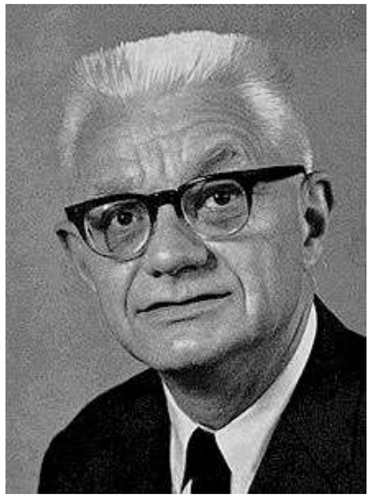
Mechanisms in molecular biology

Tudor M. Baetu

some philosophical questions

- What is a scientific explanation?
  - The DN/CL account
  - Can biological phenomena be explained in terms of laws of nature?
  - Are there laws in biology?
- What other kinds of explanations do biologists provide?
  - Many kinds (teleological, functional, evolutionary, causal …)
  - Focus on mechanisms and mechanistic explanations
- How do these explanations relate to each other?
  - How do the explanations of biology relate to those of physics and chemistry?
  - Can life be explained in strictly mechanistic terms?

explanation in science: explanations as arguments



Carl Hempel

Carl Hempel (1950s): often times, scientific explanations have the logical structure of an **argument** (especially in physics)

argument = a set of premisses followed by a conclusion

conclusion = description of the phenomenon to be explained (***explanandum***)

pre

wha ... rder for the

the

)

tween

Deductive-Nomological (or Covering-Law) account:

explanation = logical derivation (deduction) of a description of the phenomenon to be explained from the laws of nature

must include at least a **law of nature** (rule out consequences of accidental regularities → nomological necessity)

a very simple example

General laws

Boyle's gas law: $pV = constant$ ($p_1V_1 = p_2V_2$)

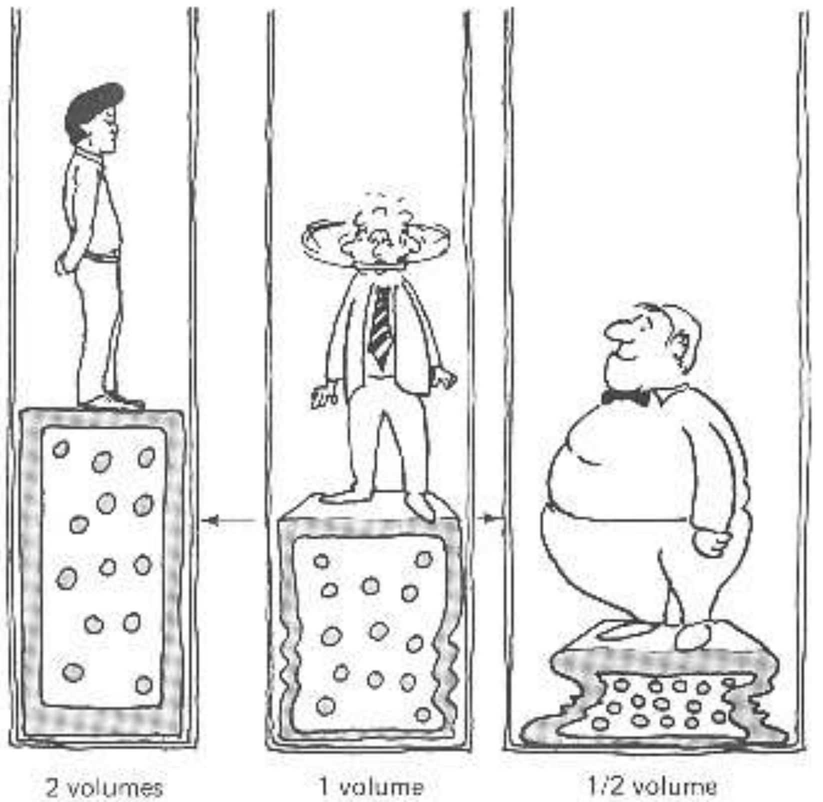
Particular facts (optional)

numerical values of p and V

∴Description of the phenomenon to be explained

increase in pressure when volume is reduced

$pV = constant \Rightarrow p \propto 1/V$



what about biology?

1) are there any distinctively biological laws?

good candidates for laws in biology would be regularities holding true for all/most living things
e.g., the genetic code, allometric laws

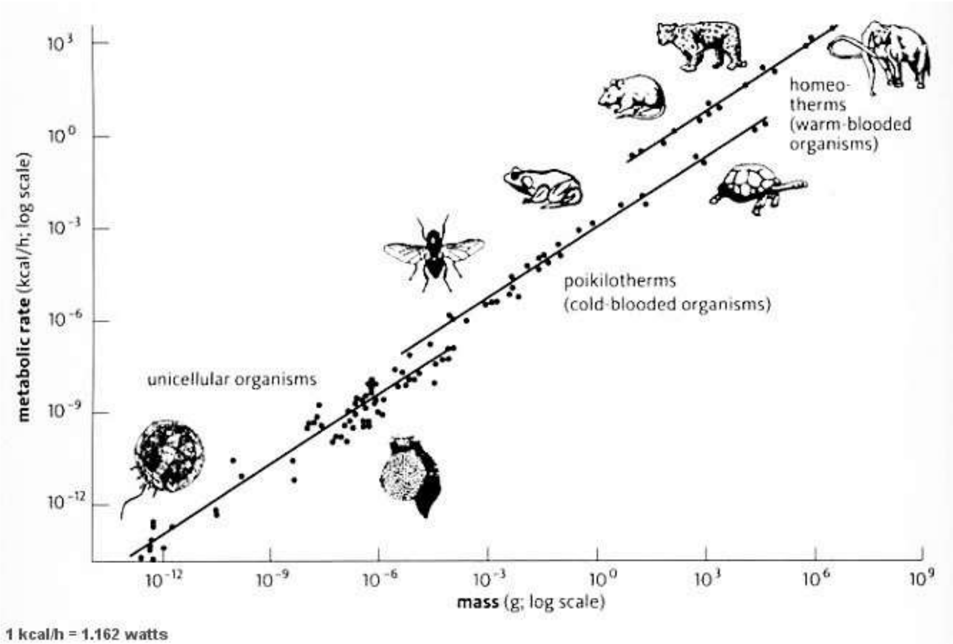
2) can biological phenomena be explained as logical consequences of the laws of physics and chemistry?

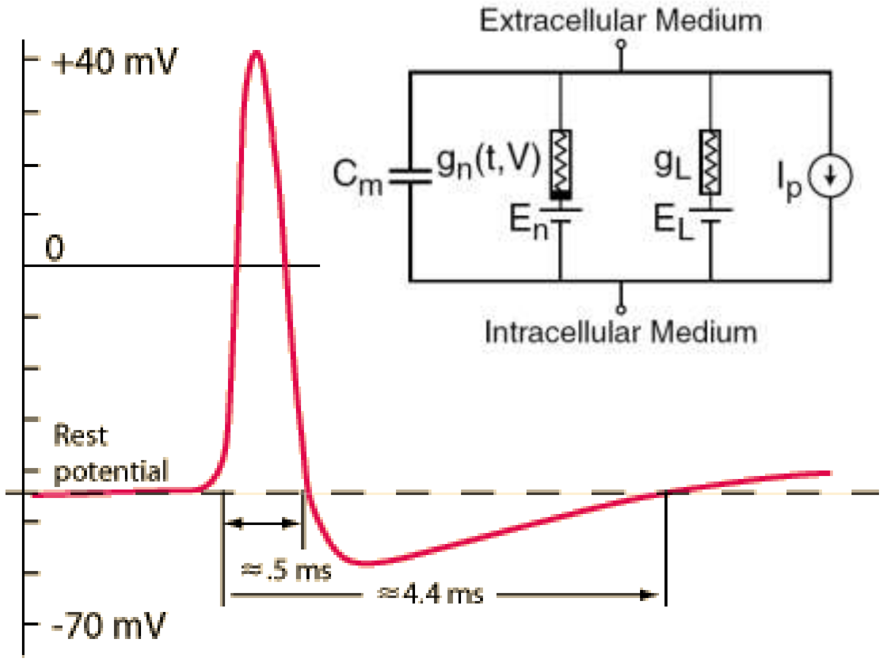
reduction (intertheoretical) of biology to physics/chemistry

derivation from biological laws

biological laws explain biological phenomena

e.g., Kleiber's law ($B \propto M^{3/4}$) explains why the metabolic rate of a 3 kg cat is only 5.6 times larger than that of a 0.3 kg rat





applied physics/chemistry

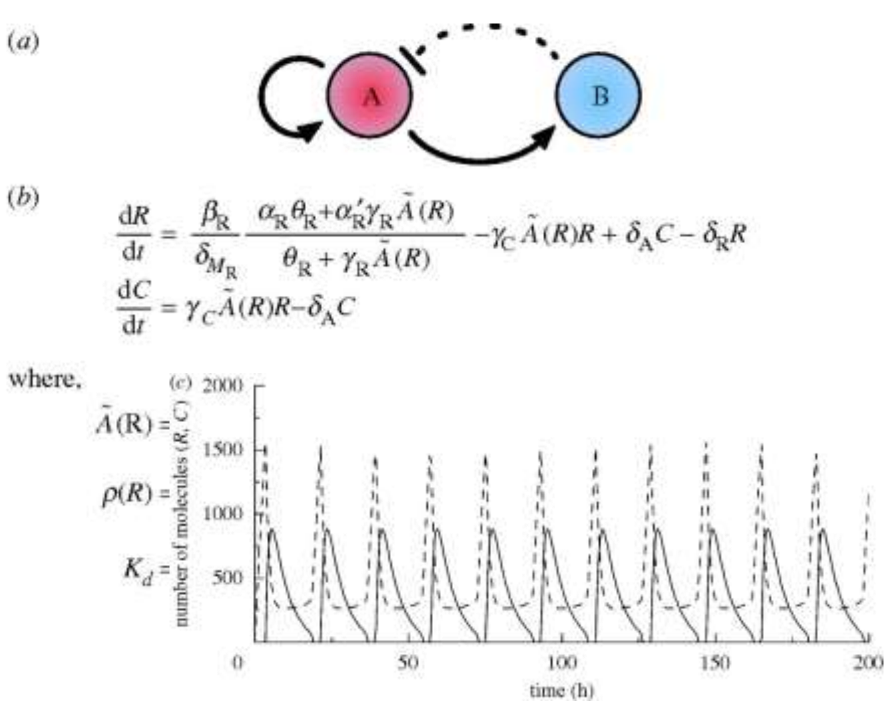
laws of physics/chemistry explain biological phenomena

e.g., the Hodgkin and Huxley model of the action potential

mathematical models & computer simulations

mathematical models predict/simulate the behavior of biological systems

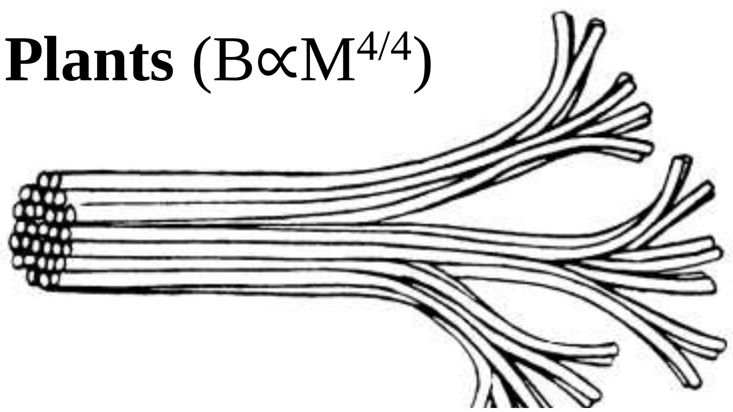
e.g., model of a regulative feedback loop



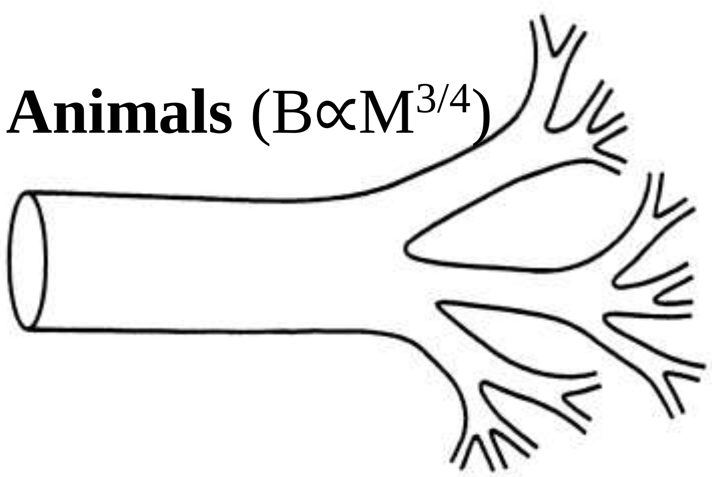
some difficulties
no universal regularities in biology

- putative laws are plagued by many exceptions and limitations

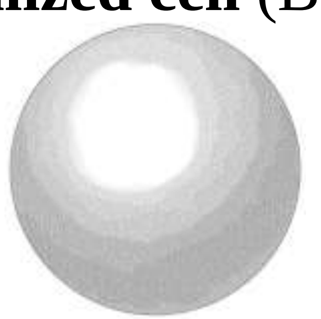
Plants (B∝M$^{4/4}$)



Animals (B∝M$^{3/4}$)



Idealized cell (B∝M$^{2/3}$)



Gln
Diplomonads
Acetabularia
Paramecium

UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
UUA	Leu	UCA	Ser	UAA	Stop	UGA	Stop
UUG	Leu	UCG	Ser	UAG	Stop	UGG	Trp
CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
AUA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
AUG	Met/Start	ACG	Thr	AAG	Lys	AGG	Arg
GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

Ser
Candida

nonsense
Micrococcus

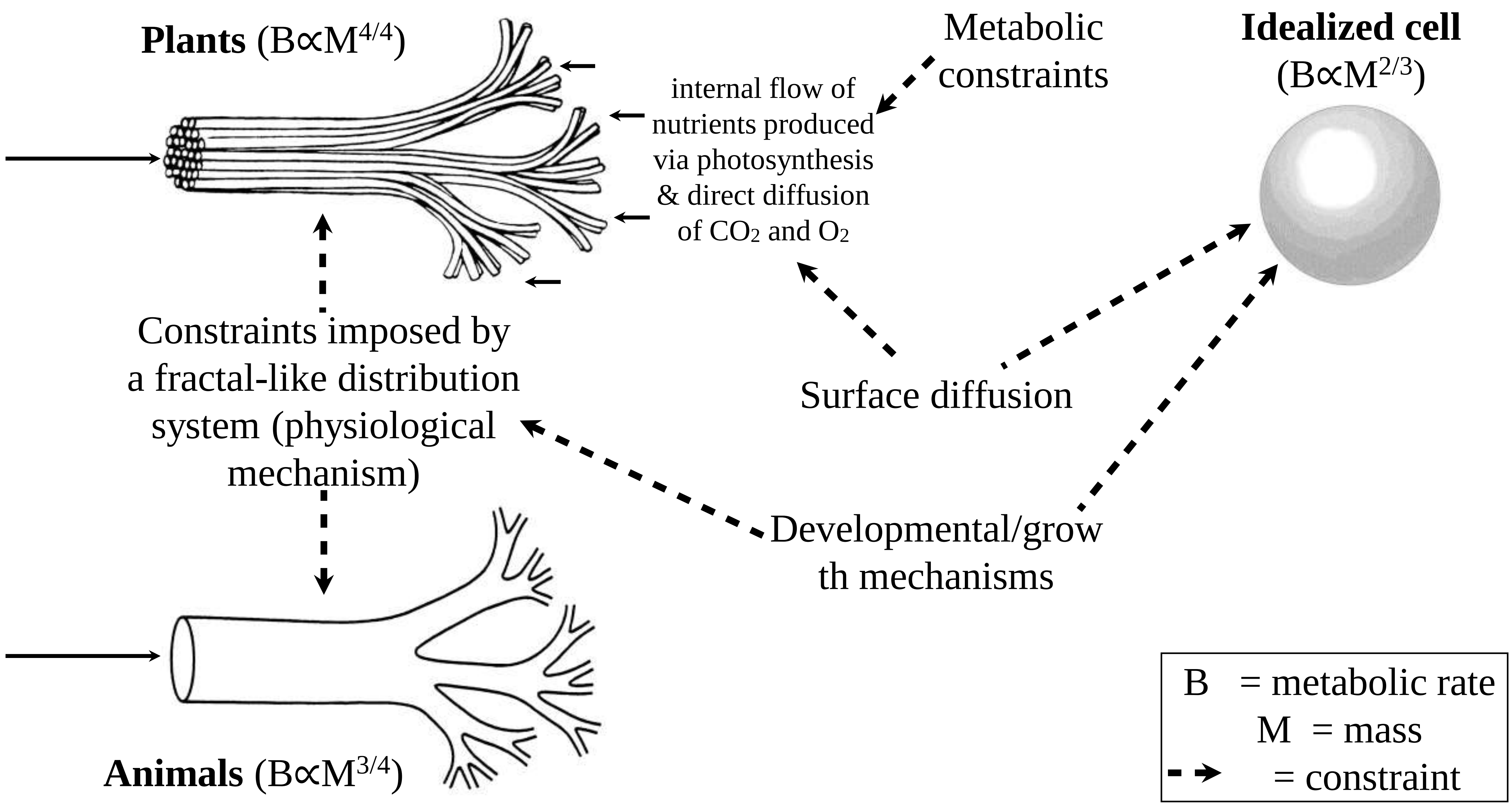
Trp
Mycoplasma
Spiroplasma

Cys
Euplotes

nonsense
Mycoplasma
Spiroplasma

nonsense
Micrococcus

some difficulties
mechanistic basis of biological regularities



mechanisms vs. biological regularities

- correlations (including regularities) in biological sciences are not fundamental & universal laws (akin to the laws of physics)
- they are contingent; they remain dependent on the peculiarities of biological systems → individual differences
- correlations/regularities are caused (and explained) by mechanisms → individual differences are explained by differences in mechanisms

Some Difficulties
Biological Explanations as Applied Physics

- biological explanations as applied physics/chemistry
- use the laws of other sciences
  - *e.g., the Hodgkin and Huxley model of the action potential (1952)*
  - *Nernst equation explains why ions move across axon membrane (Weber 2005)*

$$
\begin{aligned}
Cv' &= -g_1 m^3 h(v - E_1) - g_2 n^4 (v - E_2) - g_3 (v - E_3) + I_{\text{in}} \\
m' &= (1 - m)\alpha_m(v - E_0) - m\beta_m(v - E_0) \\
n' &= (1 - m)\alpha_n(v - E_0) - n\beta_n(v - E_0) \\
h' &= (1 - h)\alpha_h(v - E_0) - h\beta_h(v - E_0),
\end{aligned}
$$

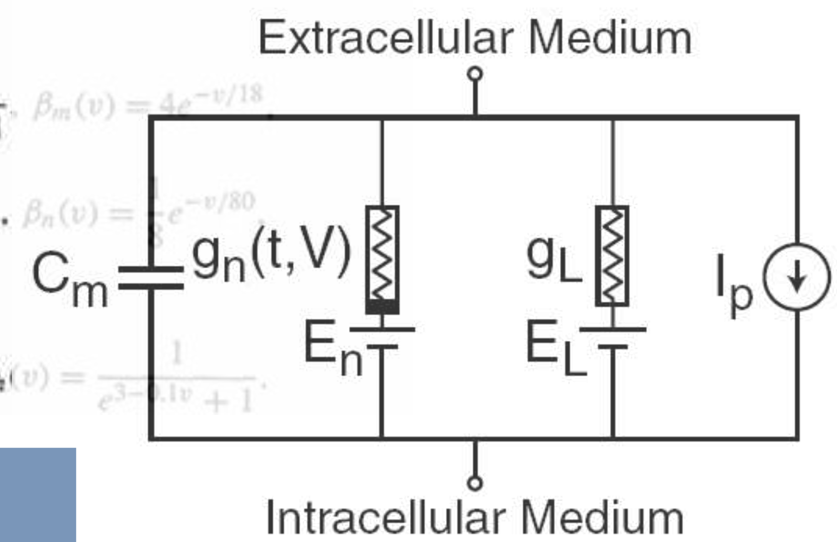
where

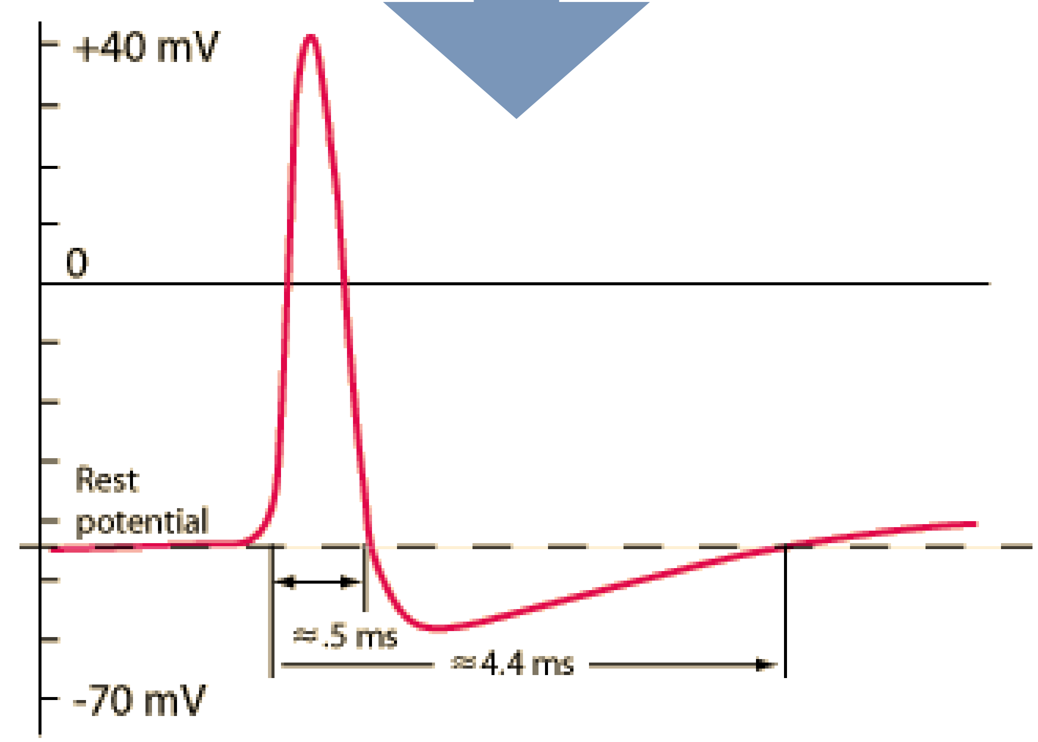
$$\alpha_m(v) = \frac{2.5 - 0.1v}{e^{2.5-0.1v} - 1}, \quad \beta_m(v) = 4e^{-v/18}$$

$$\alpha_n(v) = \frac{0.1 - 0.01v}{e^{1-0.1v} - 1}, \quad \beta_n(v) = \frac{1}{8}e^{-v/80}$$

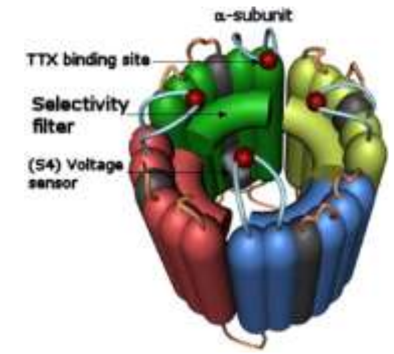
and

$$\alpha_h(v) = 0.07e^{-\frac{v}{20}}, \quad \beta_h(v) = \frac{1}{e^{3-0.1v} + 1}.$$

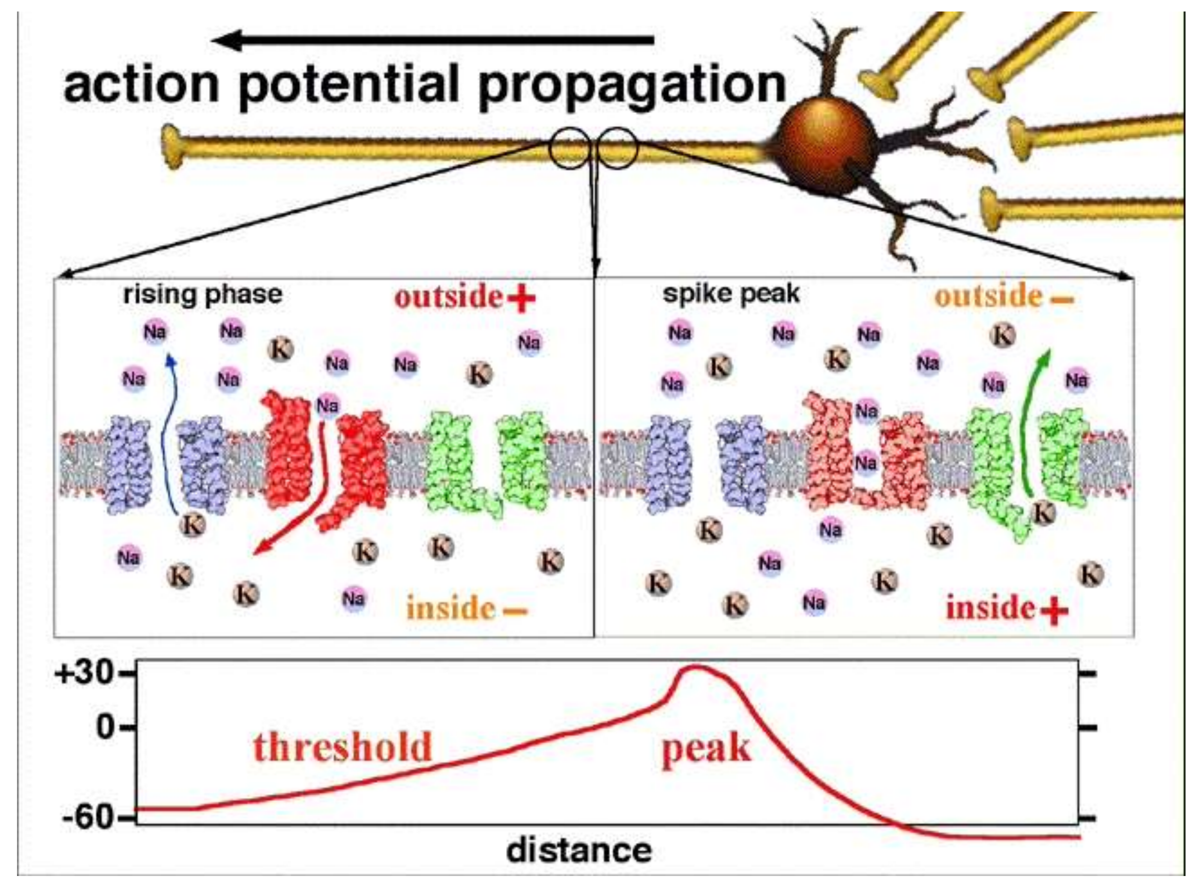




some difficulties
incomplete explanations



- partially instrumental nature of the HH model
  - incomplete physical interpretation
    - *e.g., uninterpreted parameters*
  - multiple physical interpretations
    - *e.g., how many ion currents?*
  - missing details
    - *e.g., how do ions travel across membranes?*
  - no real targets for experimentation/treatment
    - *e.g., what are the cellular and molecular structures implementing the model*



more generally, no clear physical (including causal) interpretation

Is the DN account complete?

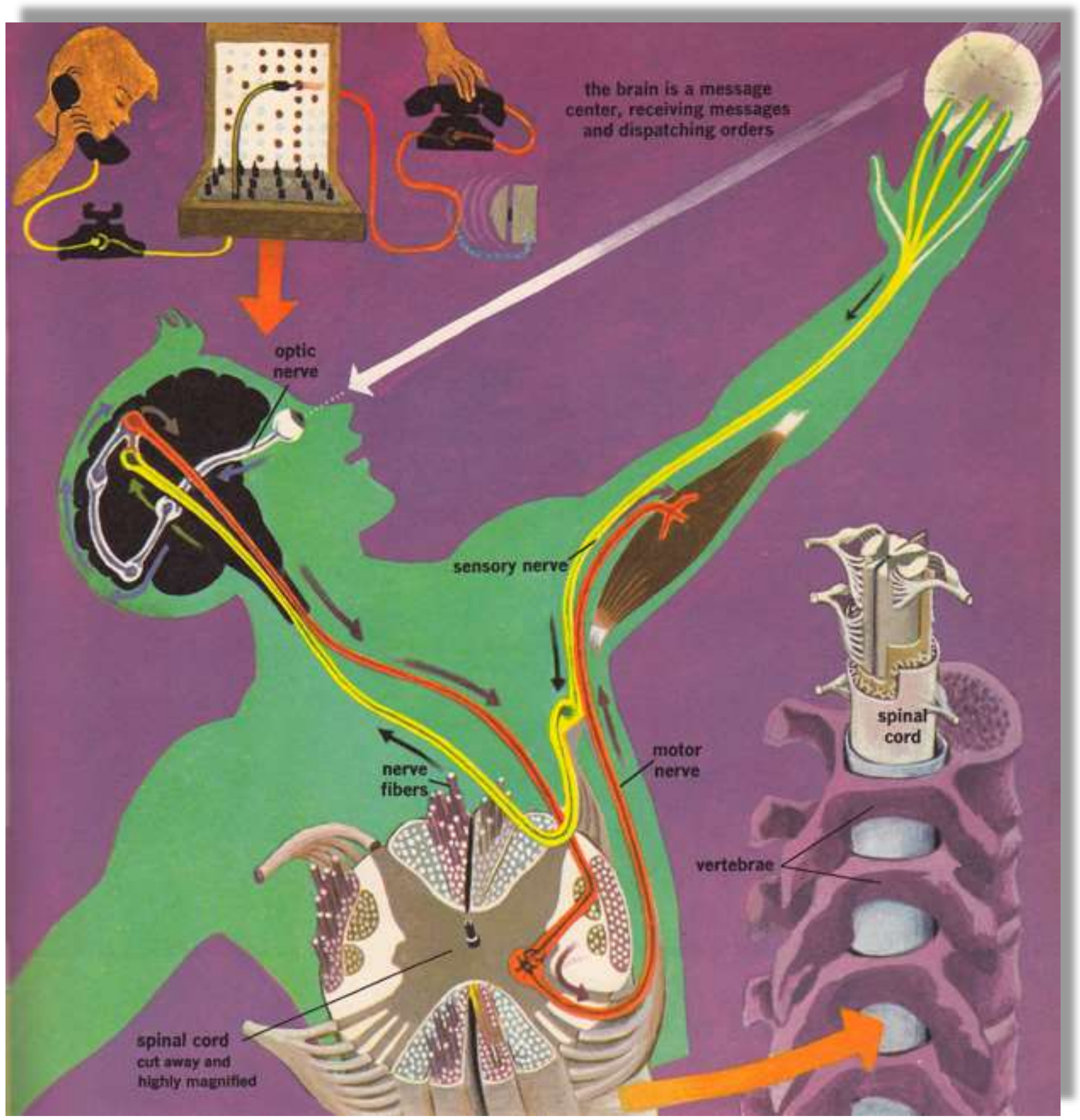
$$\vec{F} = m\vec{A}$$

the law

... and its causal interpretation

Is prediction enough to have an explanation?

the ‘new’ mechanistic philosophy



- the traditional deductive-nomological approach to explanation has a very limited domain of applicability in biology (absence of biological laws, incomplete explanations based on the laws of physics/chemistry, etc.)
- scientists in the life sciences, including medicine and clinical science, usually characterize their explanations as descriptions of mechanisms *causally* productive of phenomena

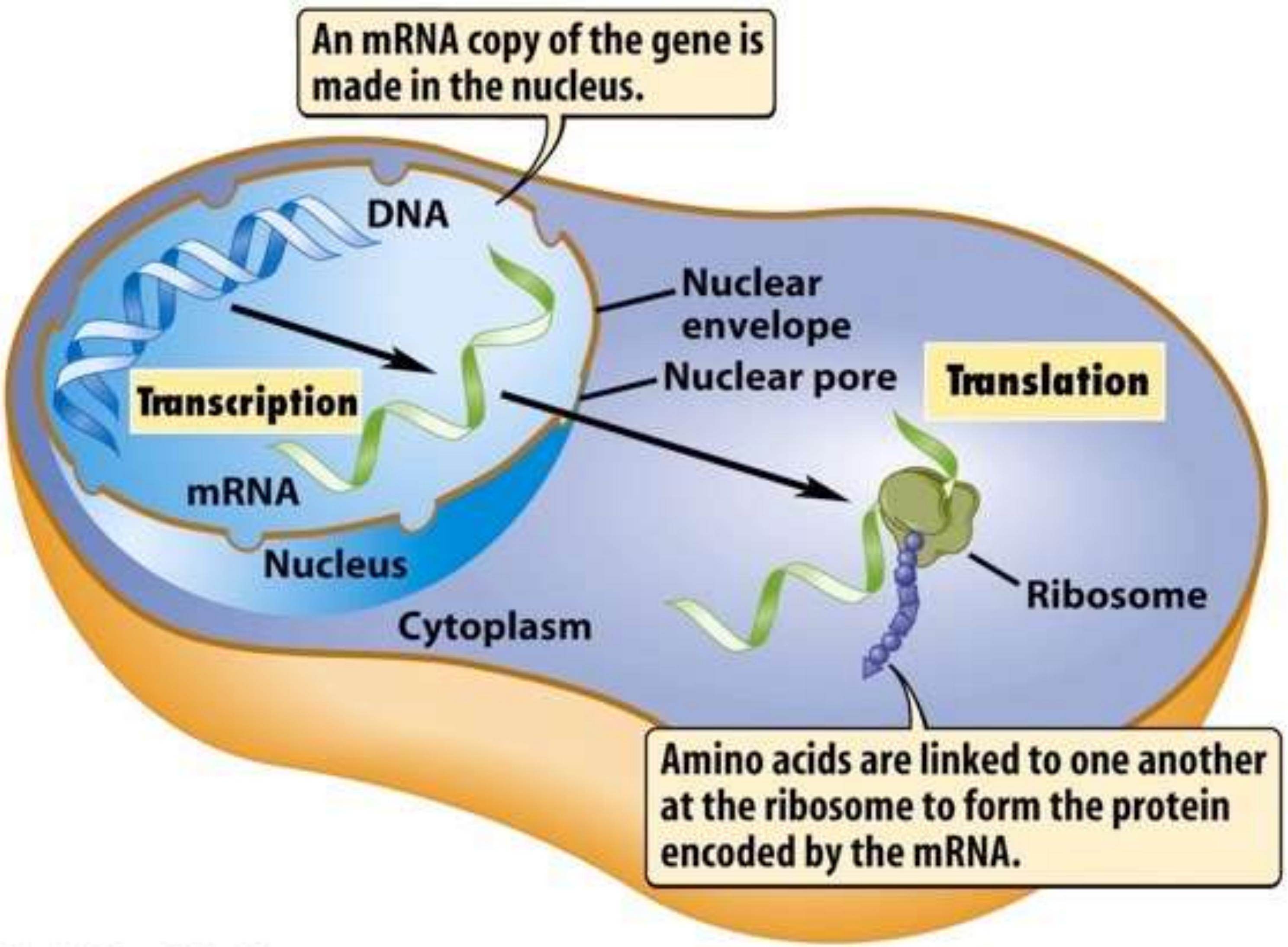


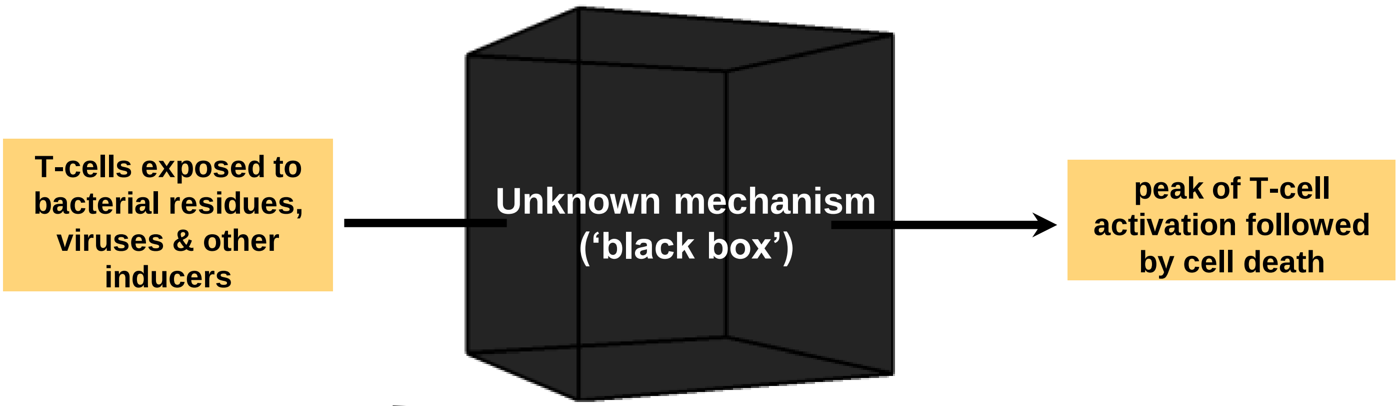
Figure 13-2 Discover Biology 3/e

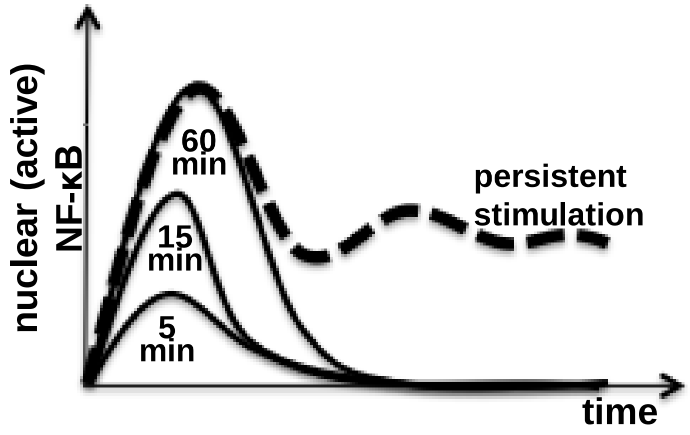
mechanism = entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions

(Machamer, Darden et Craver 2000)

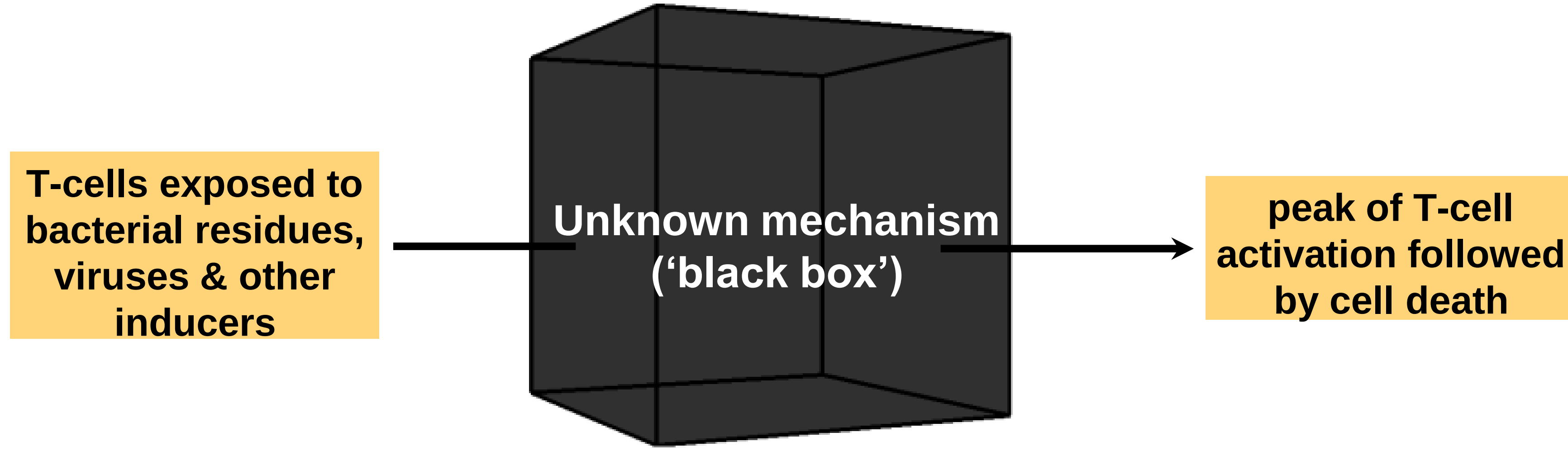
delineating the phenomenon

- first step in mechanistic explanation is specifying the phenomenon to be explained
  - what happens and under what conditions does it happen
  - not just any data reports (measurements, observations) but characterizations of stimulus-response sequences (“regular changes from start or set-up to finish or termination conditions”)
  - often it is important to characterize phenomena quantitatively, for it is the detailed behavior that the mechanism must explain

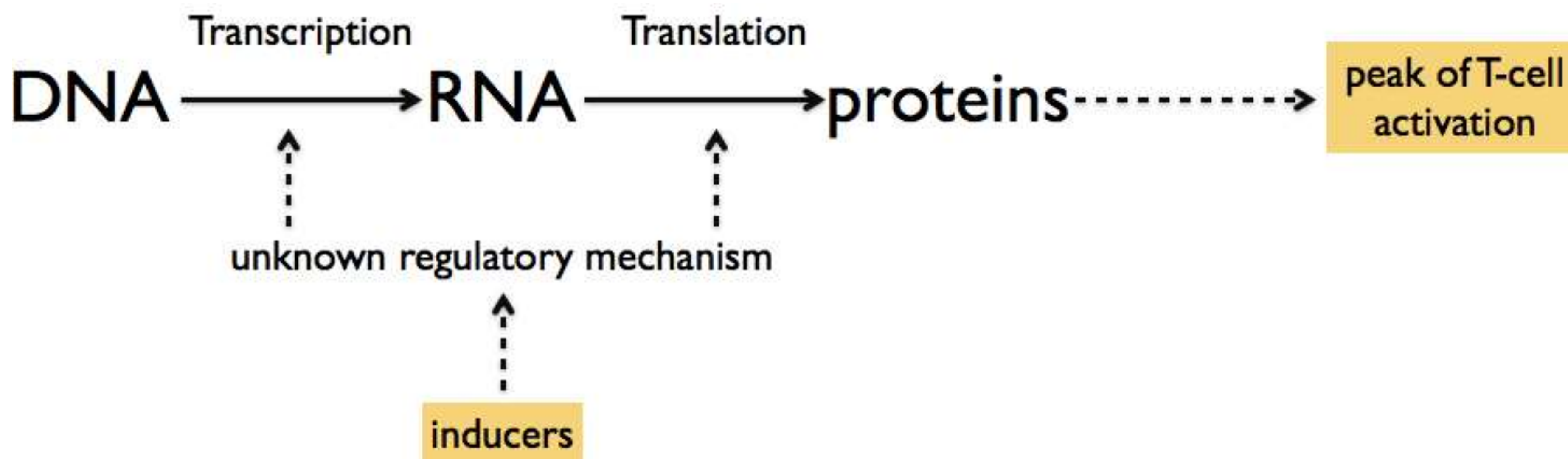




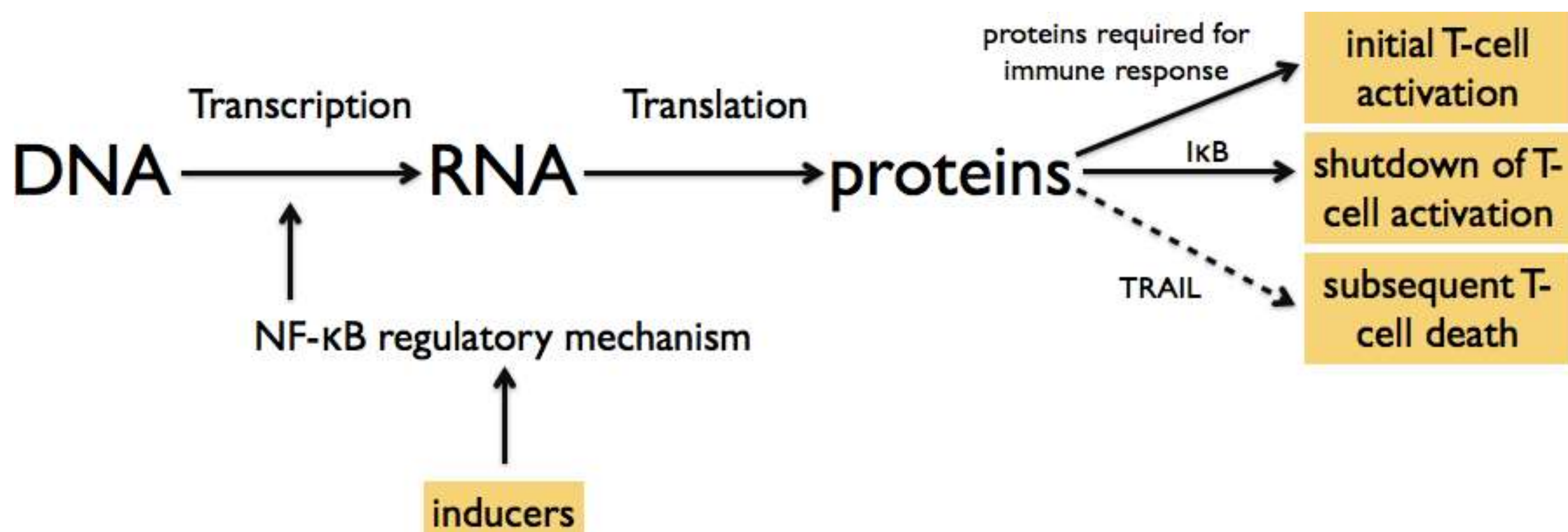
Description of the phenomenon to be explained

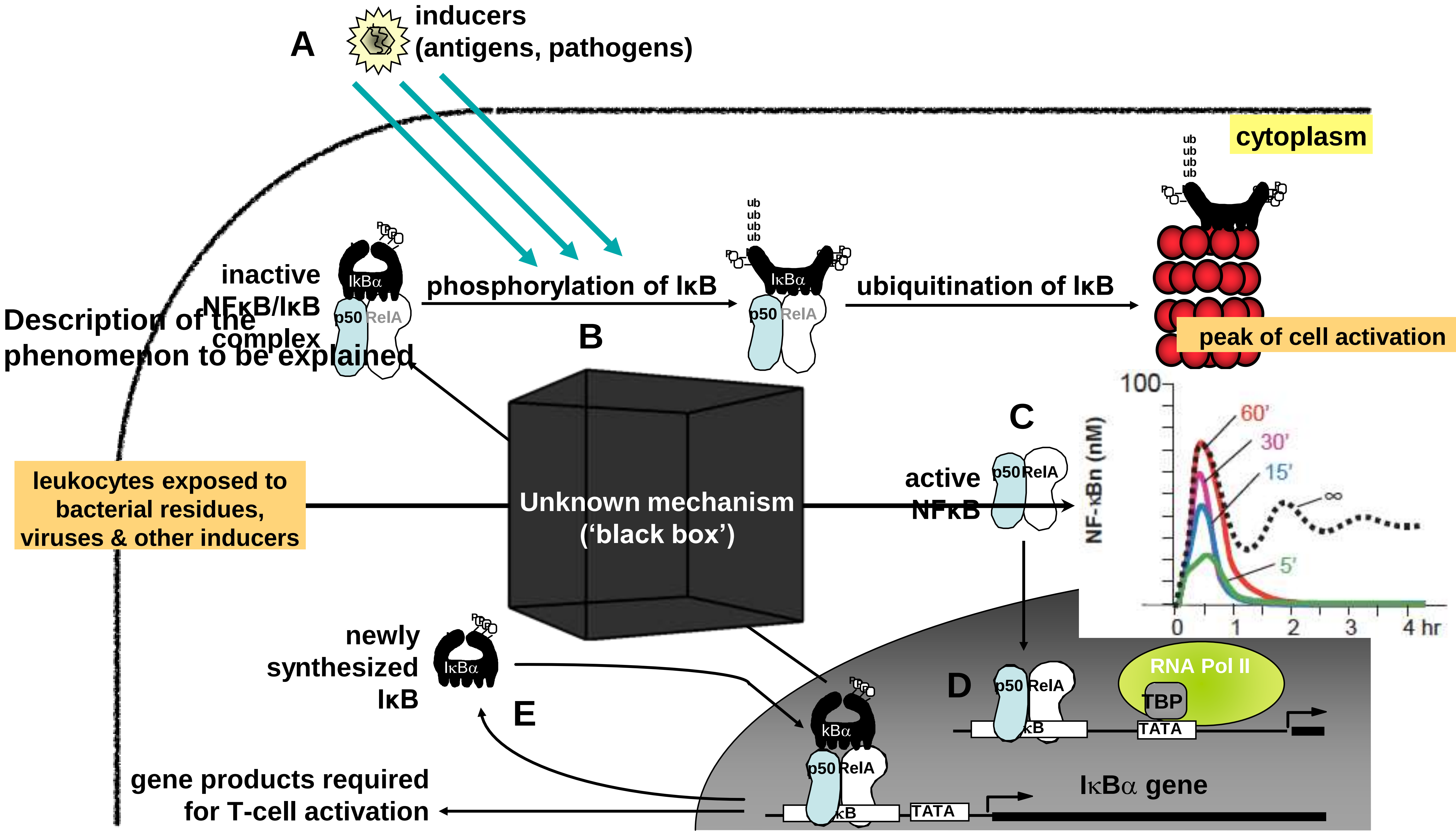


Initial mechanism sketch



Partially elucidated mechanism schema





A more complete, qualitative description of the regulatory mechanism

Adapted from (Baetu 2001, Sun et al. 1993)

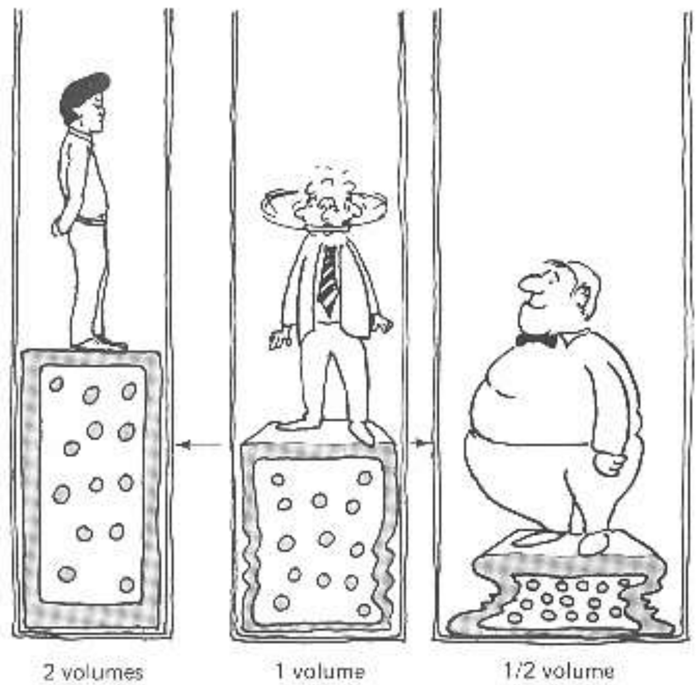
how do mechanisms explain?

- the ‘**intuitive/analogical understanding**’ view (Bogen 2004; Machamer 2004): mechanistic explanations render phenomena intelligible to us (*e.g., a narrative relating a sequence of happenings; similarities with macroscopic processes and devices*)
- the ‘**epistemic**’ view (Bechtel 2008; Glennan 2002): mechanisms describe the causal structures by means of which phenomena are actually produced
- the ‘**ontic**’ view (Craver 2007; Salmon 1984): mechanisms explain because they are the actual causes of phenomena (i.e., mechanism = mechanistic explanation = real thing in the world)
- the ‘**counterfactual**’ view (Woodward 2002): mechanisms explain by showing how the manipulation of the factors mentioned in the explanation would affect the phenomenon

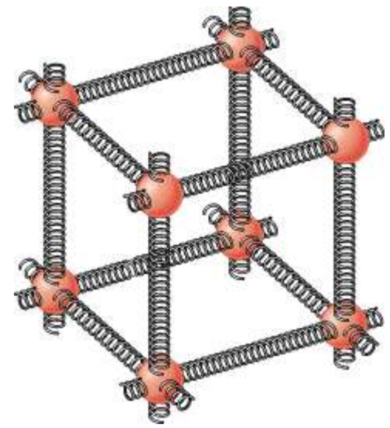
laws vs. mechanisms

$$P \,\alpha\, \frac{1}{V} \rightarrow PV = x$$

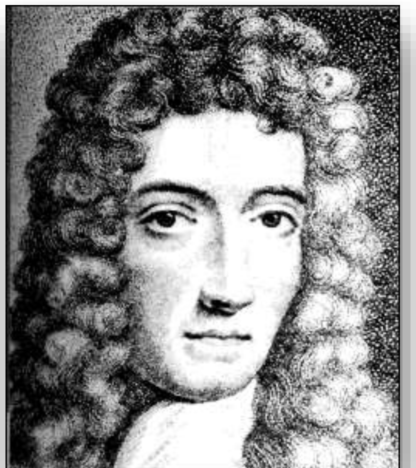
the law of ideal gases formulated by Robert Boyle in1660



the phenomenon to be explained = increase of pressure when the volume decreases



the mechanism behind the law (Boyle's 'structural [mechanistic] explanation')



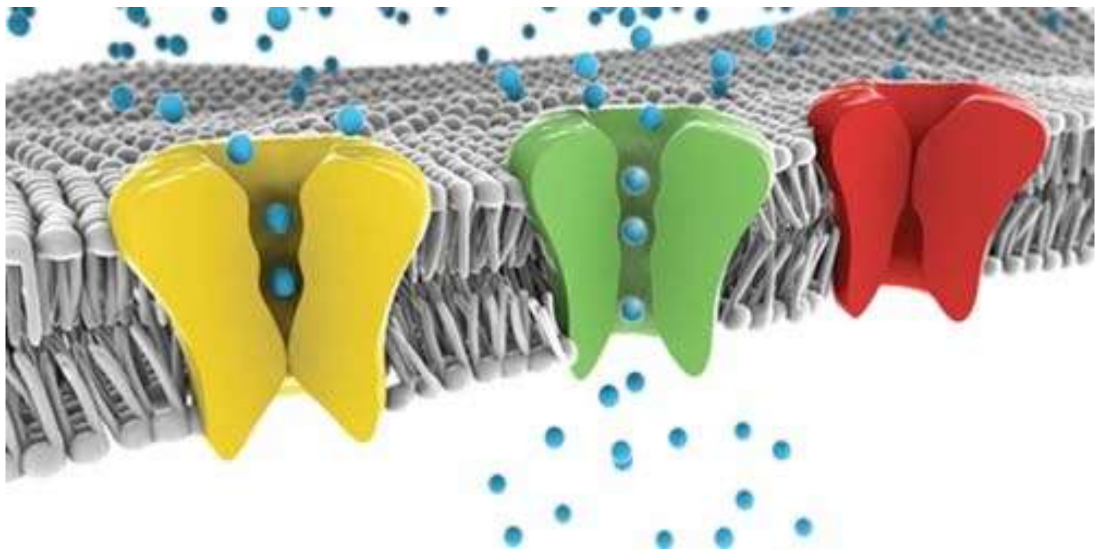
Robert Boyle (1627–1691)

Robert Boyle became famous for discovering the law of ideal gases, stating the pressure times volume is constant. Interestingly however, in his works he often claims that what explains the behavior of gases is not the law, which he treats as a 'mathematical way of speaking', but the physical structure of the gas, which consists of an unseen mechanism: he imagined the gas as a lattice of atoms linked by springs

new debate... same old dilemma

- Marcel Weber (2005) on the Hodgkin and Huxley (1952) model of the action potential:
  - “it is a physicochemical law [the Nernst equation] that ultimately explains why ions move across membranes when action potentials spread”
  - mechanistic descriptions merely “describe the conditions under which this ion transport occurs” and specify “how the physicochemical theory should be applied” (i.e., they specify initial and background conditions)
- Carl Craver (2007) disagrees:
  - mechanisms provide more complete explanations because they tell us how phenomena are produced, identify tangible causes, and make possible interventions that serve experimental and pragmatic purposes
  - mathematical models (e.g., HH model) explain only in as much as they are reasonably complete models of actual mechanisms; a model is complete when it includes all the relevant features of the mechanism, their causal role, and productive continuity

mechanistic explanation



physical structures that **cause** a phenomenon

vs.

general laws unifying several domains of empirical reality

hidden structures (spatial-temporal organization of matter)
→ *qualitative notion of mechanism focused on structural features that play a causal role*

vs. dynamics of complex systems
→ *quantitative approach focused on understanding how a system behaves over time based on knowledge of the laws or rules according to which the parts of the system operate or interact*

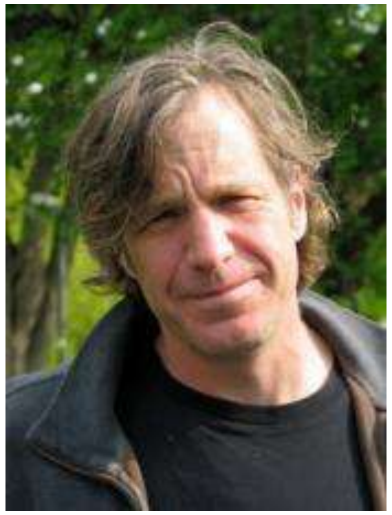
why mechanisms are better than laws

a good explanation must point to the **real causes** of the phenomenon

experimentation and technological applications (ex., medical treatments) require **interventions** on the real causes of a phenomenon

Wesley Salmon

James Woodward



Carl Craver

critique of the deductive-nomological approach

the derivability of a description of a phenomenon from a model doesn’t guarantee that the model correctly identifies the cause of the phenomenon

many models for any given phenomenon, where each model can have **several causal interpretations**

limitations of the mechanistic framework

experimental interventions can demonstrate

that a set of mechanistic components (entities, activities, organizational features) are actually involved in the production the phenomenon of interest

and that causal pathways that do not rely on these mechanistic components are not actually involved in the production the phenomenon

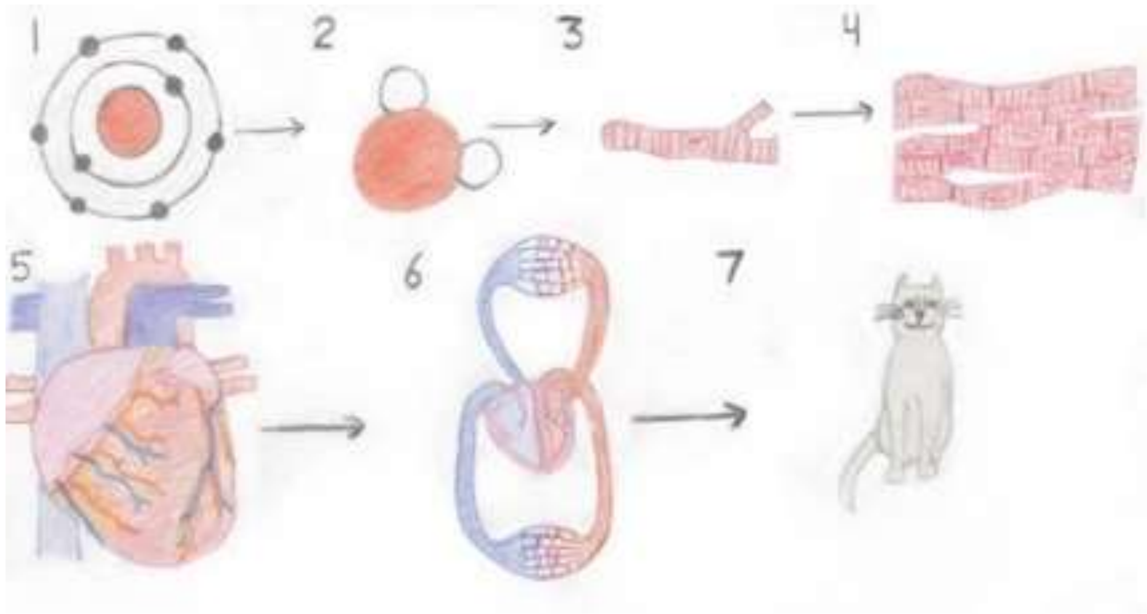
... but it is not clear how this also demonstrates that all the causally relevant components of a mechanism have been identified and that there are no gaps in productive continuity

the completeness of mechanistic explanations

problem of (non-)modularity

is it possible to separate a mechanism from the system in which it is embedded and treat it as an independent module?

e.g., is a living thing an organic whole that cannot be decomposed into a set of independent mechanisms?



bottoming out problem

given the possibility of an indefinite descent to lower levels of composition, how deep does one need to go in order to claim that the explanation is complete for the purposes of accounting of a phenomenon?

e.g., how much detail is explanatorily relevant?

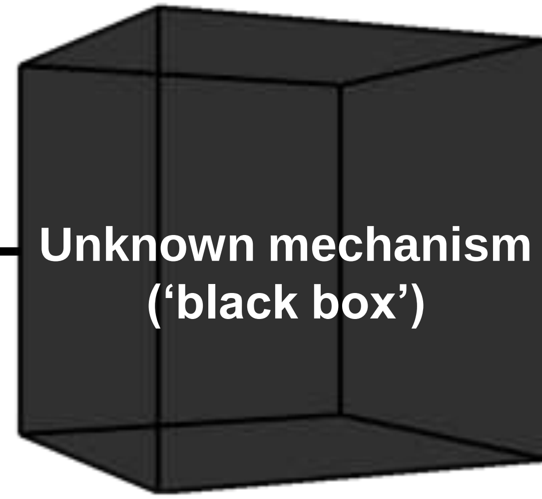
even when constructing detailed and highly realistic mathematical models of previously elucidated molecular mechanisms, and even when the values of the parameters of model are based on empirical measurements, these *models can only be as complete as the knowledge of the modeled mechanisms is*

bright side to this limitation: if the output of the model fails to closely match the phenomenon known to be produced by the modeled mechanism, then this can be an indication that something is missing from the mechanistic explanation

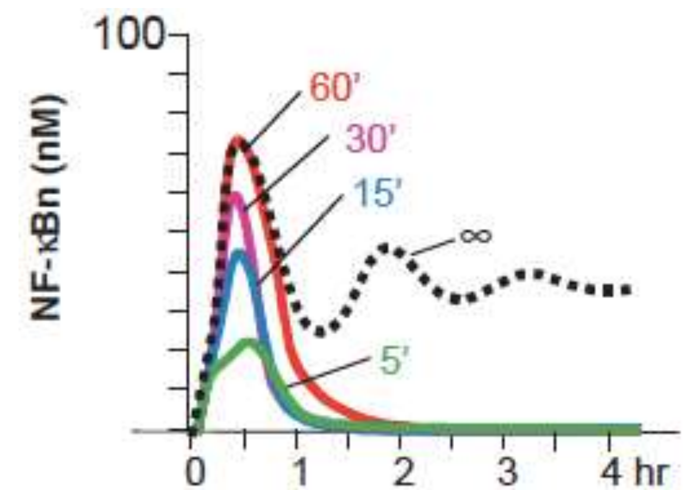
one way to evaluate the completeness of mechanistic explanations is to develop and test mathematical models of mechanisms

Description of the phenomenon to be explained

leukocytes exposed to bacterial residues, viruses & other inducers

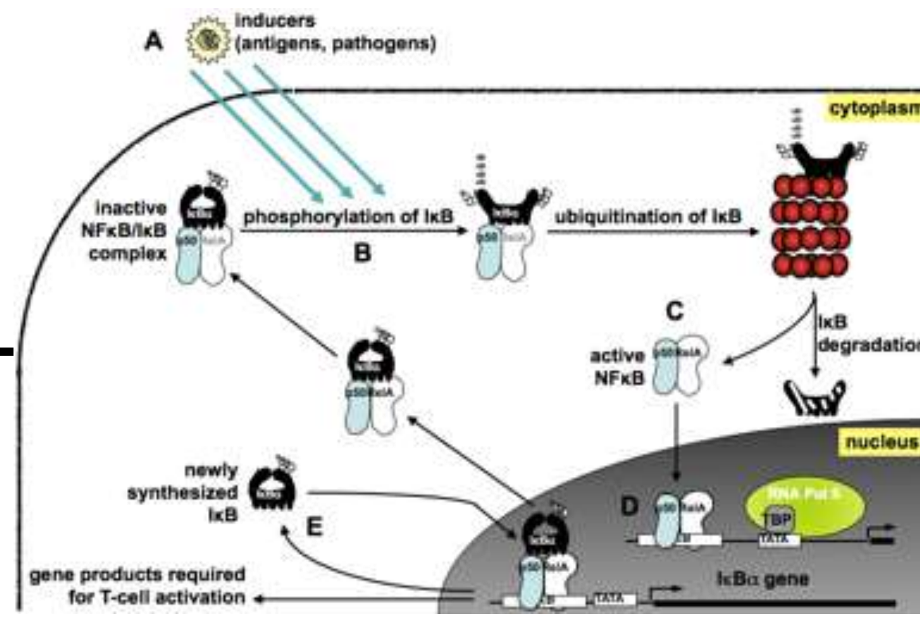


peak of cell activation



Mechanistic explanation (qualitative)

leukocytes exposed to bacterial residues, viruses & other inducers



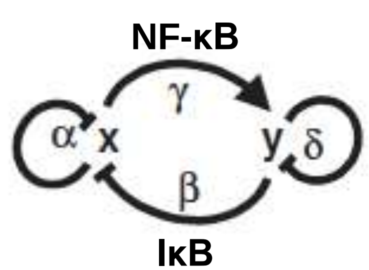
The NF-κB regulatory mechanism

peak of cell activation

Kinetic ODE model (quantitative)

leukocytes exposed to bacterial residues, viruses & other inducers

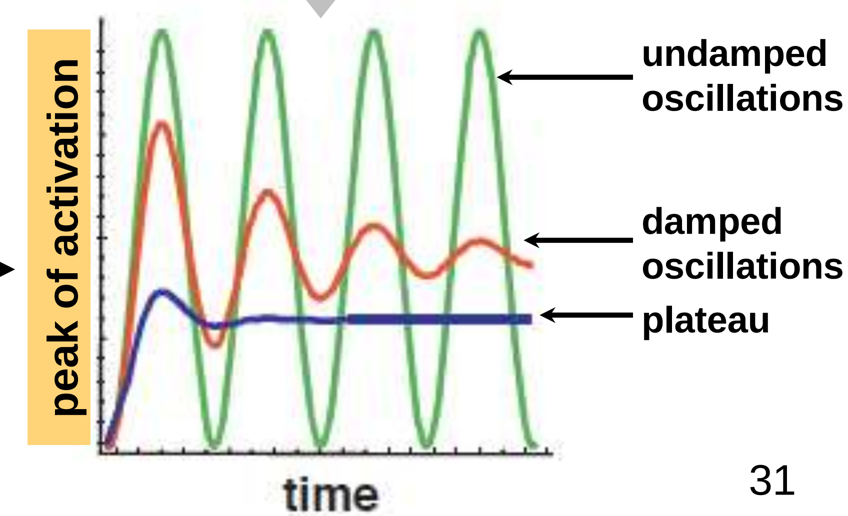
damping (e.g., protein turnover)

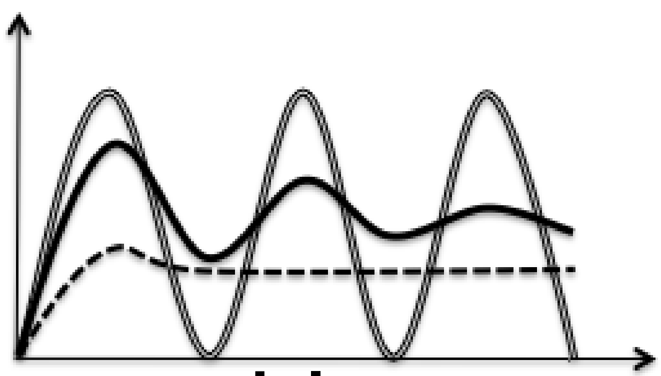


damping (e.g., protein turnover)

negative feedback loop (minimal mechanism schema of the NF-κB regulatory mechanism)

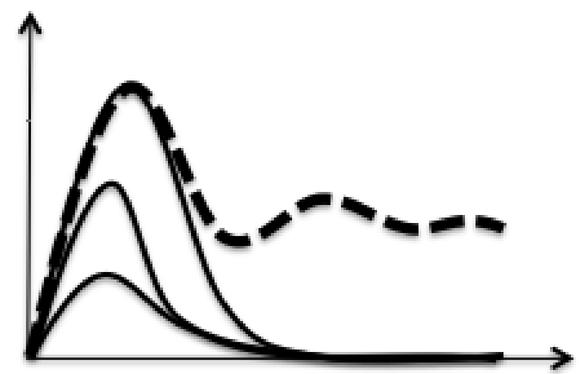
possible outcomes





model output
(prediction, simulation)

predicted
≠
observed



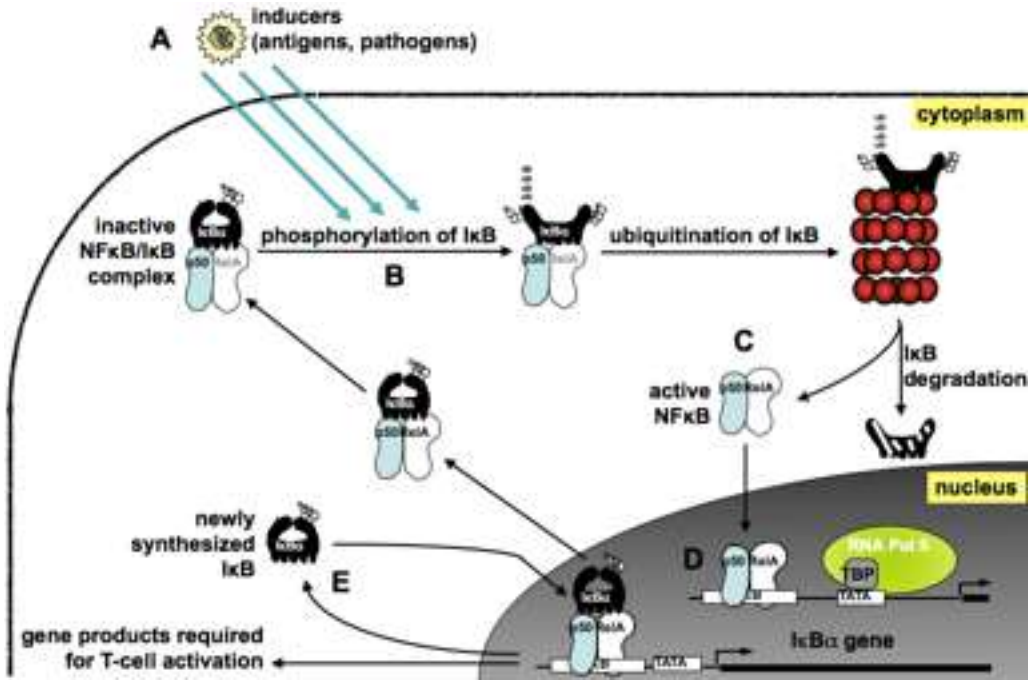
phenomenon
(as measured experimentally)

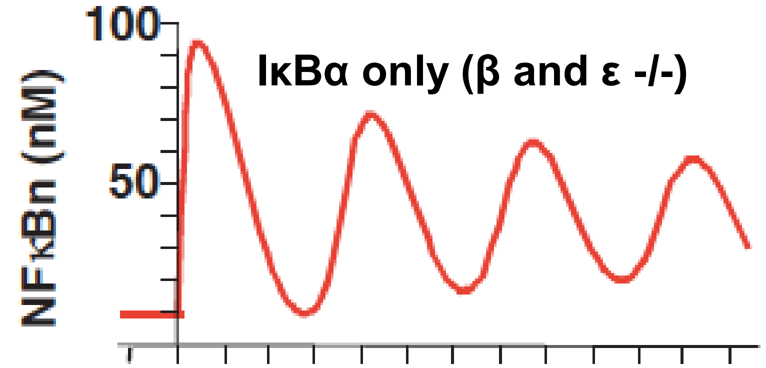
potential 'black box'

discrepancy between output of the model and the observed phenomenon

→ as modeled, the mechanism fails to account for the phenomenon

→ revision of the assumptions on which the model is built OR further experimental investigation and eventual revision of the mechanism

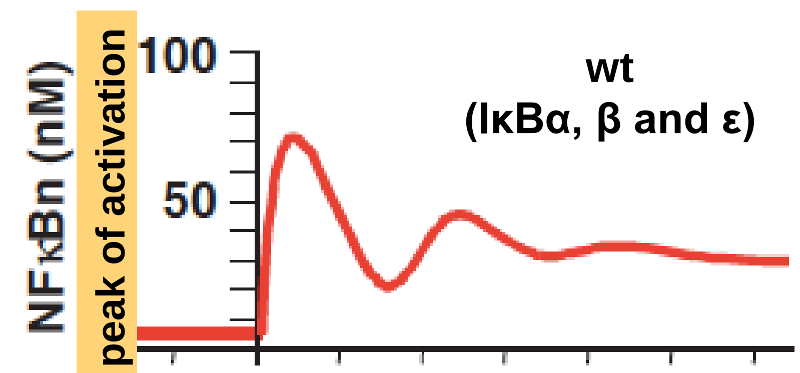




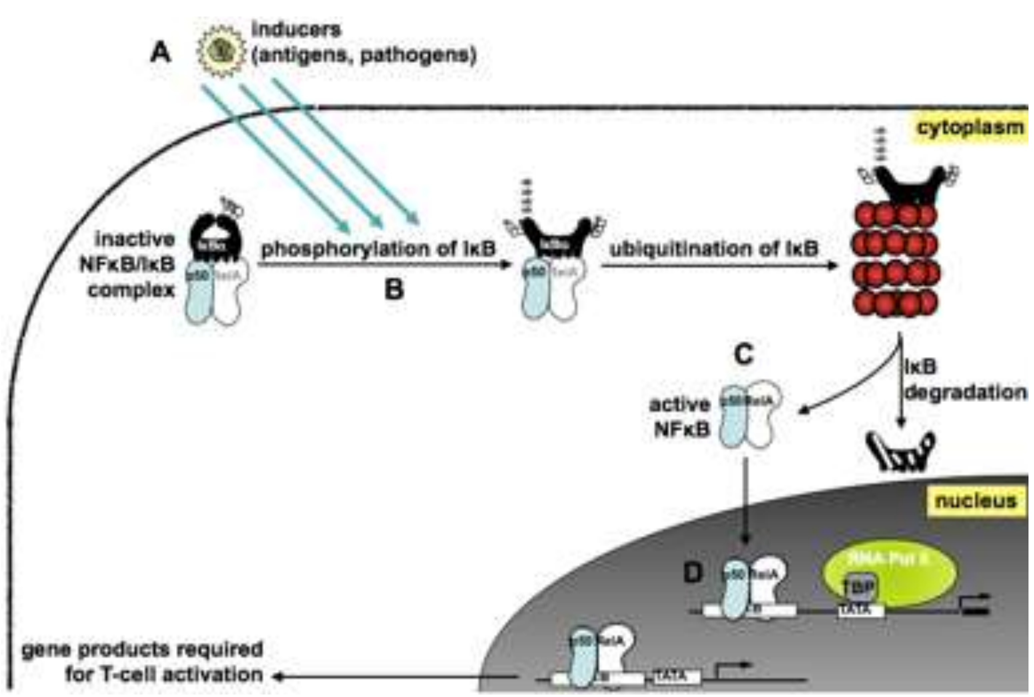
IκBα: negative feedback loop

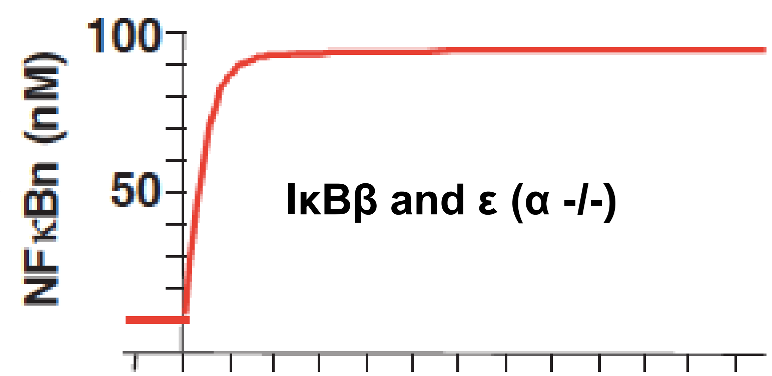
persistent **TNFα stimulation**

finding: the negative feedback loop mechanism needs to be augmented to include a parallel pathway of activation not subjected to negative feedback

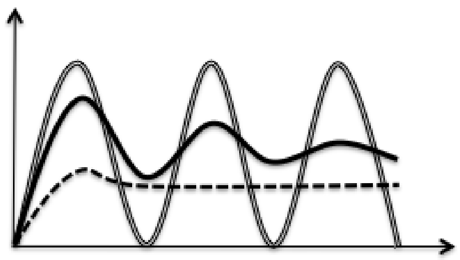


IκBβ and ε: no feedback loop



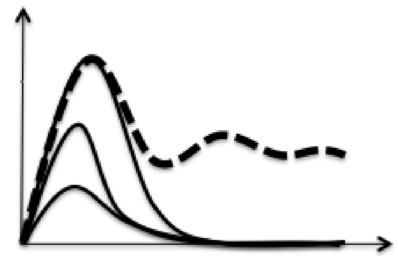


Adapted from (Hoffmann 2002)



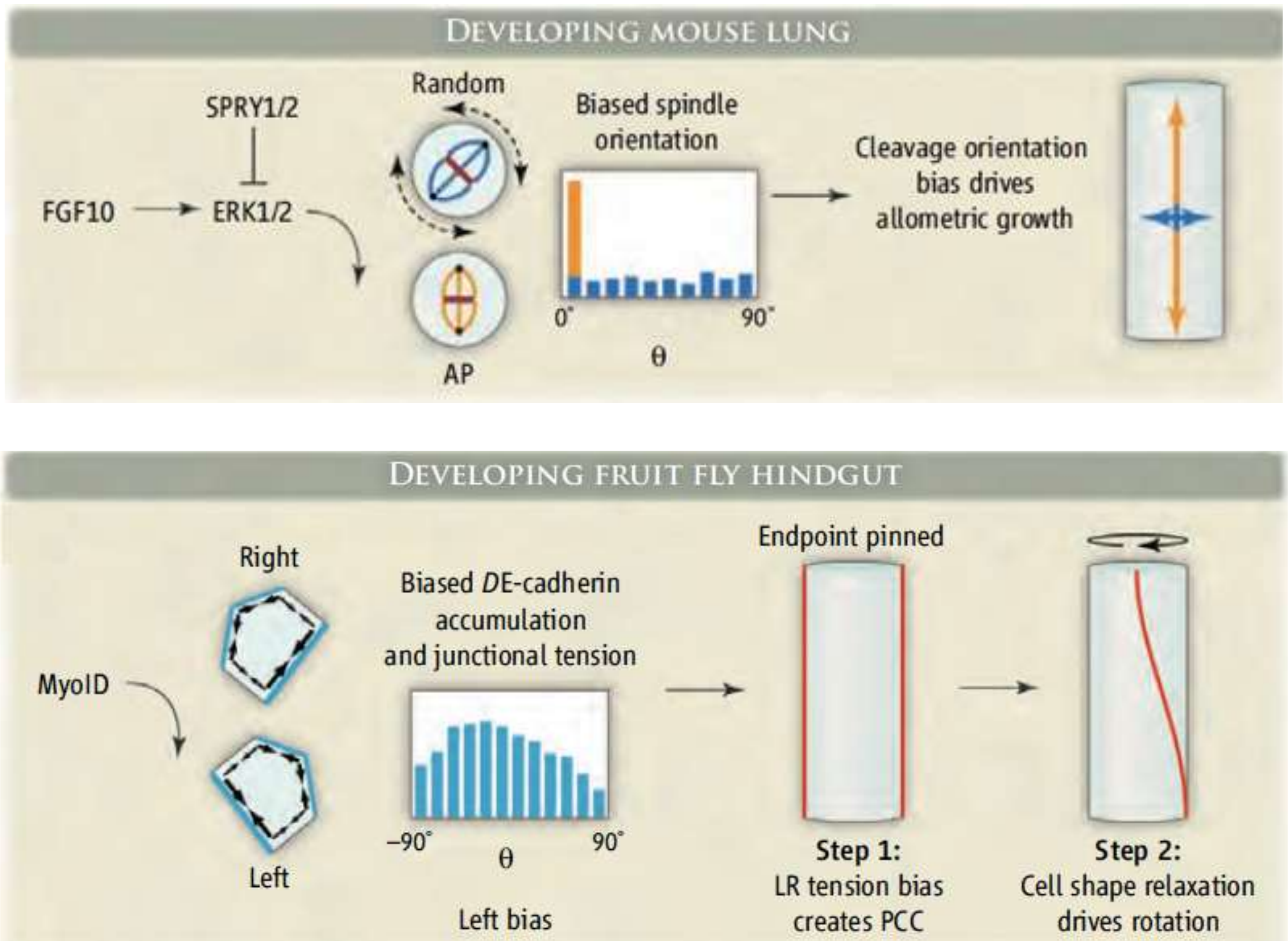
model output
(prediction, simulation)

predicted ≠ observed



phenomenon
(as measured experimentally)

Adapted from (Hoffmann 2002, Horne-Badovinac and Munro 2011)



discrepancy between output of the model and the observed phenomenon

potential 'black box'

→ the mechanism described in the explanation fails to account for the phenomenon

model output matches experimental data

quantitative sufficiency

→ the proposed mechanism generates the right allometric growth ratio
→ the mechanism is sufficient to generate the target phenomenon

parameter completeness

→ a more complex model including additional parameters is not needed → all the relevant mechanistic components have been taken into consideration

model output matches observations

quantitative sufficiency

- used to evaluate stochastic mechanisms

parameter completeness

- an additional degree of complexity/detail will not result an increase in empirical adequacy
- principled solution to the **bottoming out problem**

- mechanism is expected to function as an independent module
    - if separated from the physiological context of the living cell/organism
    - if reconstructed/artificially synthesized *in vitro* from the components described in the mechanistic explanation
- answer to the **modularity question**

model output/solutions **match** description of the phenomenon

→ evidence that the proposed **mechanism can generate the phenomenon of interest in the right amount/intensity**

→ evidence that the **mechanism is sufficient to produce the phenomenon**

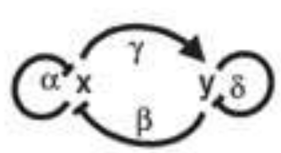
the kind of explanatory completeness evaluated by mathematical models has nothing to do with a ultimate understanding of how everything works at the level of systemic interactions between the most fundamental building blocks of physical reality

rather, it is an engineer's understanding of completeness, framed in terms of information required to *reconstruct in silico a mechanism capable of producing the phenomenon of interest starting from components organized, acting, and having the properties described in the mechanistic explanation*

explanatory complementarity

mechanisms and mathematical models account for different aspects of the same phenomenon

mechanistic explanations identify physical structures responsible for causing phenomena



$dx/dt = S - \alpha x - \beta y$
$dy/dt = \gamma x - \delta y$

mathematical models account for quantitative-dynamic features of phenomena by means of mathematical derivations

explanatory mosaic, where the different pieces of the mosaic involve different kinds of explanations