

First meeting of the NeuroMod Institute 1-2 July 2019, Fréjus

Modelling of physiological and pathological states in neuroscience: exchanges among theoreticians and experimentalists

B. Cessac (Inria), M. Mantegazza (IPMC)

In a virtuous cycle, modelling can use data obtained by experiments to capture essential features and organizing principles of biological systems at multiple scales, and provide hypotheses that can be directly tested with experiments. This can allow to gain important information on both physiological functions and pathological dysfunctions. However, the virtuous cycle is not always ignited and sometimes experimentalists are sceptical of modelling data, feeling that they are too far away from real biology to be informative. There is a delicate trade off between the theoreticians' quest of organizing mechanisms and principles obtained by simplifying reality, and the experimentalists will of staying as close as possible from the system under study. We will discuss what experimentalists expect from theoreticians and vice-versa, what are some new contemporary challenges in neuroscience, and how modelling could contribute to address them.

The modeller point of view

In a virtuous cycle, **modelling** can use **data** obtained by **experiments** to capture essential features and **organizing principles** of biological systems at multiple **scales**, and provide **hypotheses** that can be directly tested with experiments. This can allow to gain important information on both physiological functions and pathological dysfunctions. However, the virtuous cycle is not always ignited and sometimes experimentalists are sceptical of **modelling data**, feeling that they are too far away from **real biology** to be informative. There is a delicate **trade off** between the theoreticians' quest of organizing mechanisms and principles obtained by simplifying reality, and the experimentalists will of staying as close as possible from the system under study. We will discuss what experimentalists expect from theoreticians and vice-versa, what are some new contemporary challenges in neuroscience, and how modelling could contribute to address them.

What is a model ?

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A set of equations:

Variables (quantity evolving in time and space),

Parameters (quantity tuned “by hand”) ,

Causal interactions between variables depending on parameters,

Space time evolution,

Scales.

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Studying equations

Mathematics is not (only) a tool, it provides a conceptual framework which guides but also constrains the analysis.

Physics, makes the link between nature and mathematics: use of -and- - seek for principles, which guides but also constrains the model structure.

Simulation, is not a magic stick, don't stimulate if you have no idea of what to expect.

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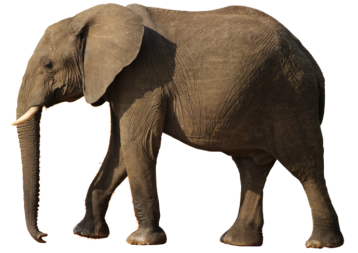
Simulation, is not a **magic stick**, don't stimulate if you have no idea of what to expect.

Each equation imposes **implicit constraints** on the model-description

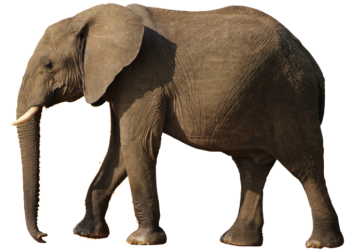
What is not a model ?

A model is **not** reality

Simplify to understand



What is their common feature ?

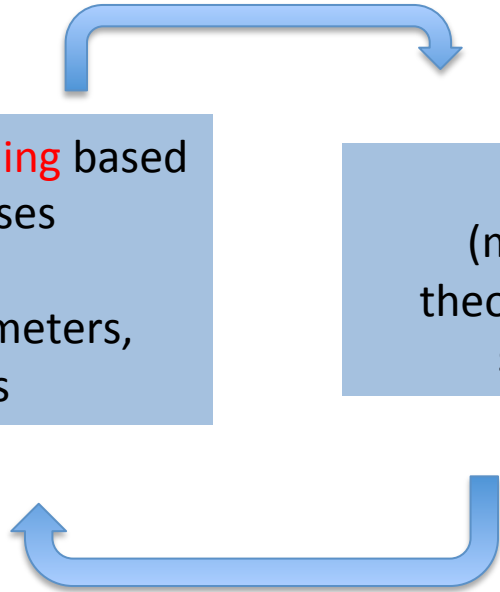


What is their common feature ?

Simplify to understand

Biophysical modelling based
on hypotheses
=>
Variables, parameters,
equations

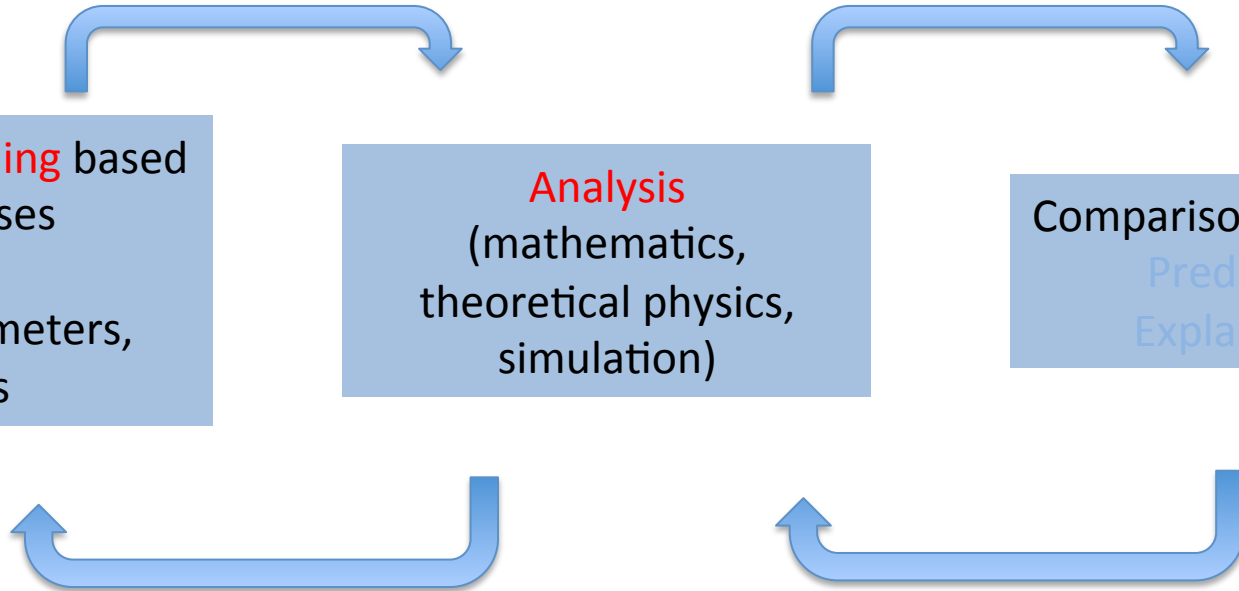
Analysis
(mathematics,
theoretical physics,
simulation)



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Comparison with **data**
Prediction
Explanation



Data

Modellers are **not** data analysts.

Data

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Data are useless without underlying **hypotheses** on their
structure

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Models may help unravelling this structure

Goals of modellers

The goal is **not** to tell biologists something they already know

Not to reproduce experiments / “**reality**” => just a step

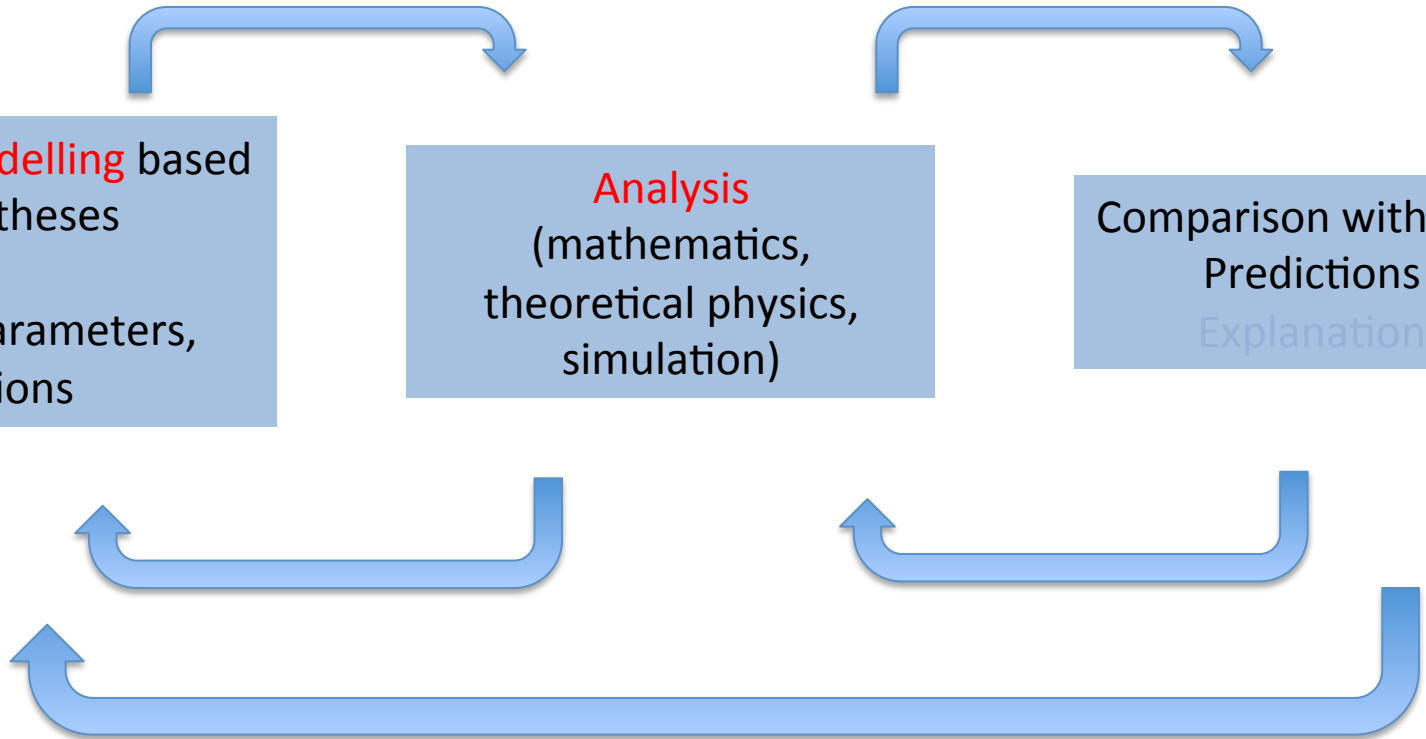
Make predictions

Explain

Biophysical modelling based
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=>
Variables, parameters,
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Analysis
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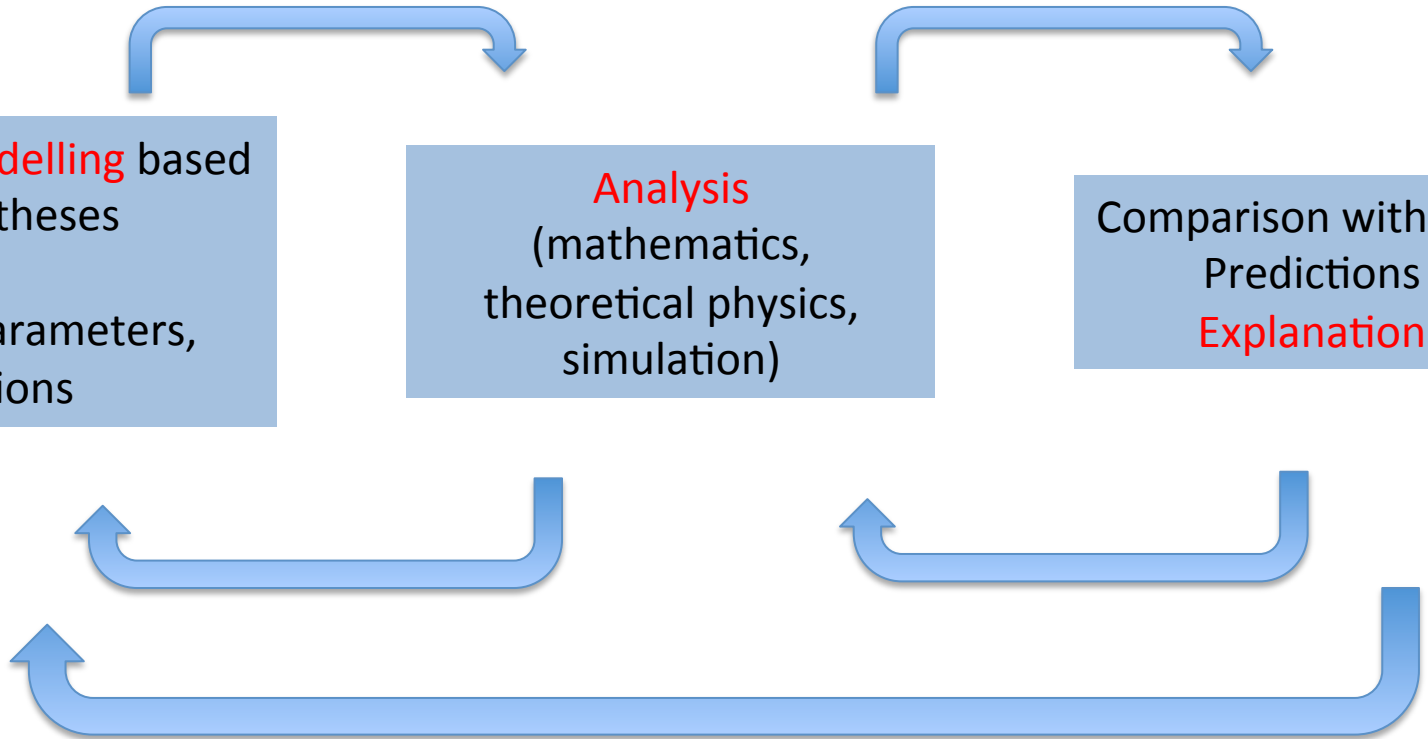
Comparison with data
Predictions
Explanation

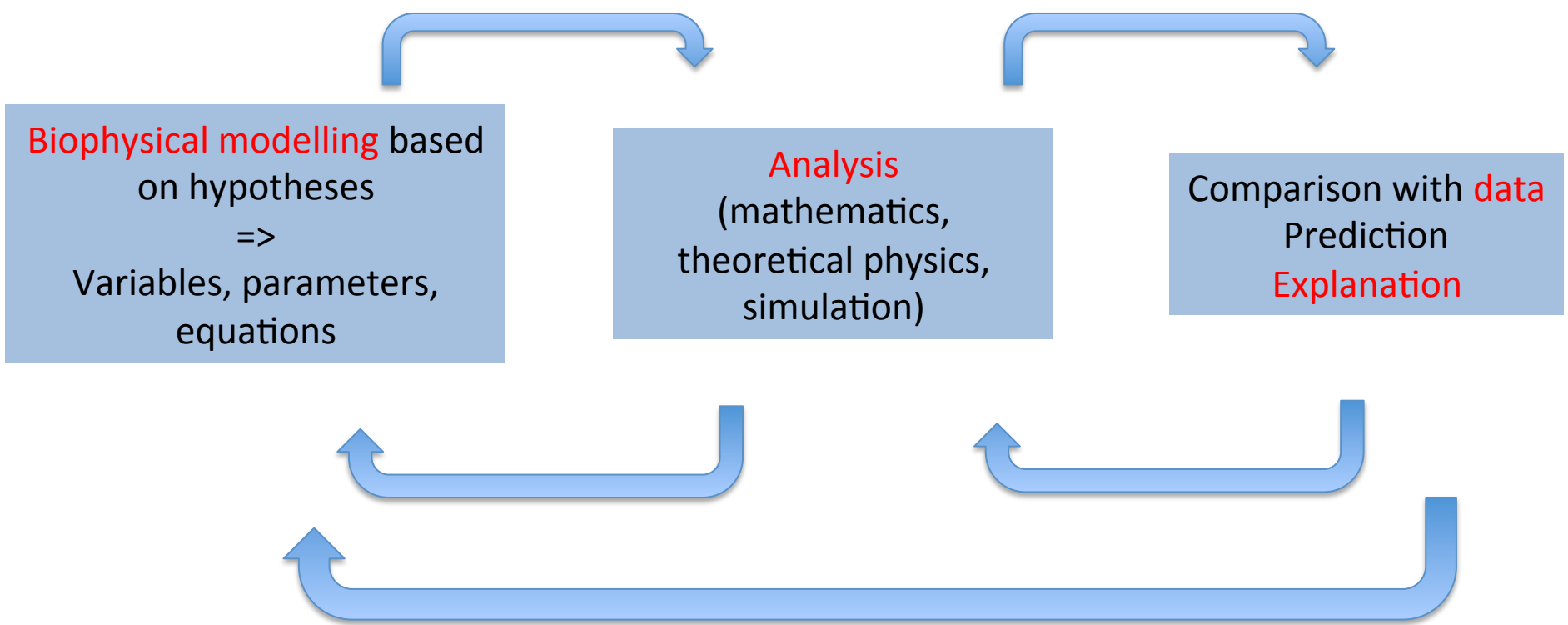


Biophysical modelling based
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(mathematics,
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```
graph LR; A["Biophysical modelling based on hypotheses => Variables, parameters, equations"] --> B["Analysis (mathematics, theoretical physics, simulation)"]; B --> C["Comparison with data Prediction Explanation"]; C --> A; C --> B; C --> D["To predict is not to explain (R. Thom)"];
```

Biophysical modelling based
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Variables, parameters,
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Comparison with data
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To predict is not to explain (R. Thom)

Generic mechanisms, organizing principles

A neurobiologist point of view

A neurobiologist point of view *

* Disclaimer: I think modeling is scientifically useful, not just a way to obtain funding...

What is a model ?

What is a model ?

The best model of a cat is a cat,
possibly the same cat.

Uwe Heinemann
1944-2016



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A perceived feeling of individuality,
possibly linked to **robustness** of biological systems

Biophysical modelling based
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Variables, parameters,
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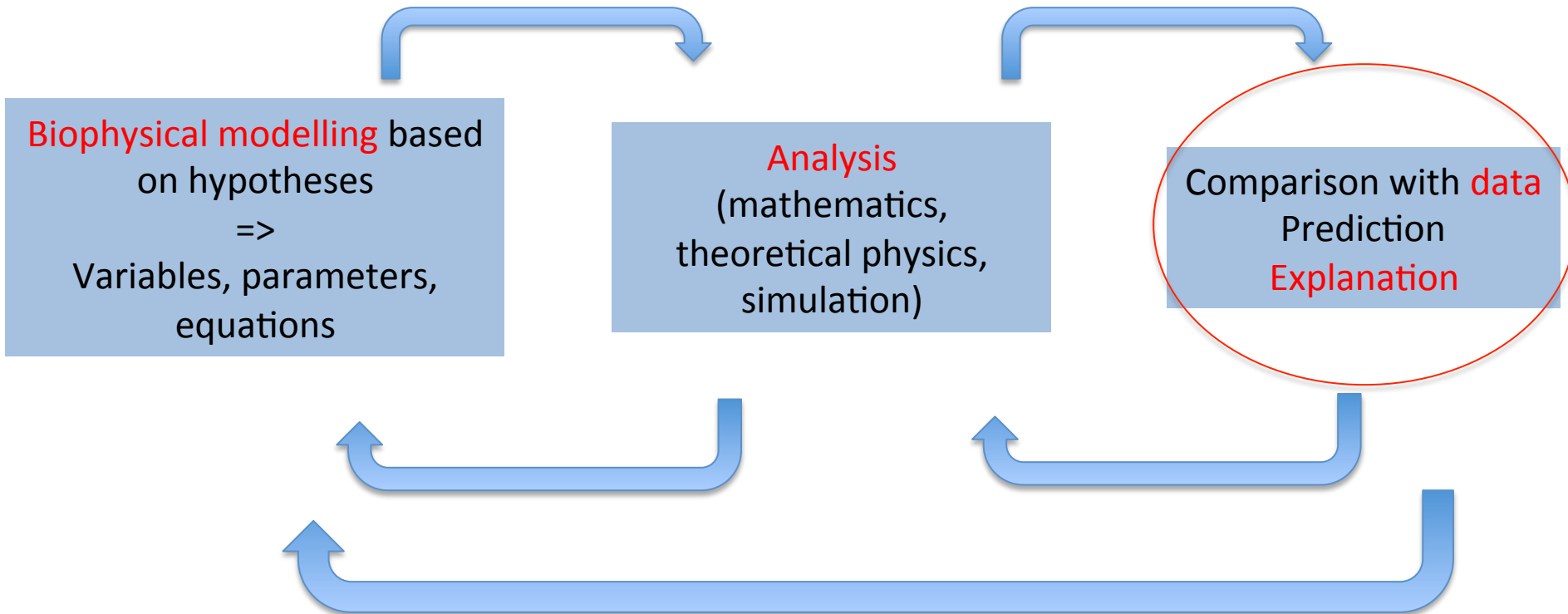
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To predict is not to explain (R. Thom)

Generic mechanisms, organizing principles

Trade off




To predict is not to explain (R. Thom)

Generic mechanisms, organizing principles


Trade off

Parameters and
initial values of variables



Experimentalist

Modeler



Explanations and predictions
(comparison with experimental data)

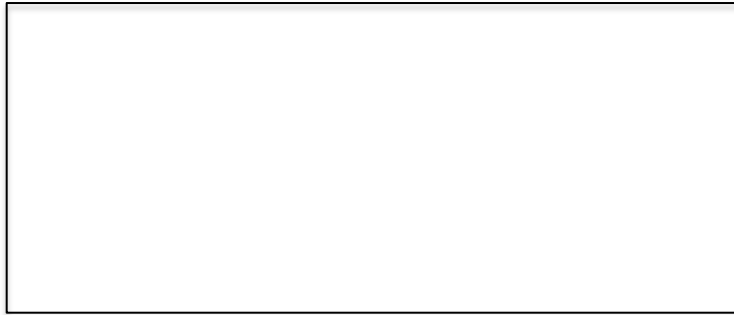
Modeling

Top down



Phenomenological **prediction**.

Explanation: identification of specific features implicated in the observed phenomena.

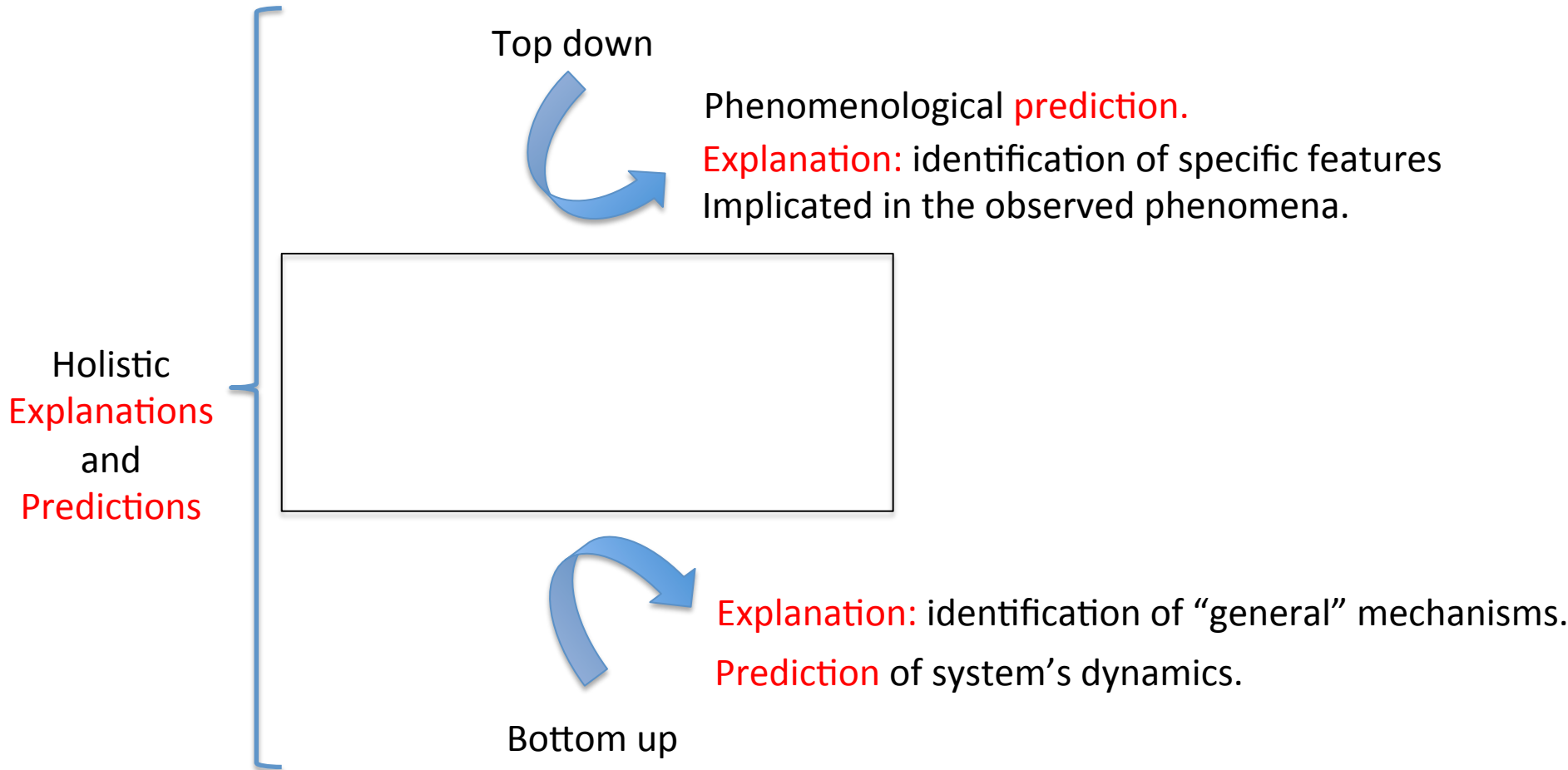


Explanation: identification of “general” mechanisms.

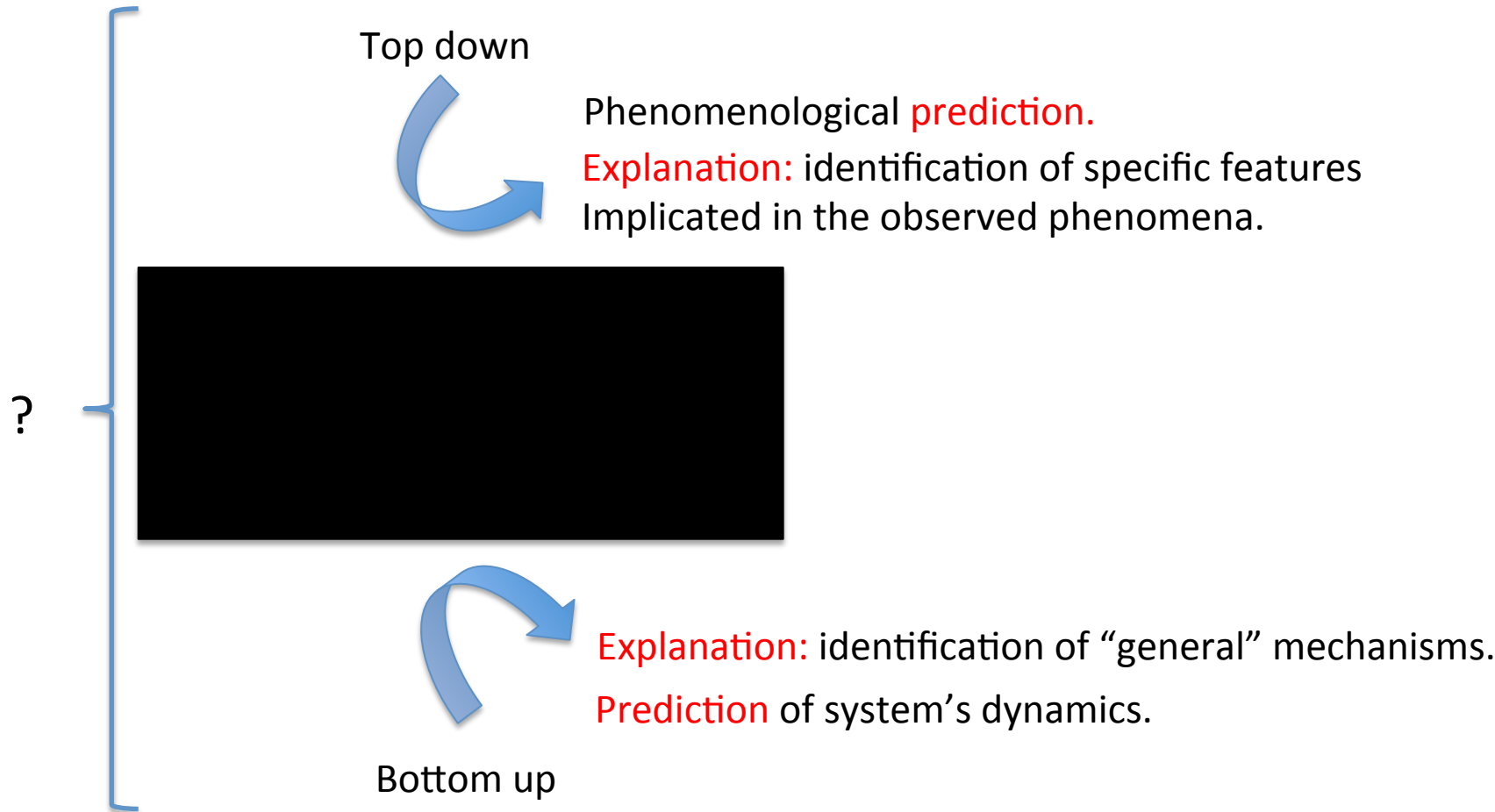
Prediction of system’s dynamics.

Bottom up

Modeling



Modeling





spatial scales



metres
(10^0)



centimetres
(10^{-2})



millimetres
(10^{-3})



micrometres
(10^{-6})



micrometres
(10^{-6})



micrometres
(10^{-6})



nanometres
(10^{-9})



structure

time scales



years
(10^7)



days
(10^2)



hours
(10^1)



minutes
(10^2)



seconds
(10^0)



milliseconds
(10^{-3})



microseconds
(10^{-6})



nanoseconds
(10^{-9})



pico-seconds
(10^{-12})



function

Quantity of
information
(measurements);
how to
implement it

Impossible to measure everything
(robustness is a limit, among others)

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(robustness is a limit, among others)

Very difficult to implement models of complex systems and fit them to biological data
(at every single level, even more with interconnected levels)

A personal experience

A personal experience

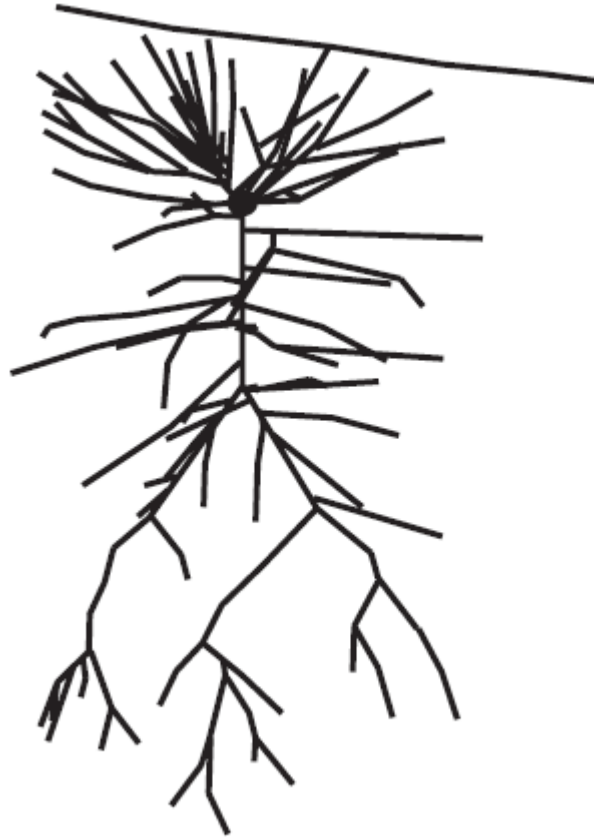
(of a poor neurobiologist)

Functional effect of human pathogenic mutations of voltage-gated sodium channels

Functional effect of human pathogenic mutations of voltage-gated sodium channels

Realistic computer model of a neuron

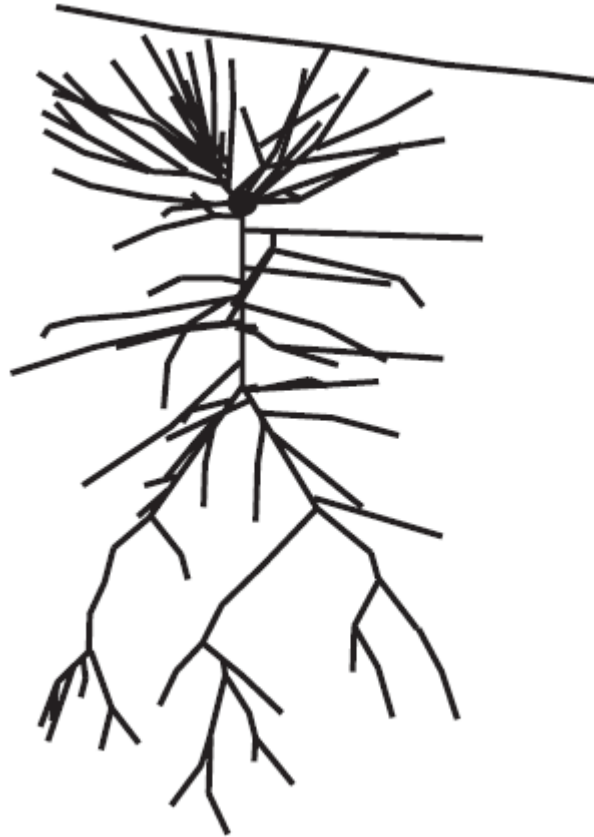
(morphology, type and subcellular distribution of conductances).



Functional effect of human pathogenic mutations of voltage-gated sodium channels

Realistic computer model of a neuron

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Slow, cumbersome to implement modifications, sometime difficult interpretation of results

Extremely simplified computer model of a neuronal axon initial segment



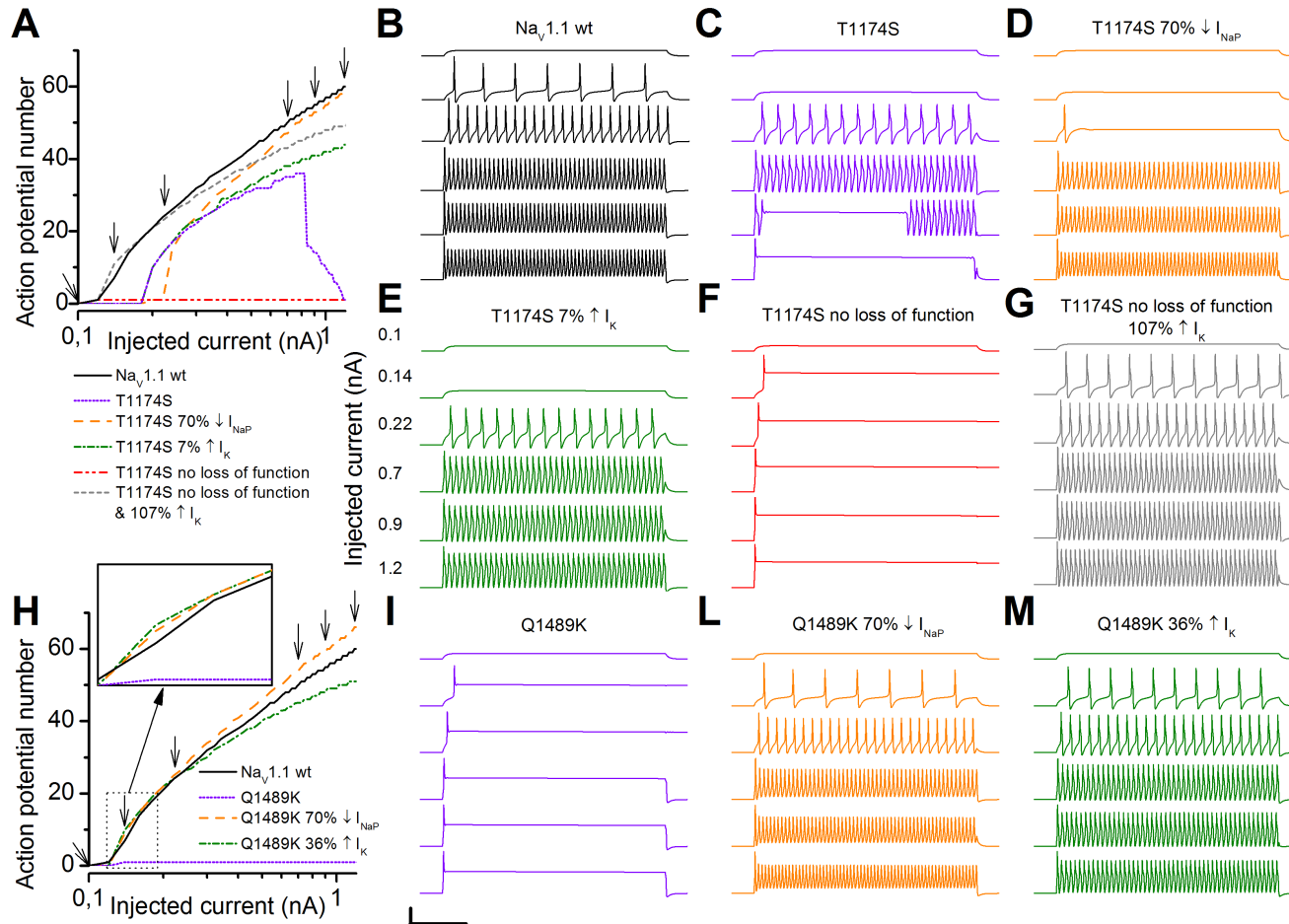
Hodgkin & Huxley formalism

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Extremely simplified computer model of a neuronal axon initial segment



Hodgkin & Huxley formalism



Cestele et al 2013 PNAS
 Cestele et al 2013 Epilepsia
 Cestele et al 2015 Neurobiology Disease

Robustness

Robustness

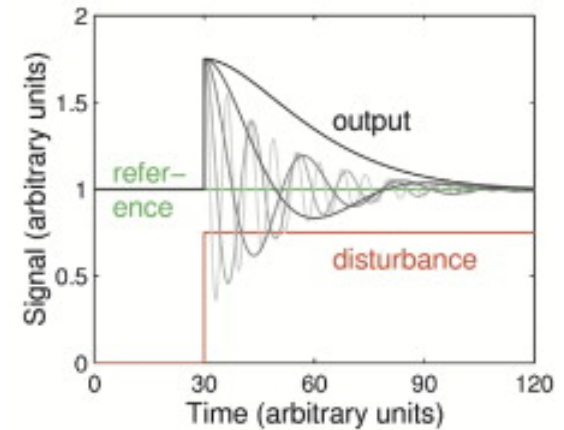
The engineering definition

the persistence of a system's characteristic behavior under perturbations or conditions of uncertainty.

Robustness

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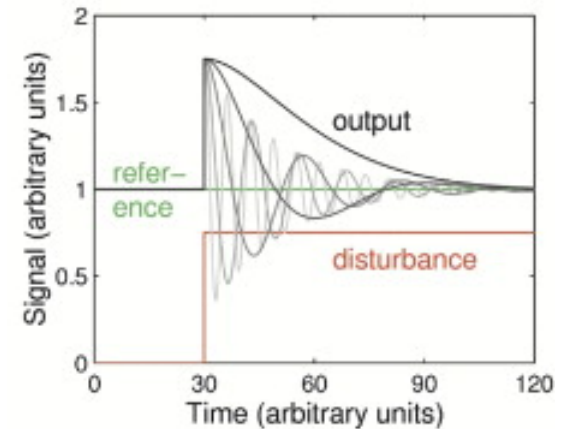


Redundancy, Modularity and Feedback controls

Robustness

The engineering definition

the persistence of a system's characteristic behavior under perturbations or conditions of uncertainty.



Redundancy, Modularity and Feedback controls

Biological robustness

Degeneracy

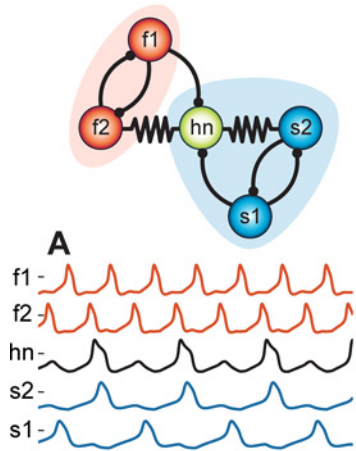
Structurally different entities perform overlapping functions.

They can act in different combinations of type of entity and “strength” of each entity.



G. Edelman, J. Gally Degeneracy and complexity in biological systems PNAS 2001

Robustness and Degeneracy in the stomatogastric neuronal network of the crab

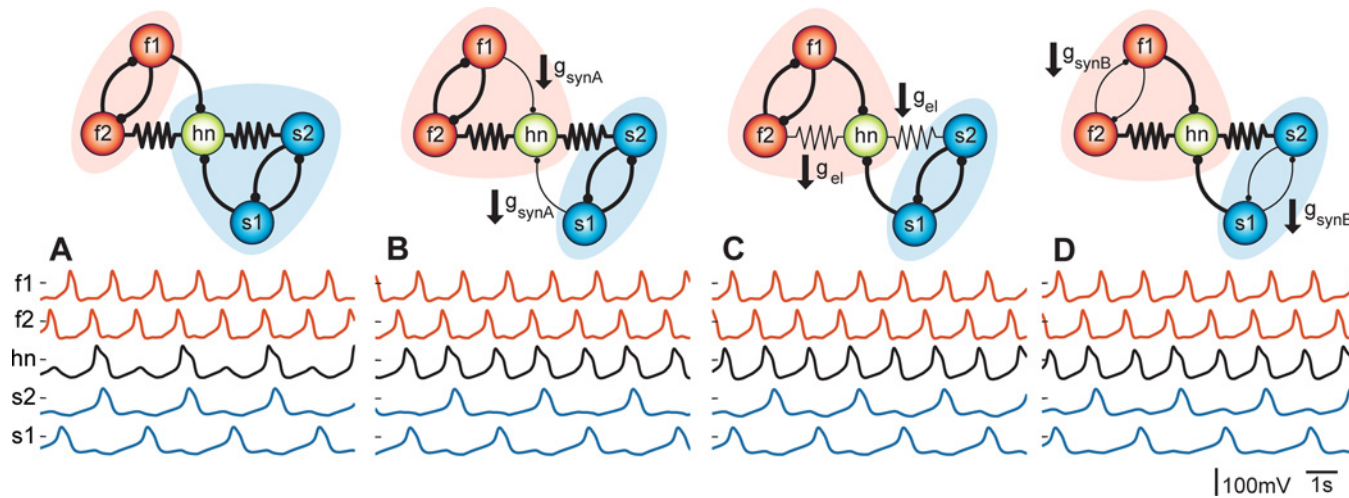


Marder et al. 2016 Curr Op Neurobiol



Eve Marder

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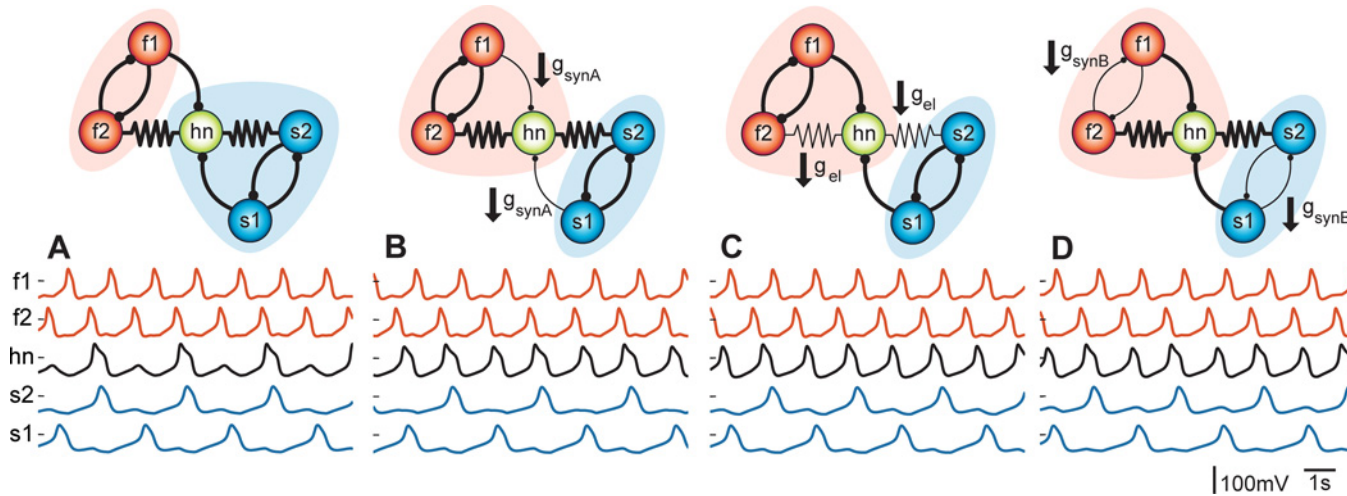


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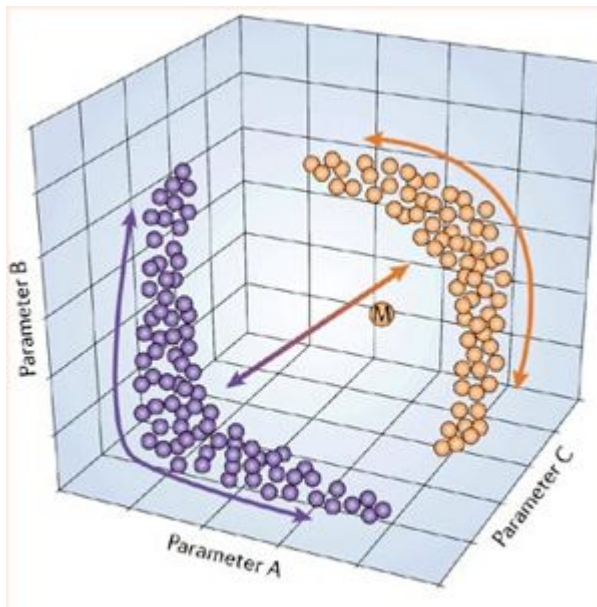
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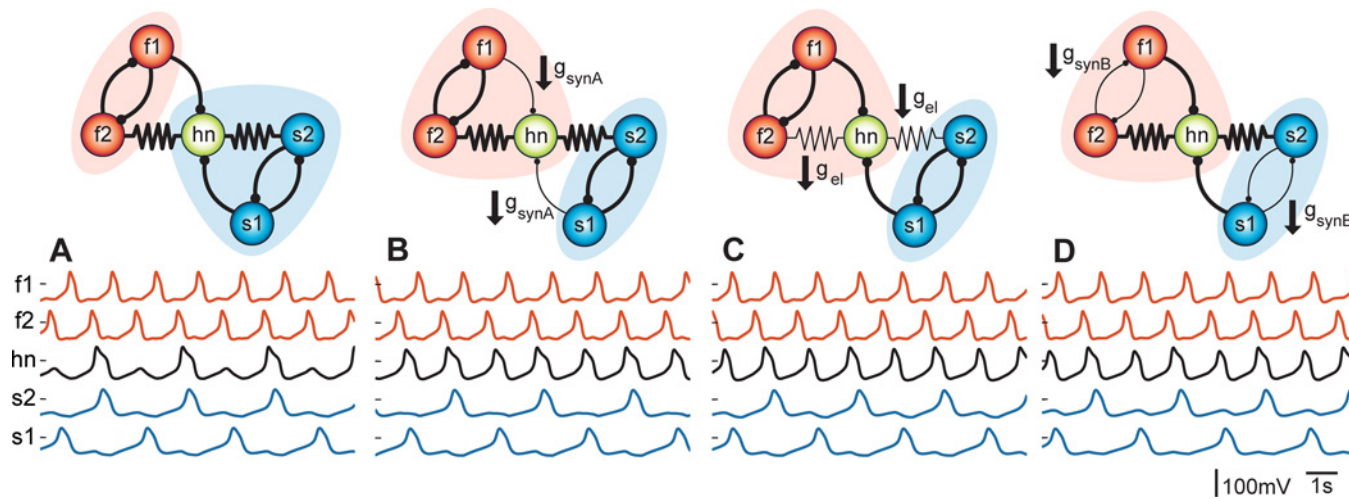


Eve Marder



Marder & Goaillard 2006 Nature Neurosci

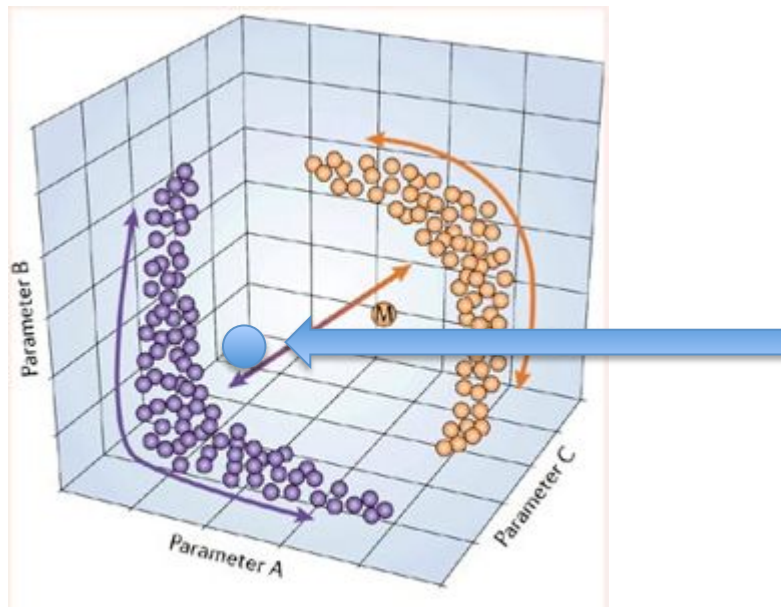
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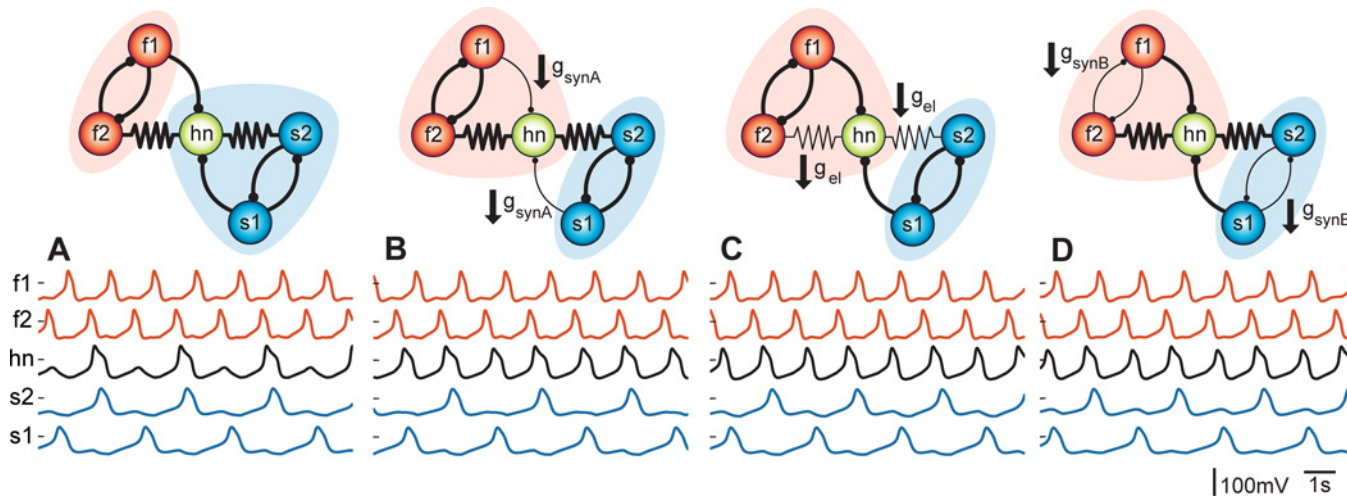
Eve Marder



The commonly used averages identify a combination of values that does not exist!

Marder & Goaillard 2006 Nature Neurosci

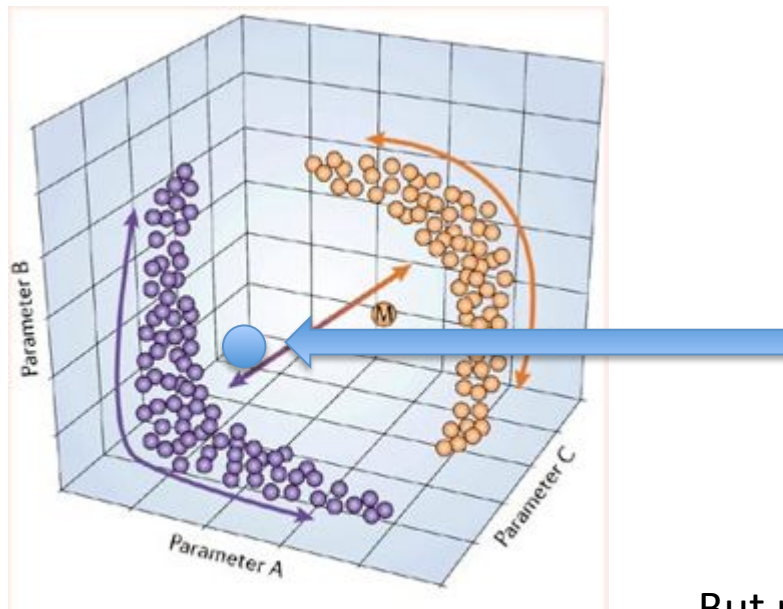
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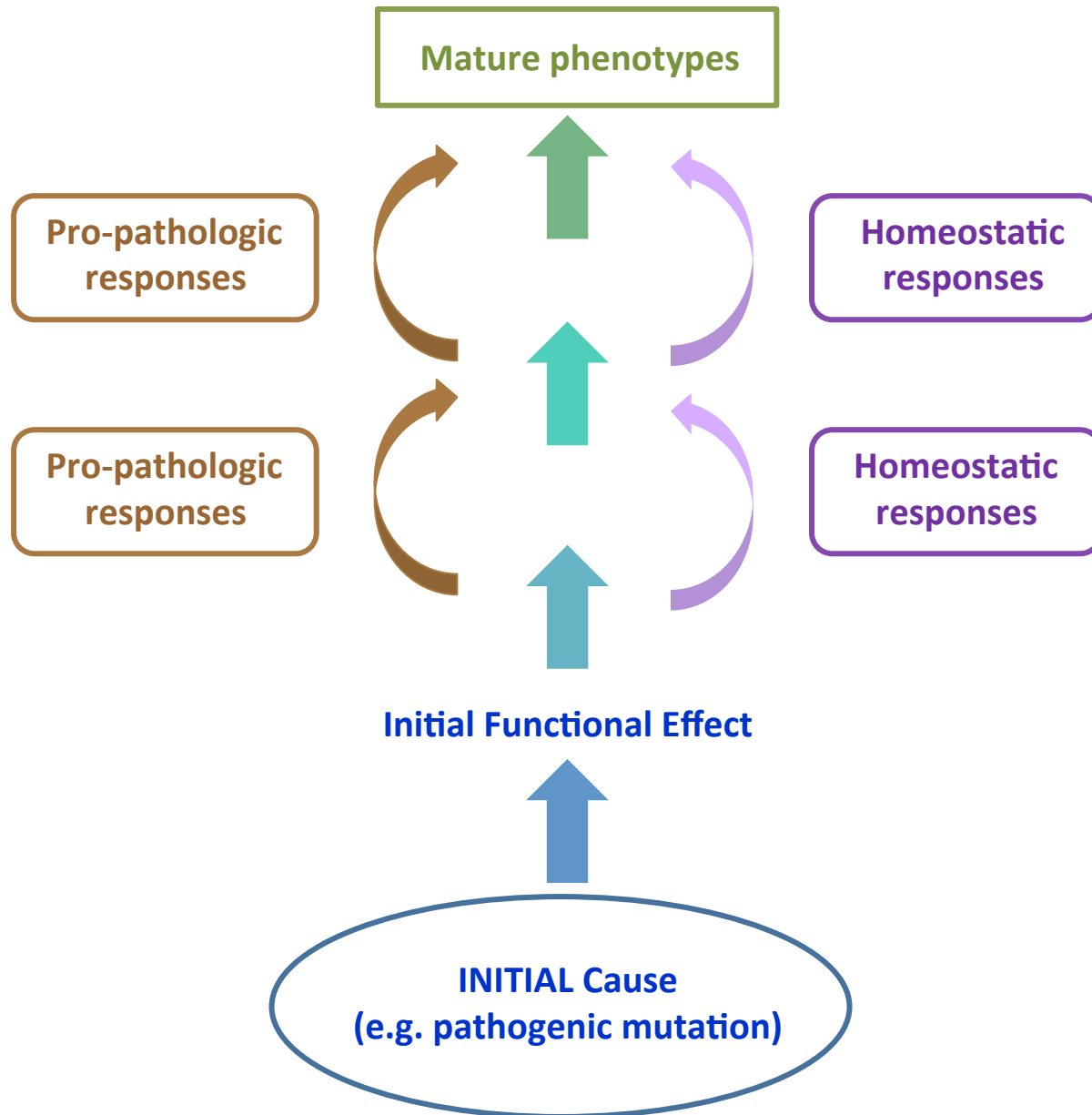
Eve Marder

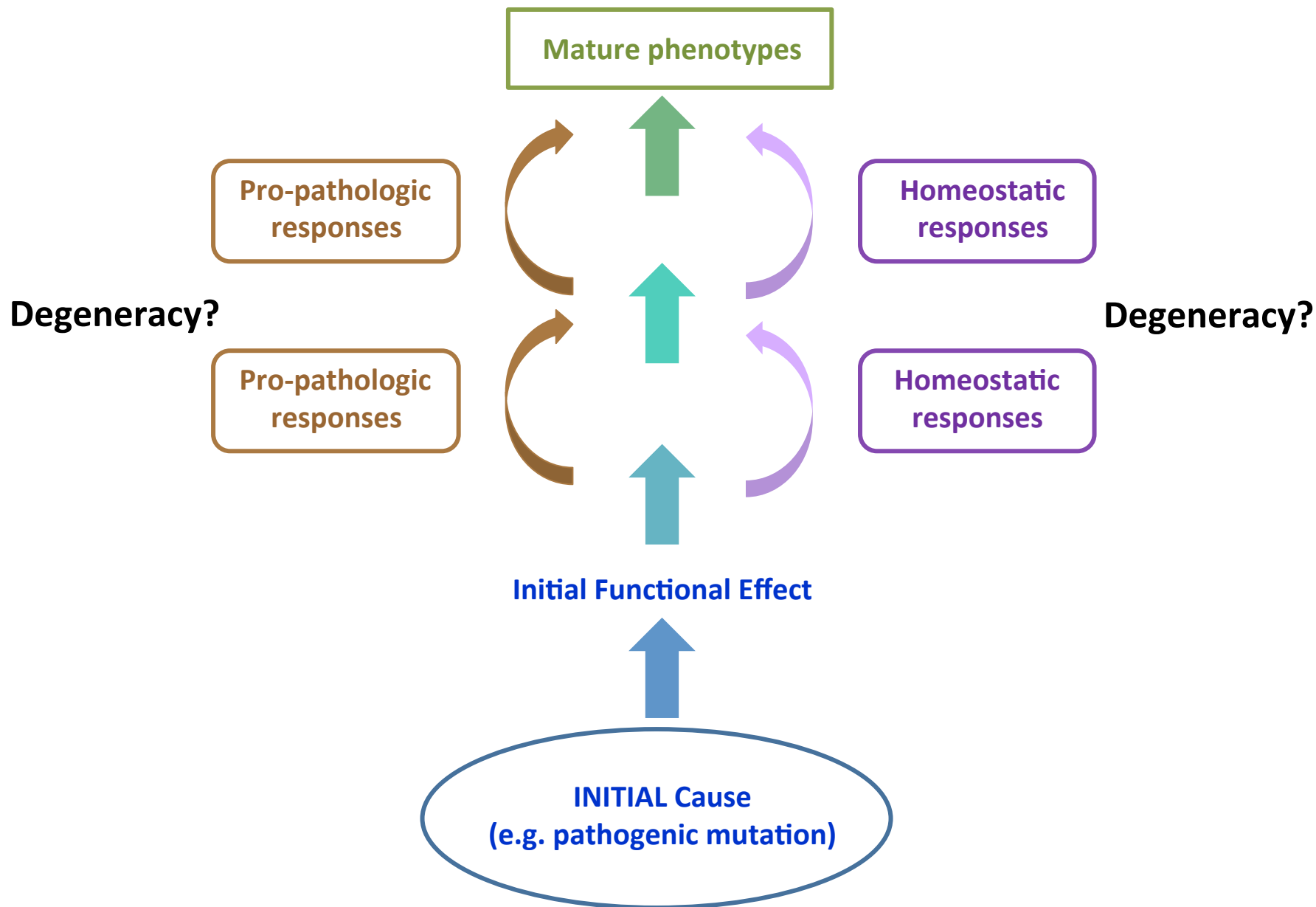


The commonly used averages identify a combination of values that does not exist!

But normally we obtain and provide mean values....

Marder & Goaillard 2006 Nature Neurosci





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absolutely
unique. Just like
everyone else.

– *Margaret Mead*



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