Chemistry Needs to be an Exact Science

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See ASBMB Today 13:36-38; http://arxiv.org/abs/1409.0243Colloquium

DOI 10.13140RG.2.2.18251.86564

Many thanks to David Minh
For this invitation and kindness through many years


Desolation Canyon
Utah
What is different at home?


Sod House
USA ~1850
What is different today?

Construction,
Plumbing,
Electricity,
Air Conditioning are Different

Each is described by an Exact Science

Exact Science Predicts Behaviors withOUT adjustable parameters
So engineers can make devices with predictable properties

Exact Sciences
describe only a tiny part of life,

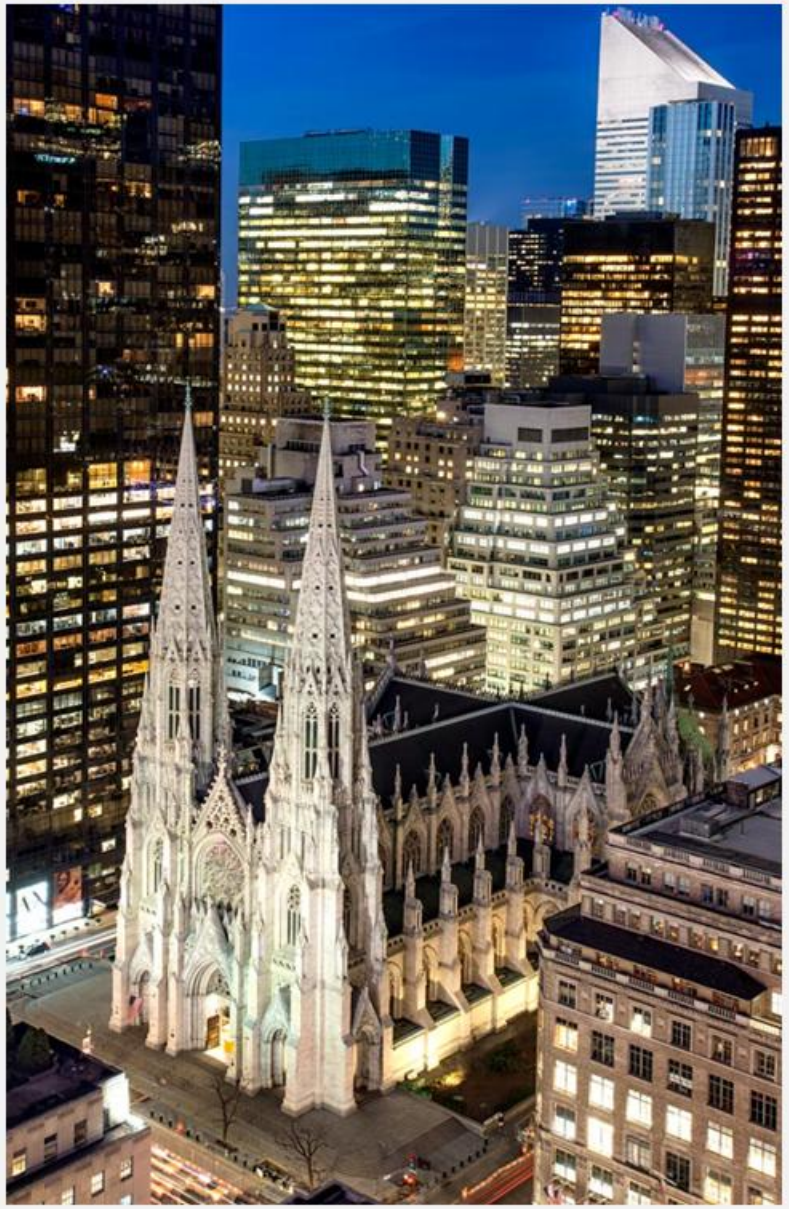
But

Exact Sciences Create

our

Standard of Living

**e.g., electricity, computers, fluid dynamics, optics, structural mechanics, ….*



St. Patrick’s New York

Trinity New York

Cathedrals over ~ 6 stories fell down!!!

King's
Cambridge UK

Hurricane Straps

Stop Roofs from Flying Off

Cost ~US$ 1

Hurricane Straps are Computed!!!

ABSTRACT

Chemistry Needs to be an Exact Science

See ASBMB Today 13:36-38; http://arxiv.org/abs/1409.0243

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September 9, 2025

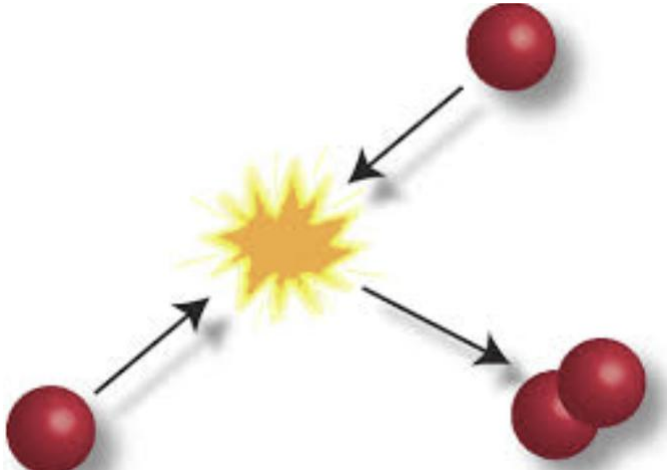
Our modern life is possible because its **devices do what they are supposed to** on a macroscopic scale in a range of conditions. Engineers design devices using exact sciences that do not adjust parameters. **Exact science deals with a range of conditions without adjusting parameters.** Exact science supports transferrable models and theories: devices work in a variety of real world conditions.

Chemical sciences often change parameters as conditions change. Chemical models are often not transferrable. Simulations of molecular dynamics rarely predict macroscopic behavior in a range of solutions.

Chemistry will be more useful when its models are transferrable.

Traditional Chemical Models

depend historically and logically on



The Law of Mass Action

Law of Mass Action at Equilibrium

$$A \underset{}{\overset{K_{eq}}{\rightleftharpoons}} B$$

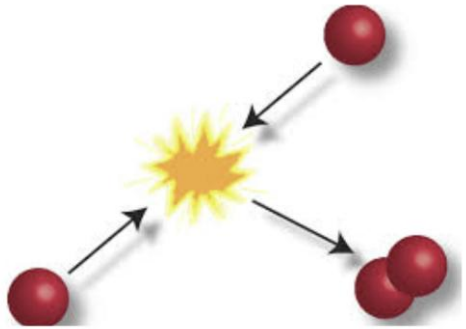
$$J_{A\to B} = k_f[A] = J_{B\to A} = k_b[B]$$

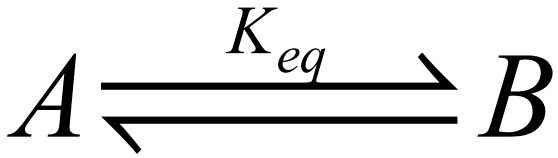
$$\frac{[B]}{[A]} = \frac{k_f}{k_b} = K_{eq}$$

Everything is hidden

in K_{eq}, k_f and k_b

$$A \underset{}{\overset{K_{eq}}{\rightleftharpoons}} B$$





Everything is hidden

Where are the salts?

Where are the buffers?

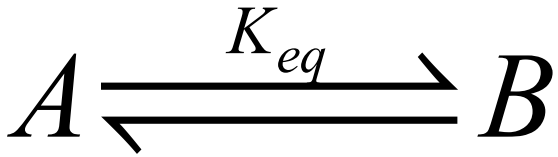
Everything is hidden in rate constants

In real experiments

Rate constants depend on concentration and type of salts

Results in NaCl ≠ Results in KCl

Results in 100 mM ≠ Results in 200 mM`



Where is the chemistry?

Where is the physics?

Where is the friction?

Where is the electric charge on the ions or the protein?

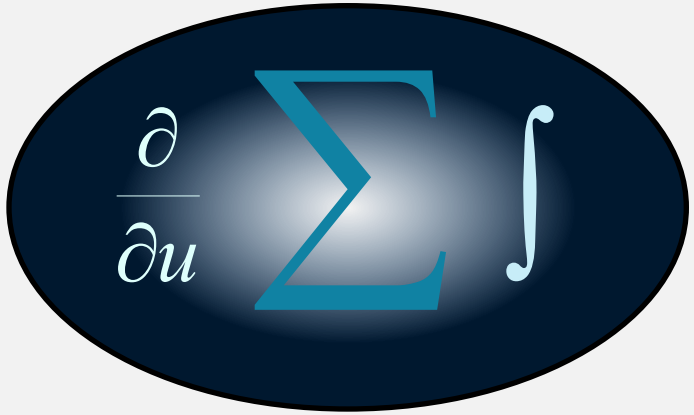
Where is the volume of the ions?

What has to be unhidden?

Friction
(diffusion coefficient)

Electricity: **Charge,Current, Potential**

Volume of Particles



Exact Sciences are Different
EVERYTHING IS EXPLICIT

Nothing is hidden

Otherwise devices will not work

Electricity is the Most Exact Science

Computers, Phones, Power Everywhere ⟸ **Maxwell Equations**
Electricity

Maxwell Equations are True within Protons

Between Earth and Sun and Stars

and (probably)

Between Galaxies

on all time scales that have been measured

Much faster than Electron Orbital Changes in Chemisry

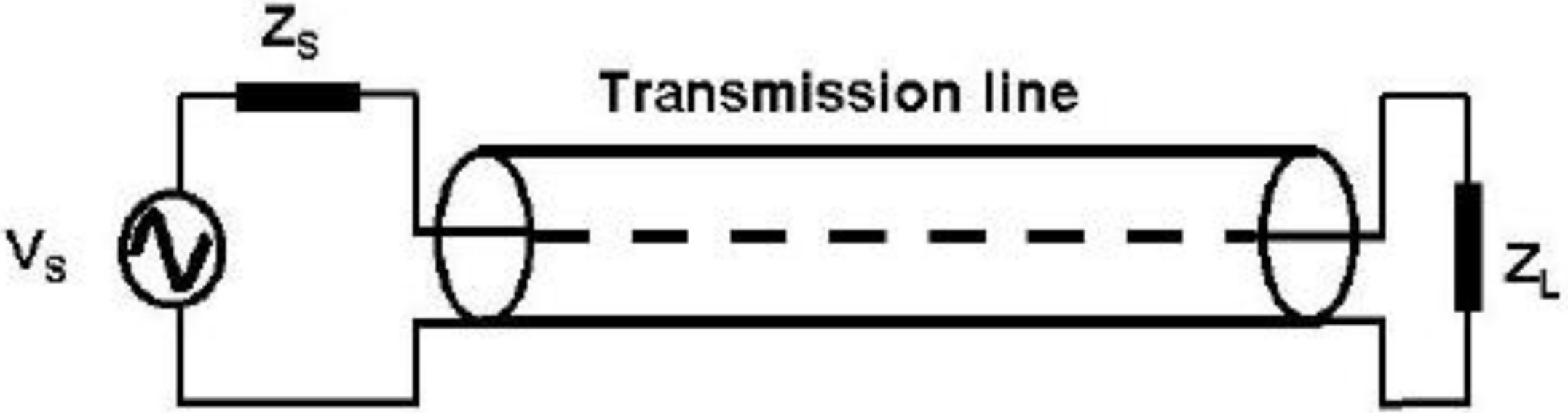
Electrical Technology is Based on Signals
and
Devices that Change Signals

What is a signal?

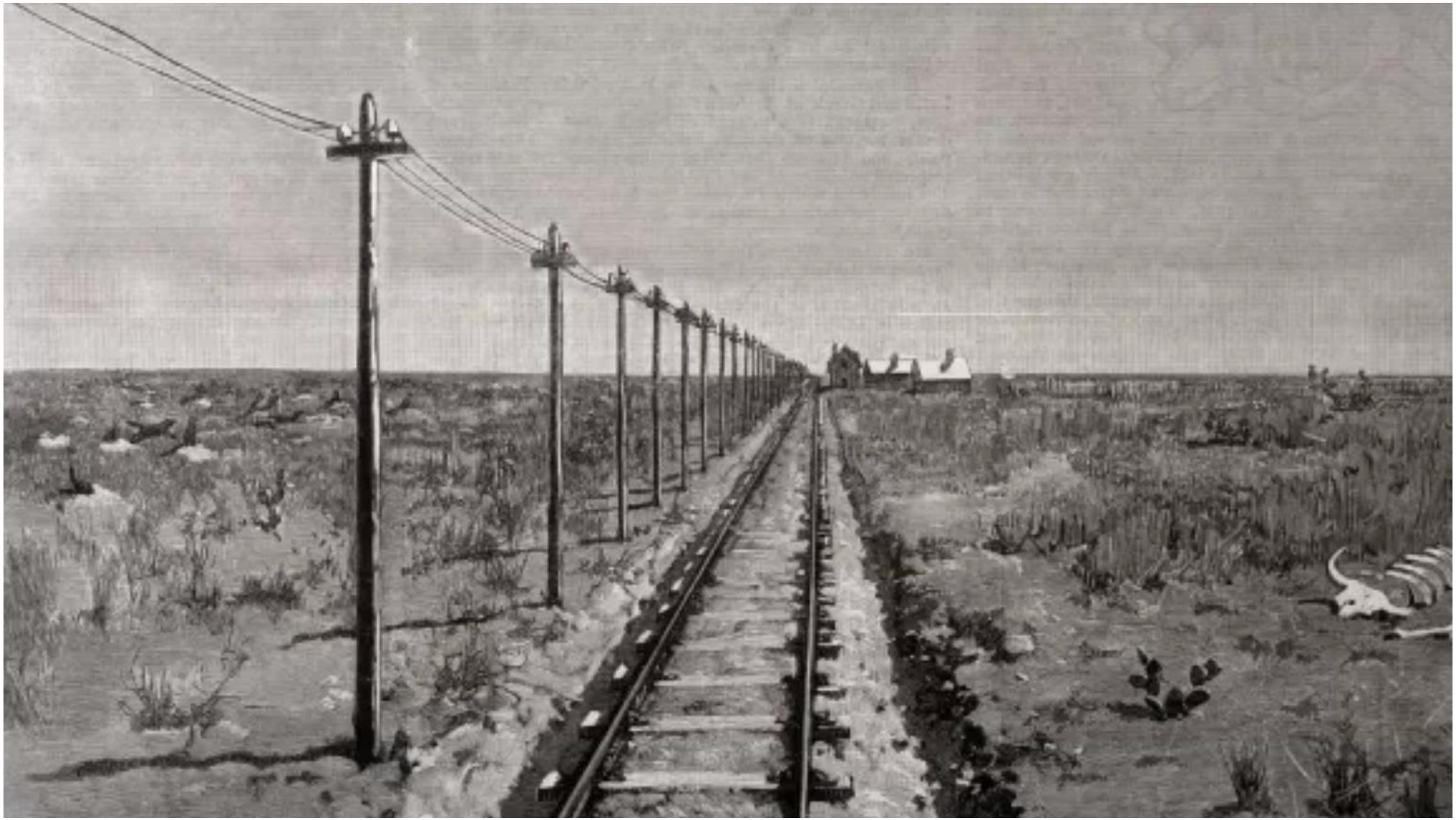
What is a signal ?

V(t) at location 1 → **V(t) at location 2**

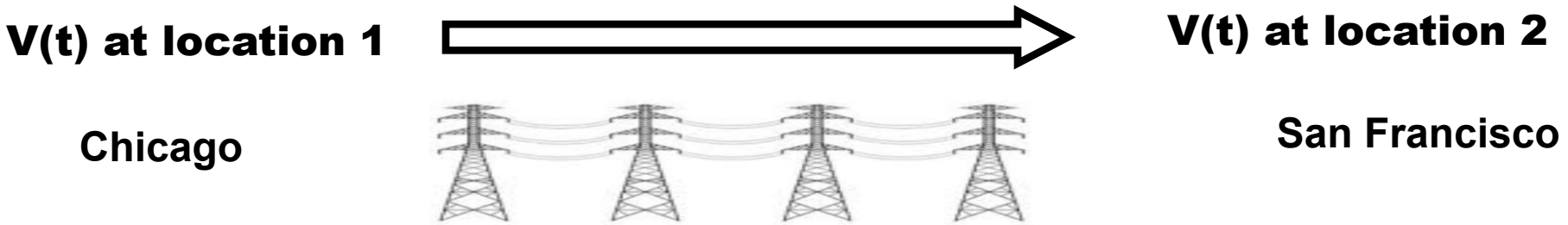
Chicago — **San Francisco**

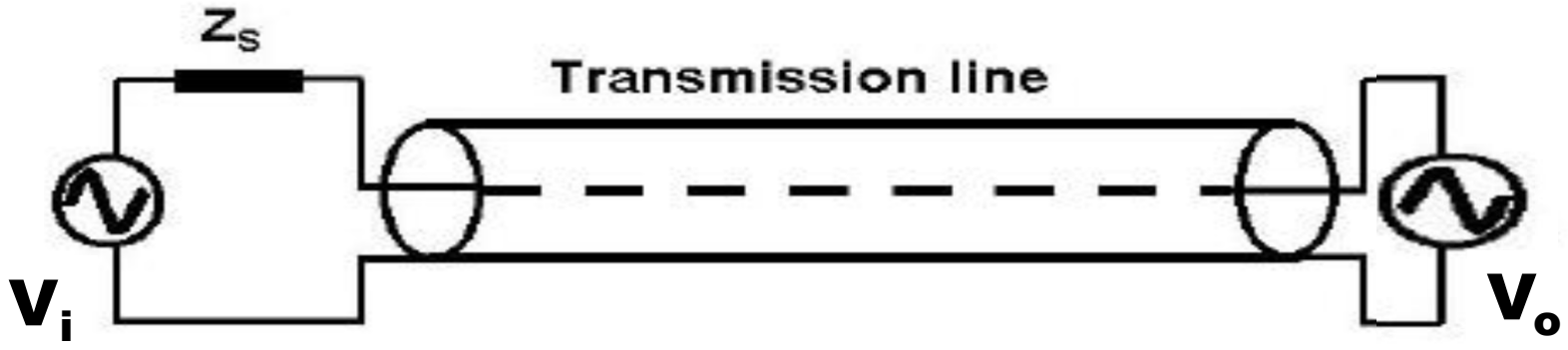


One Dimensional Telegraph Circuits in American West around 1850

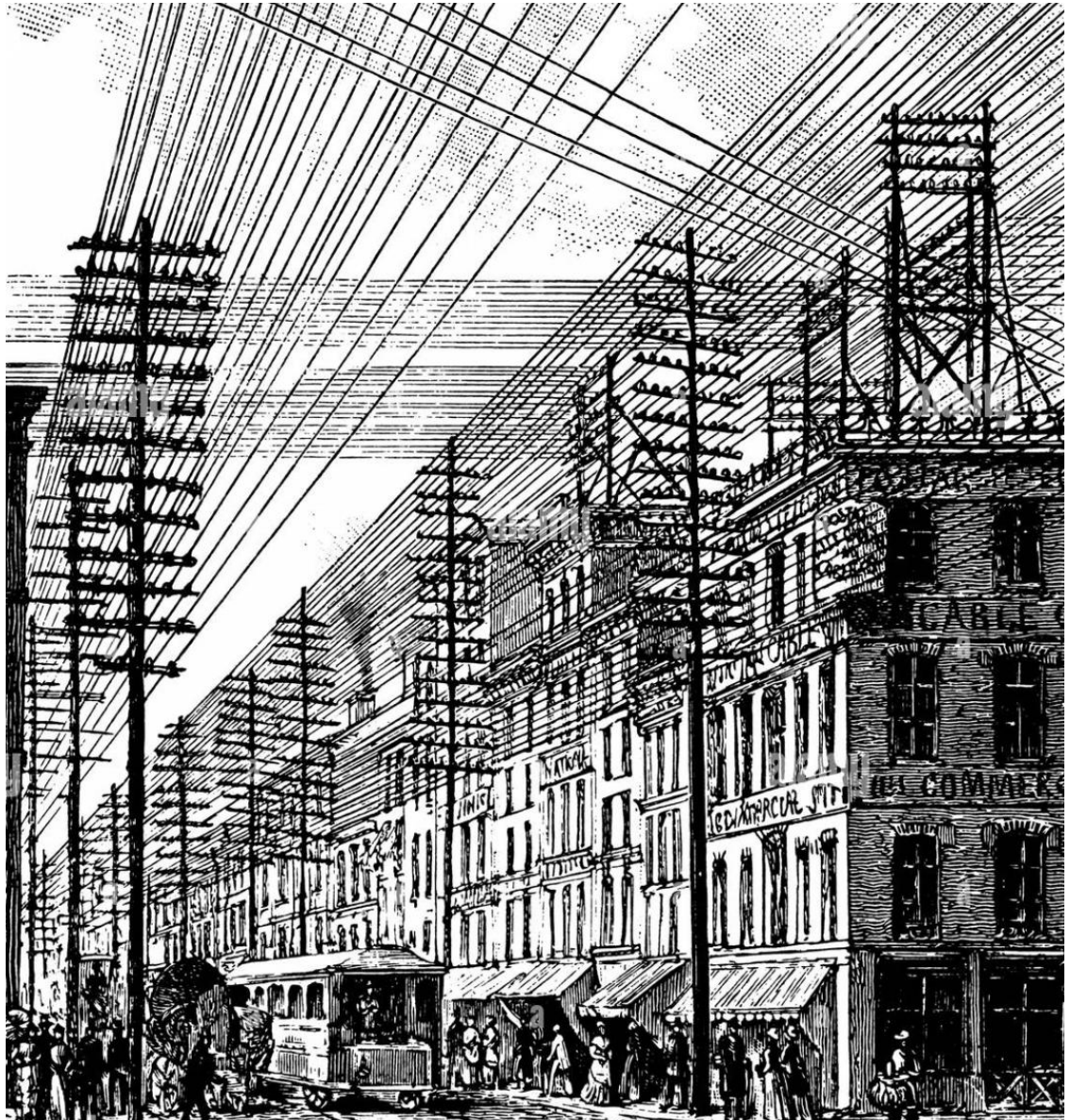


Signals are PERFECTLY Correlated



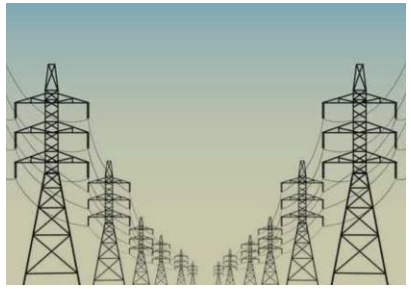


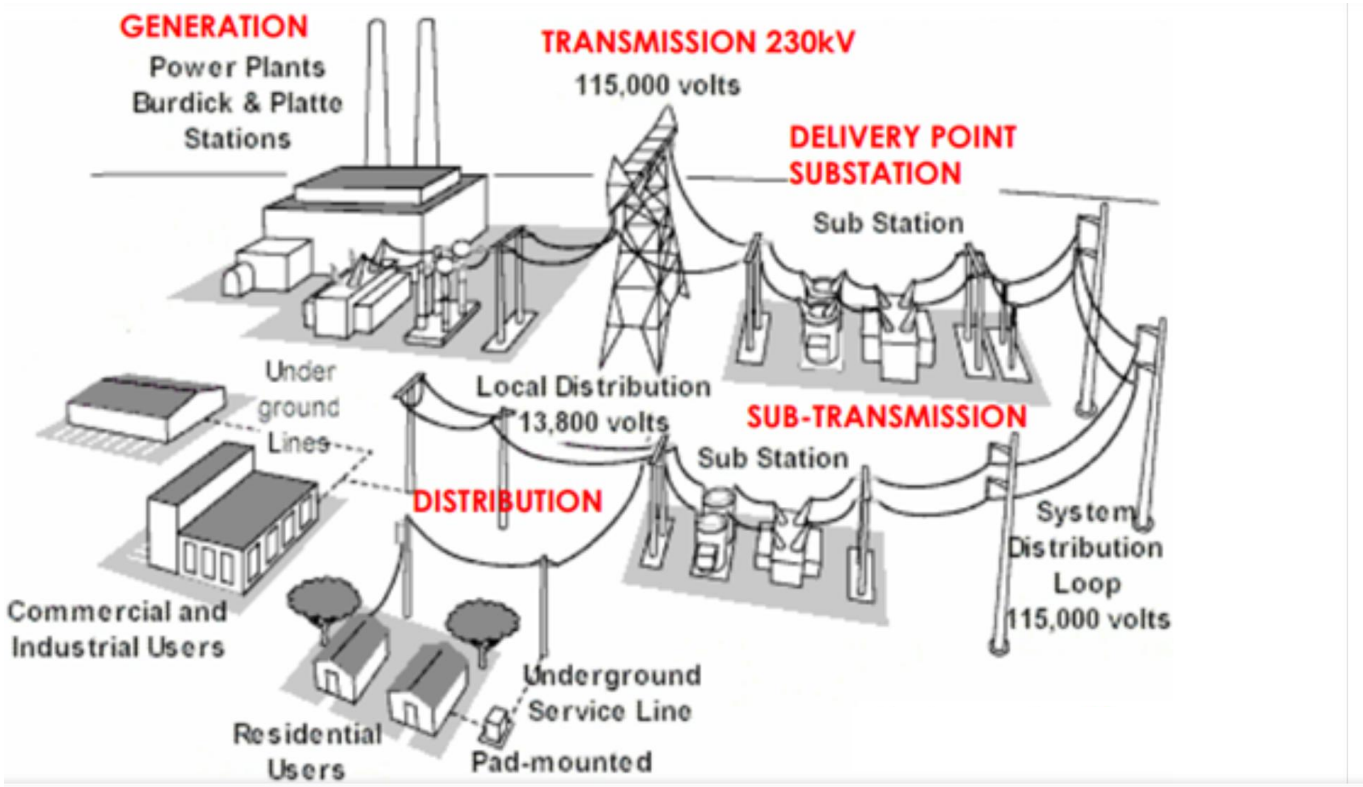
Telegraph and Telephone Wires Philadelphia 1890



Circuits Power Everything

as branched one dimensional systems



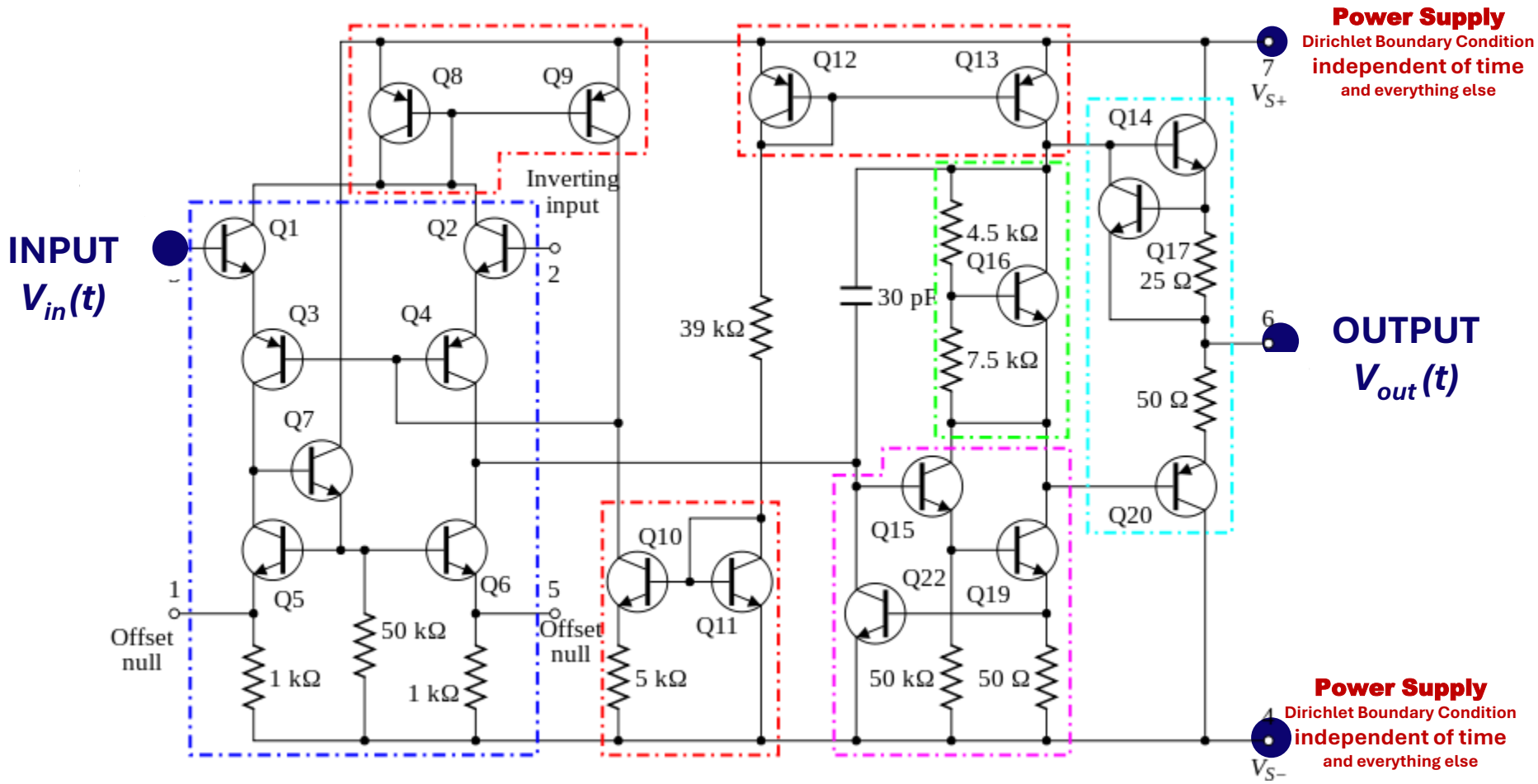


Circuits Power our Homes and Offices

Device converts Input to Output **by a simple 'law'**

Circuits Form Devices

Circuit Diagram of common 741 op-amp: Twenty transistors needed to make linear robust device

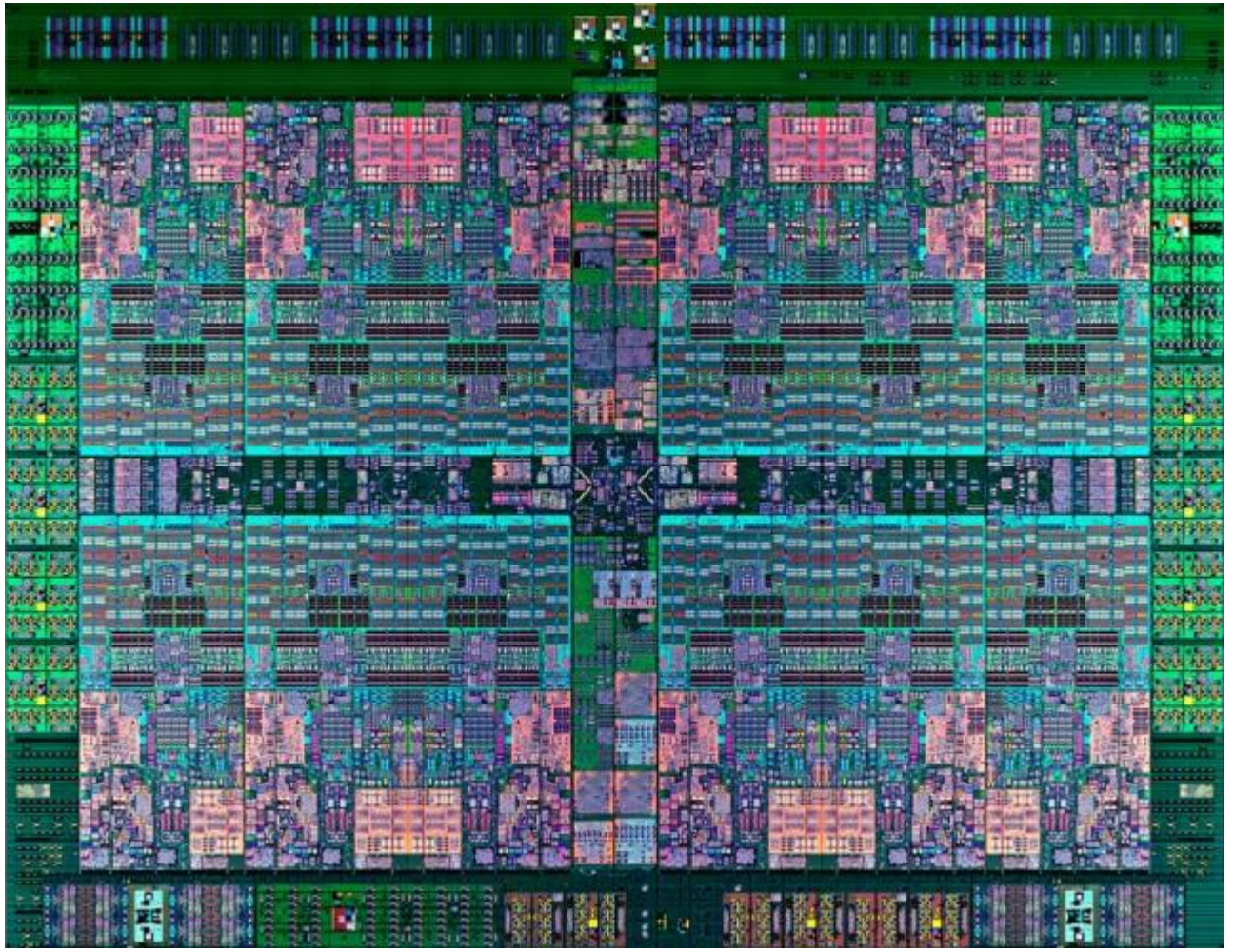


Dotted lines outline: current mirrors (red); differential amplifiers (blue);
class A gain stage (magenta); voltage level shifter (green); output stage (cyan).

Integrated Circuit

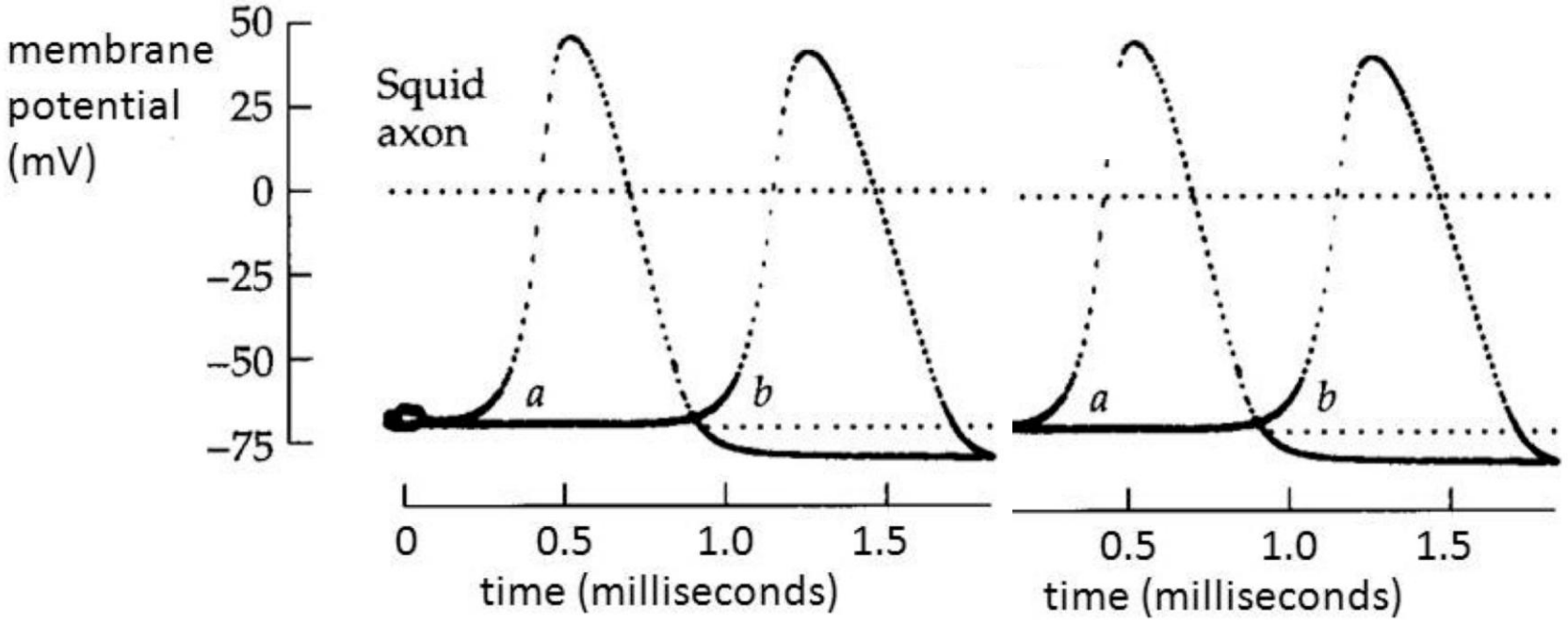
Technology as of ~2014

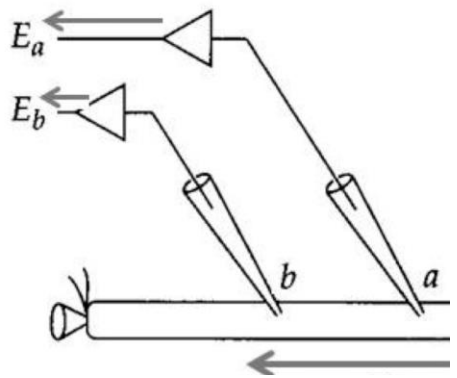
IBM Power8



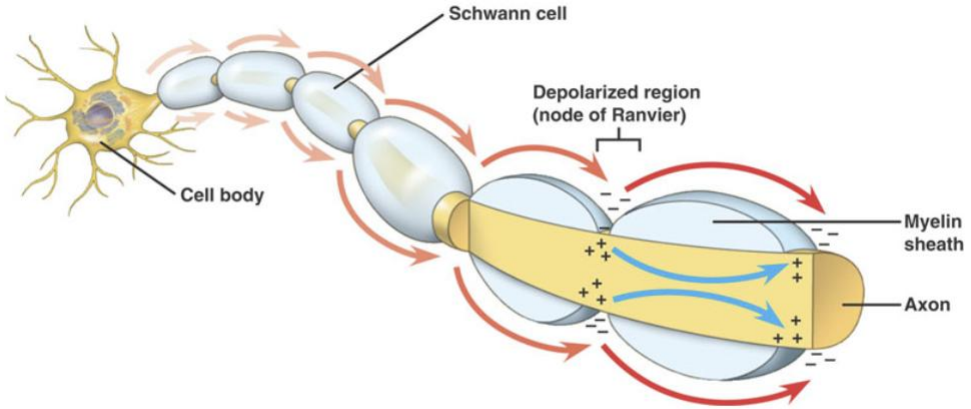
Too many branches to see!

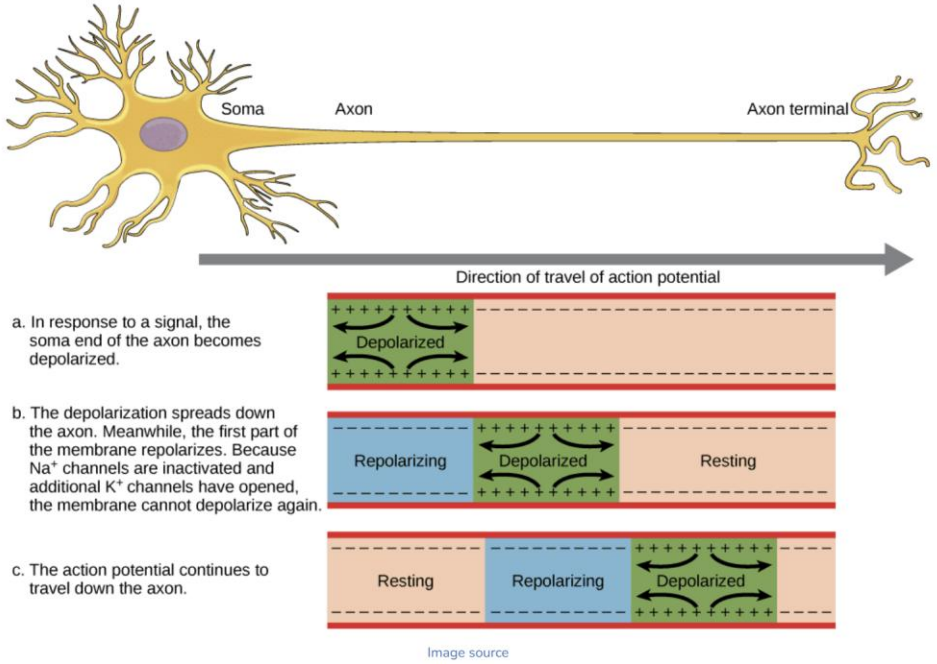
What is a signal in biology?





CIRCUITS IN NERVE SIGNALS
Long Biological Cell





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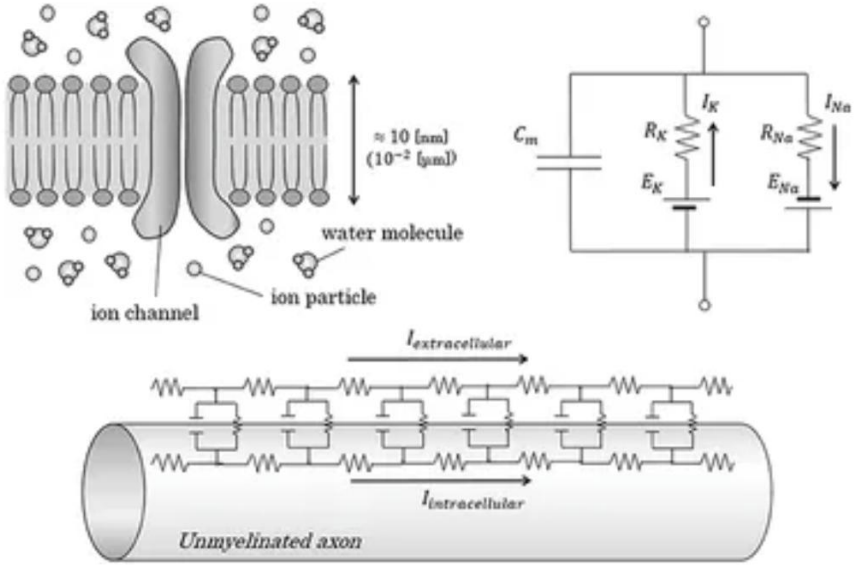
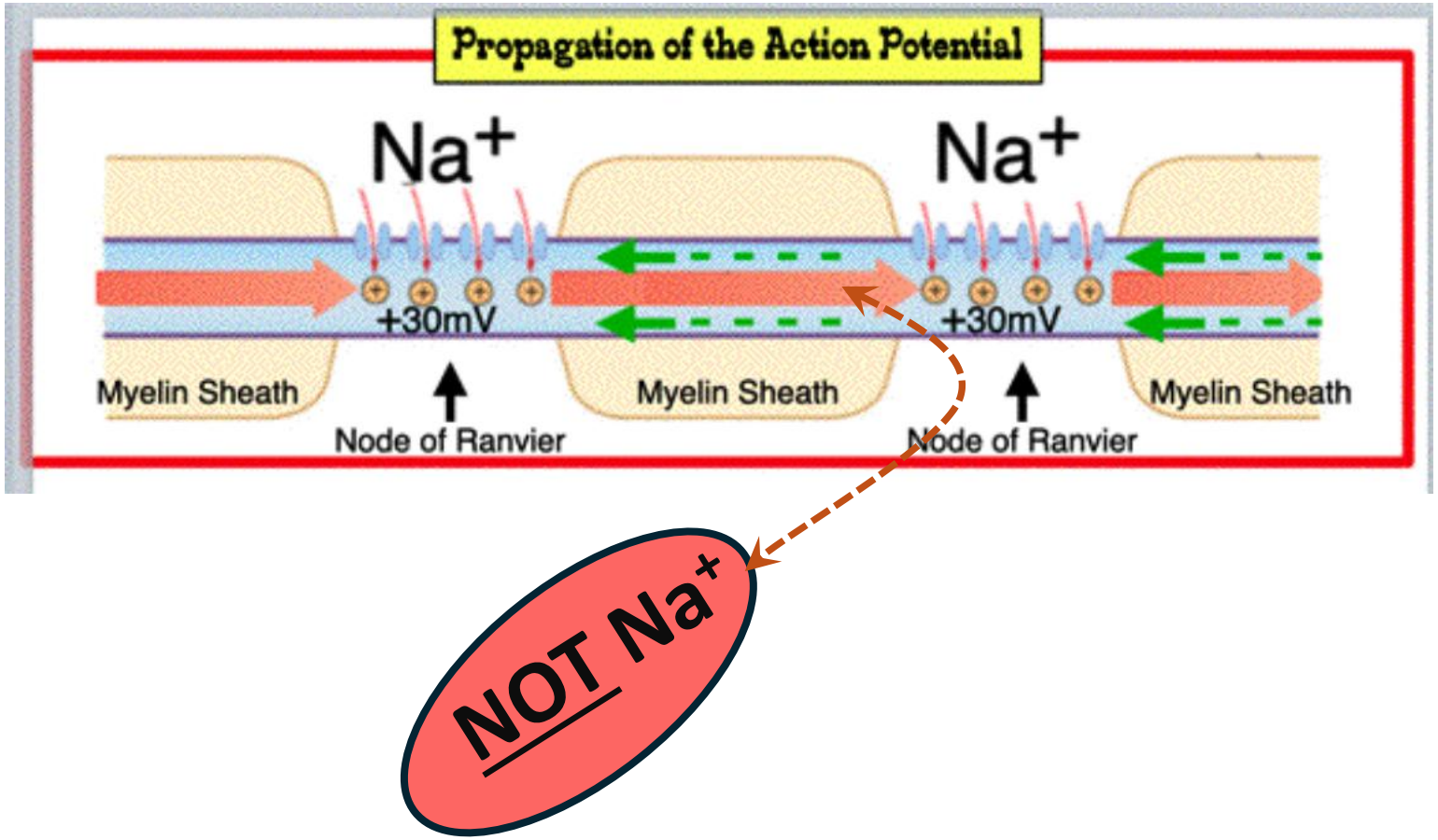
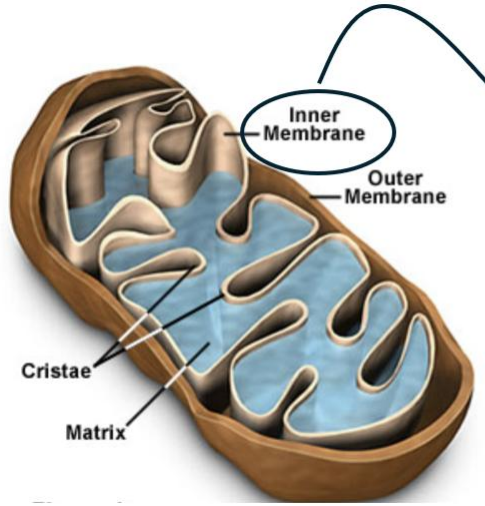
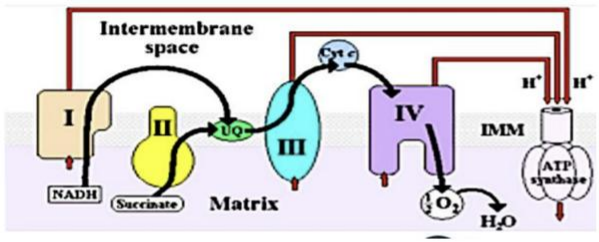


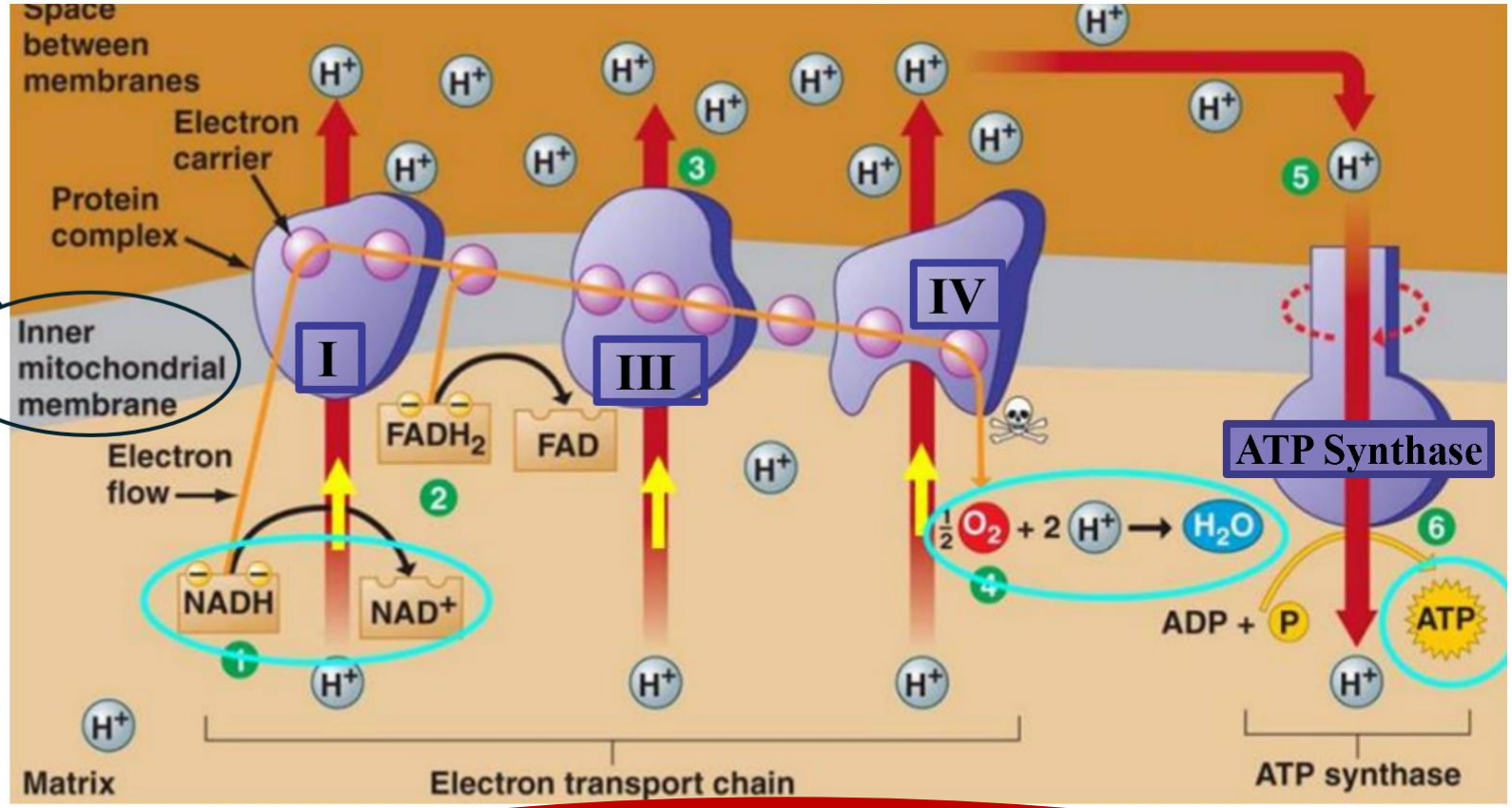
Nerve Signal Propagates Through a Circuit that carries CURRENT not Sodium Ions Na^+



Electron Transport Chain in Mitochondrion is a Circuit





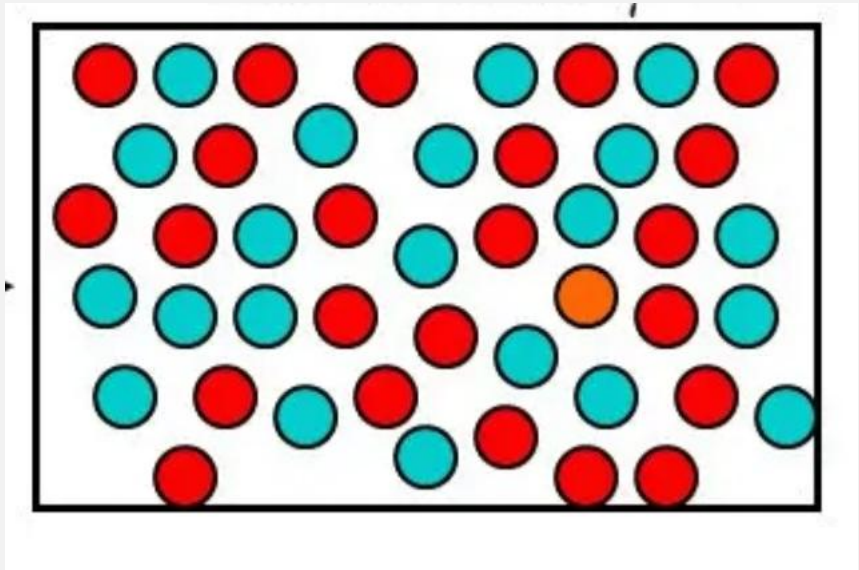


NEW:

Kirchhoff's Law for Total Current $J_{total} = 0$
Couples All Currents and Transporters in Mitochondria
If one current increases, others decrease

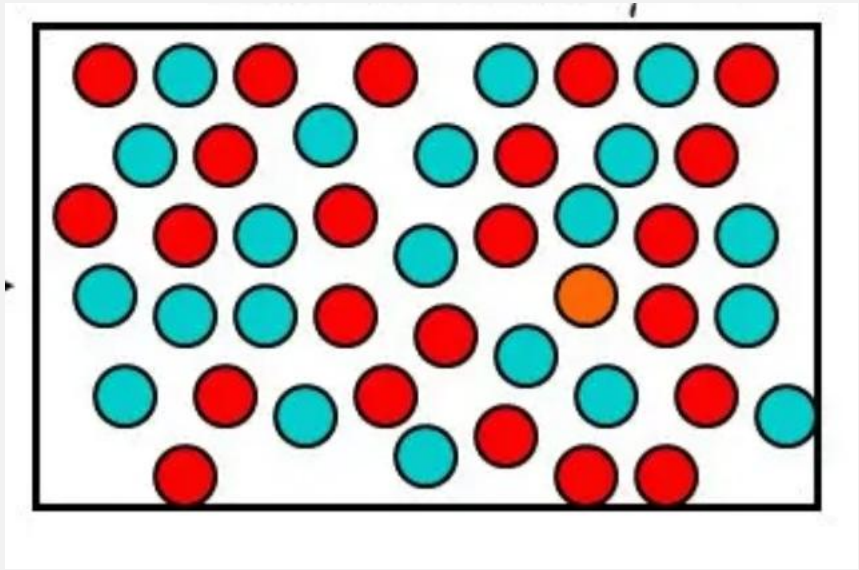
Chemistry used Ideal Gases to define Moles and Molecules

Long Before Physicists Believed Molecules Existed



What is an ideal gas or solution?

Ideal Solutions are Like Ideal Gases, UNcorrelated



Signals are Perfectly Correlated
Ideal Solutions are Uncorrelated

Can a signal exist in an ideal solution?

Why not
Compute all the atoms?

Computational Science Demands a New* Paradigm

The field has reached a threshold at which better organization becomes crucial. New methods of verifying and validating complex codes are mandatory if computational science is to fulfill its promise for science and society.

Douglass E. Post and Lawrence G. Votta Physics Today 58:35

AIChE Journal

Perspective

From discovery to data: What must happen for molecular simulation to become a mainstream chemical engineering tool

Edward J. Maginn

First published: 7 May 2009 Full publication history

DOI: 10.1002/aic.11932 View/save citation

Volume 55, Issue 6
June 2009
Pages 1304–1310

*not so new, really, just unpleasant

Many answers possible

Central Issue

Which answer is right?

Key is

ALWAYS

Large Amount of Data

from

Many Different Conditions

NaCl ≠ KCl

100 mM ≠ 200 mM

Problem Actually Solved for Open Ion Channels

Burger, Eisenberg and Engl (2007) SIAM J Applied Math 67:960-989

Good Data
Thousands of Data Points

NaCl ≠ KCl
100 mM ≠ 200 mM

Good Data > 152,076 Data Points*

Molecular Dynamics ~1 Data Point

* *VC-SEP Tech Univ of Denmark* Sept 2025 *https://www.cere.dtu.dk/expertise/data-for-aqueous-salt-solutions*

Exact Science Uses and Fits **All Data Points**

Many answers possible

Which answer is right?

Key is

Large Amount of Data from **Many Different Conditions**

Otherwise problem is 'ill-posed' and has no answer or even set of answers

Molecular Dynamics

usually yields

ONE data point

at one concentration

MD is not yet well calibrated

(i.e., for activity = free energy per mole)

for ionic mixtures like seawater or biological solutions

NaCl ≠ KCl

100 mM ≠ 200 mM

Chemically Specific Properties

come from

Interactions

with Ions as Well as Proteins

Life occurs in Interacting Solutions

Results in NaCl ≠ Results in KCl

Results in 100 mM ≠ Results in 200 mM`

Force Fields are Calibrated
Ignoring Interactions
among ions themselves

but

Many Chemically Specific Properties
come from
Interactions

Results in NaCl ≠ Results in KCl

Results in 100 mM ≠ Results in 200 mM`

Difficulties for all-atom calculations

Most of biology occurs in mixtures

MD is calibrated in ZERO concentration

MD of mixtures does not exist because calibration fails

MD is designed for zero concentrations of pure monovalents

MD force fields are calibrated in distilled water, using "free energy of formation"

Membrane phenomena depend on the free energy per mole
(activity, approximated by concentration)
NOT free energy of formation

MD does not calculate activities very well

NaCl ≠ KCl
100 mM ≠ 200 mM

Force Fields must be RE-calibrated
in each Biological Solution
to verify equilibrium potentials (chemical potentials)

Fitting Real Experiments
requires Accurate Chemical Potentials in mixtures

NaCl ≠ KCl

100 mM ≠ 200 mM

Calibration is Hard Work

Much of biology is controlled by trace concentrations of Ca ion

and coenzymes/cofactors

first and second **messengers,**
transmitters,
hormones,
vitamins
etc.

Difficulties for all atom calculations

10^{-7} M Ca occurs in 55 M water

for each Ca ion
have 5.5×10^{7} water molecules
1.65×10^{8} atoms

need ~1000 calcium ions for statistics
Must calculate 1.65×10^{11} atoms
and all their interactions!

Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Time 10^{-15} sec	10^{-4} sec	$\mathbf{10^{11}}$
Length 10^{-11} m	10^{-5} m	$\mathbf{10^{6}}$

DEVICES DEPEND ON FINE TOLERANCES
parts must fit

Atomic and Macro Scales are BOTH used by channels because they are nanovalves
so atomic and macro scales must be
Computed and CALIBRATED Together

This may be impossible in all-atom simulations

Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Spatial Resolution	***Three Dimensional*** $(10^4)^3$	10^{12}
Volume 10^{-30} m^3	$(10^{-4}\ m)^3 = 10^{-12}\ m^3$	10^{18}

DEVICES DEPEND ON FINE TOLERANCES
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Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Solute Concentration *including Ca^{2+} mixtures*	10^{-11} to 10^{1} M	**10^{12}**

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Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

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Computed and CALIBRATED Together

This may be impossible in all-atom simulations

What is needed for MD to be an exact science

Almost no MD calculations exist of divalents

NO MD calculations exist of trace concentrations of ions

NO MD calibrations exist of mixtures of ions

Calibrated electrodynamics instead of periodic electrostatics