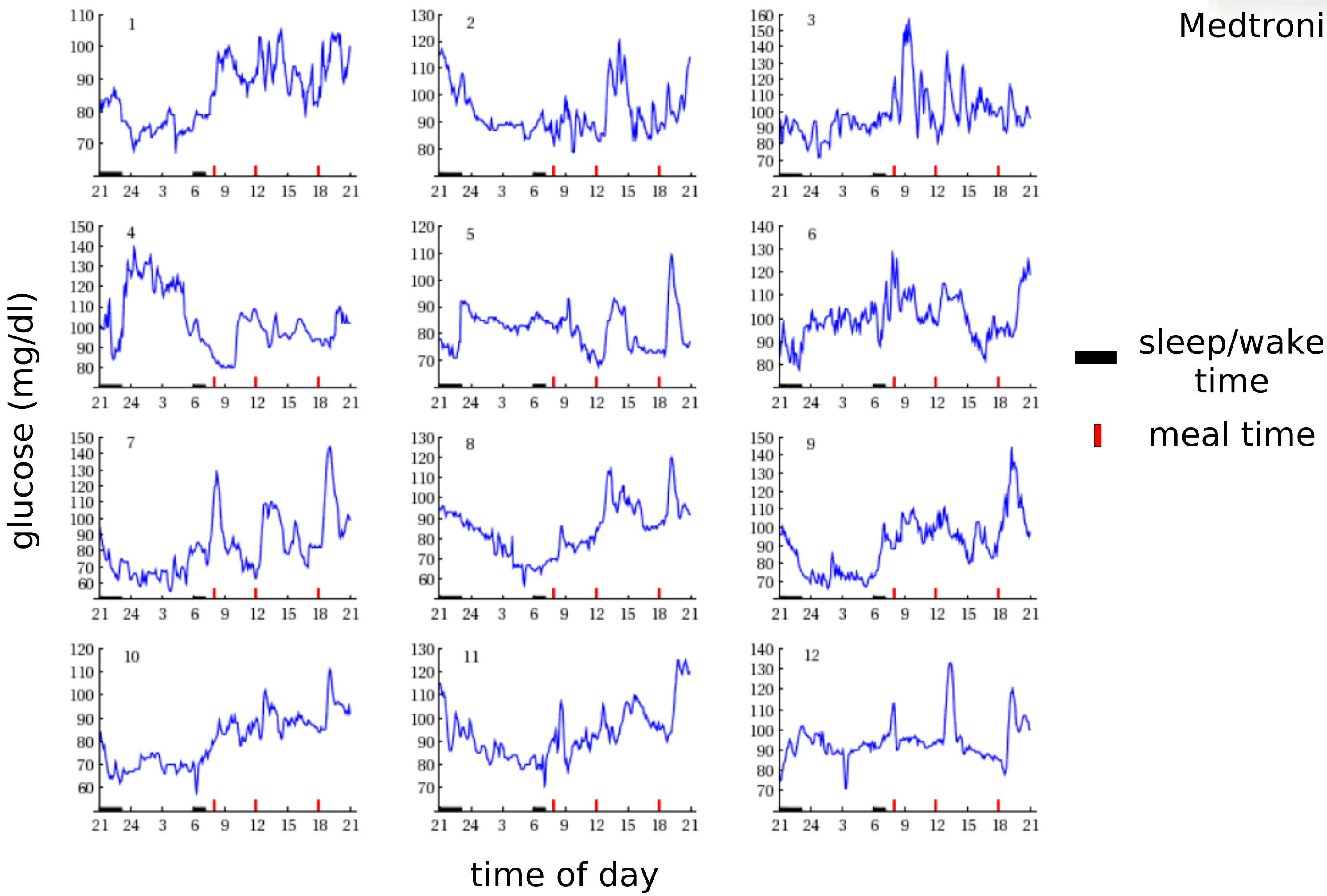


$$\frac{dx}{dt} = f(x;p)$$

looking under the average

glucose levels in 12 healthy non-diabetic subjects, taken every 5 mins by a continuous glucose monitoring system

Medtronic MiniMed



data acquired and replotted from Ogata et al,*"Long-range correlation in of glucose dynamics in humans and its breakdown in diabetes mellitus"*, Am J Physiol Regul Integr Comp Physiol **291**:R1638-43 2006

physiology of an open system

the subjects in the previous experiment were eating and undertaking normal activities. they are **open systems** subject to **external forcing**.

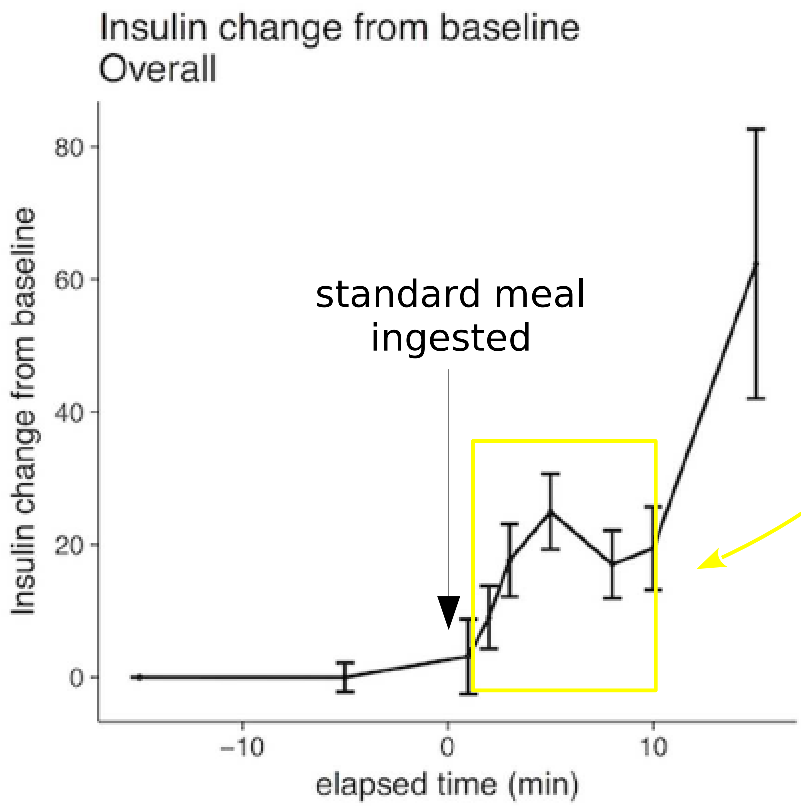
$$\frac{dx}{dt} = \underbrace{f\left(x;p\right)}_{\text{internal dynamics}} + \overbrace{e(t)}^{\text{external forcing}}$$

open questions –

- what is a minimal mathematical model for physiological variables in an individual over time?
- does the observed complexity arise internally or externally?
- is the balance between these different in different individuals?
- does the internal dynamics exhibit chaos?

feed-forward anticipation in physiology

cephalic phase insulin secretion – the brain anticipates an increase in glucose level before any feedback error arises



mean and 95% CI for 31 healthy (non-diabetic) men aged 30-55 yrs

1849-1936

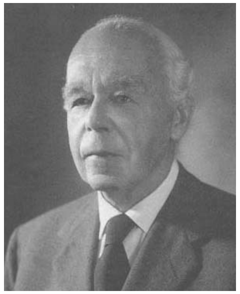
sham-feeding after esophagus re-routing showing cephalic secretion of digestive enzymes

Elisasson et al ,*"Cephalic phase of insulin secretion in response to a meal is unrelated to family history of type 2 diabetes"*, PLoS ONE **12**:e0173654 2017; Wood,*"The first Nobel prize for integrated systems physiology: Ivan Petrovich Pavlov, 1904"*, Physiol **19**:326-30 2004

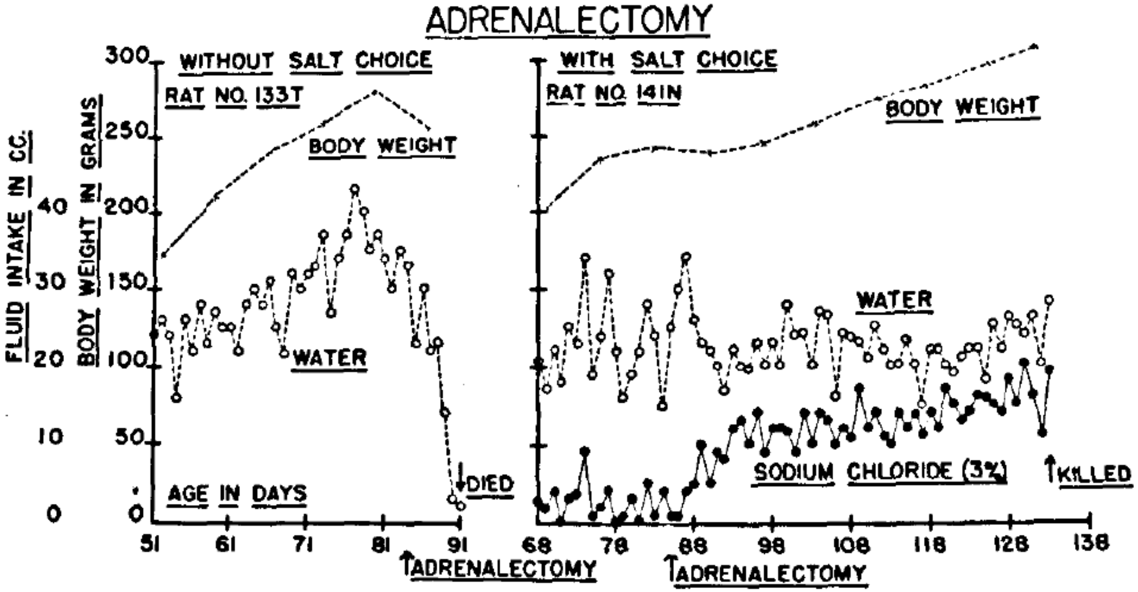
behaviour in physiological regulation

“Both Bernard and Cannon concerned themselves almost entirely with the physiological and chemical regulators of the internal environment.”

“The results of our experiments have shown that behavior or total organism regulators also contribute to the maintenance of a constant internal environment.”



1894-1988

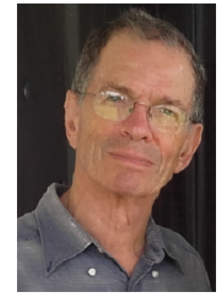


(left) control rat without access to NaCl
(right) experimental rat with access to water and NaCl

Richter, *“Total self-regulatory functions in animals and human beings”*, Harvey Lectures **38**:63-103 1942-3

allostasis

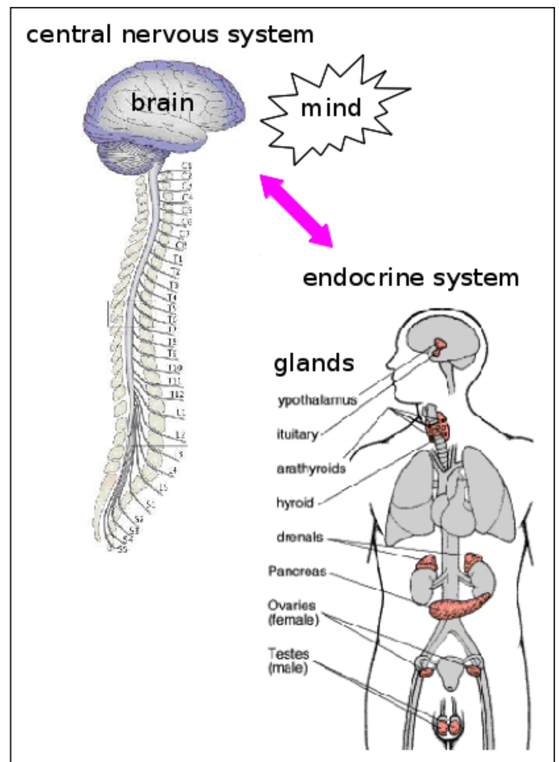
"The premise of the standard regulatory model, homeostasis, is flawed: the goal of regulation is not to preserve constancy of the internal milieu. Rather, it is to continually adjust the milieu to promote survival and reproduction. ... A newer model, allostasis, proposes that efficient regulation requires anticipating needs and preparing to satisfy them before they arise. ... This regulatory strategy requires a dedicated organ, the brain."



1940-

1938-

"Neuroendocrinology was originally focused on how the brain controls the endocrine system via the pituitary gland, but it now also investigates how hormones affect the development and function of many behaviors and neural and cognitive functions throughout the nervous system. ... The brain and body are no longer separate and are mechanistically linked to each other in health and disease"



Sterling, "*Allostasis: a model of predictive regulation*", Physiol Behav **106**:5-15 2012; Interview with Bruce McEwen, Trends Neurosci **36**:207-8 2013

in summary

1. the internal milieu of an organism exhibits homeostasis

2. homeostasis may be implemented by negative feedback mechanisms that respond to departure from a set point

3. in controlled experiments, averaged across individuals, variables like glucose levels show zero steady-state error to sustained perturbation

4. this suggests that the underlying negative feedback uses integral control, for which evidence exists in several contexts

5. control theory has provided a mathematical foundation for classical physiology but often neglects time delays. these can lead to chaotic dynamics.

6. data on free-running individuals shows remarkably variable dynamics

7. allostasis extends homeostasis to include feed-forward anticipation, behaviour and brain-body interaction, which may contribute to the variable dynamics

8. **what is a minimal mathematical foundation for allostasis?**