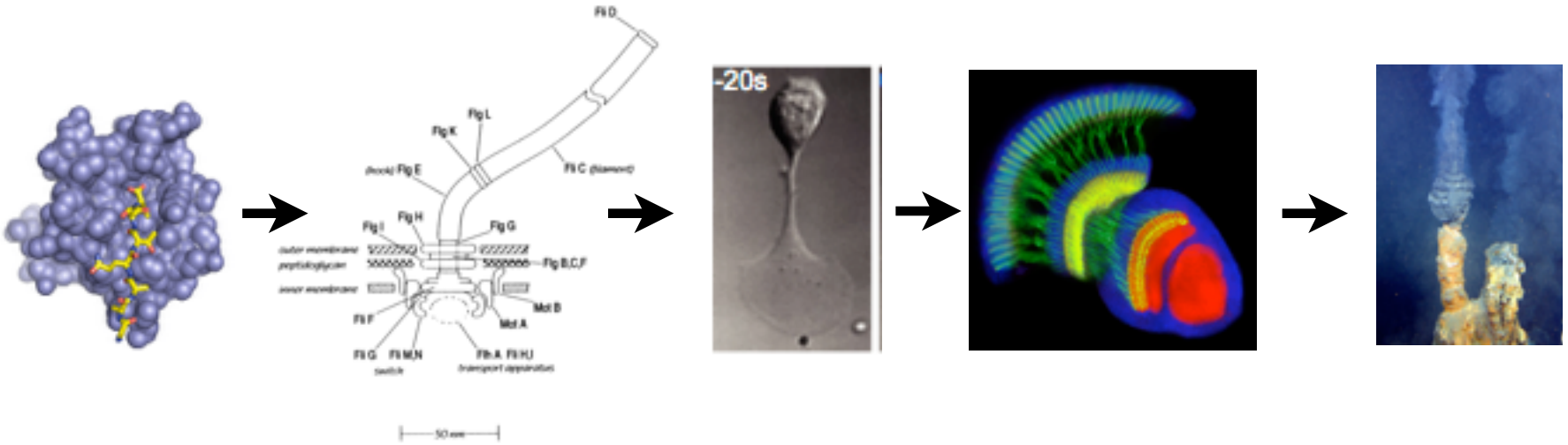
Quantitative Biology (The Science of Complexity)

Winter 2017

Rama Ranganathan
The Green Center for Systems Biology, ND11.120E



Administrative matters…

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(1) We will have 16 lectures…

1/09 **Introduction**…the principles of modeling

1/11 **Linear systems theory I**…simple systems, graphical tools, decomposability
1/16 **Linear systems theory II**…the space of possible solutions, understandability
1/18 **Stochastic models**…models at the limit of small numbers, new behaviors.
1/23 **Diffusion and driving forces**, thermodynamic analysis
1/25 **Diffraction theory**…the spatial Fourier transform
1/30 **Decomposition**…low dimensional representations of big data

simplicity of linear systems

2/1 **Introduction to non-linear systems**…the origins of complexity
2/6 **A detailed example I**…the van der Pol oscillator and the Chua circuit, theory.
2/8 **A detailed example II**…simulation and experiments of simple non-linear systems
2/13 **Small non-linear systems**…the MAP kinase switch
2/15 **Mesoscale non-linear systems**…the problem of cellular signaling
2/20 **Large non-linear systems**…the problem of proteins
2/22 **Epistasis**…genetic and evolutionary principles, fitness landscapes
2/27 **Information Theory**

complexity of nonlinear systems

3/1 **A conclusion**…so what is complexity? A proposal for a general strategy

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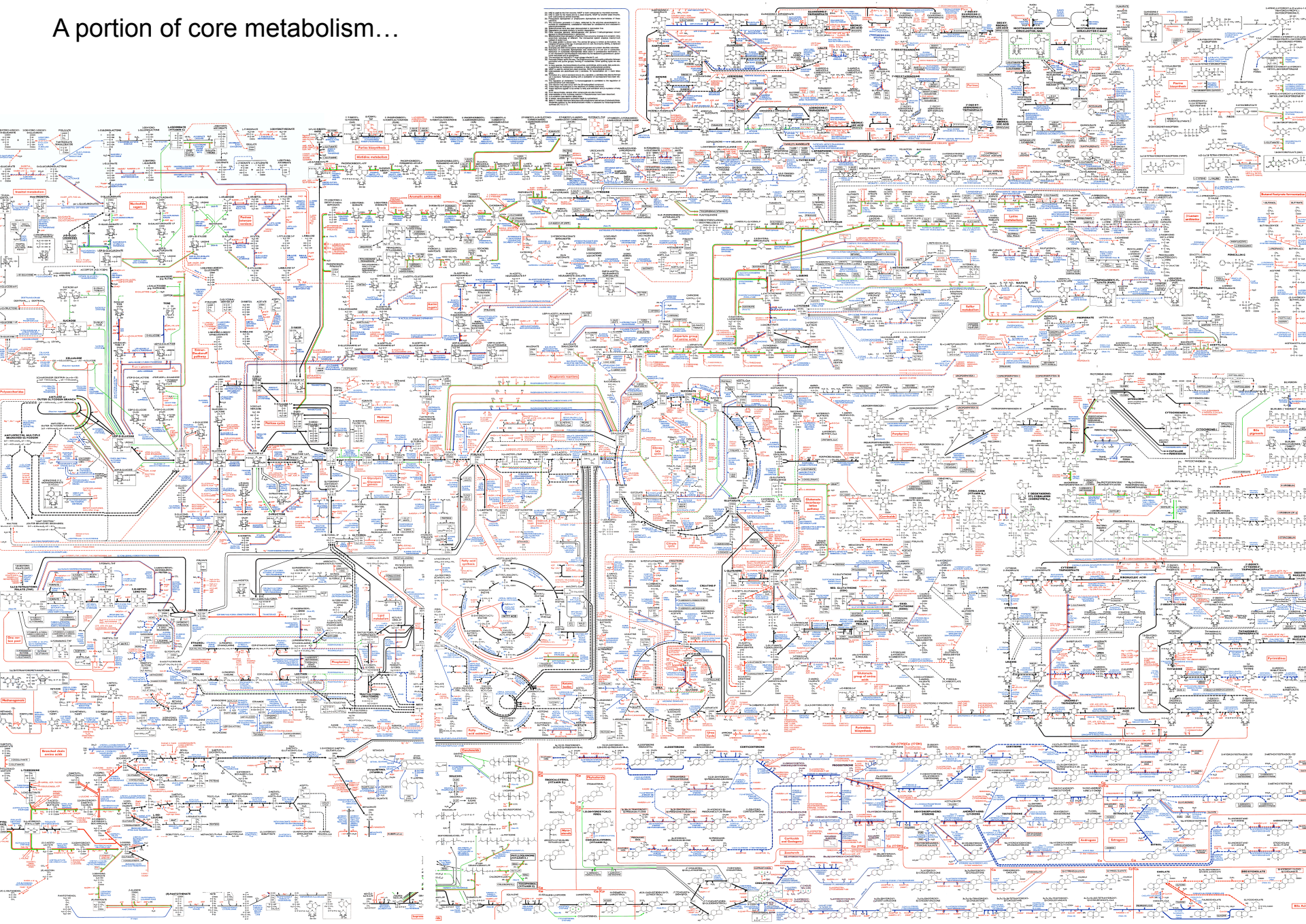
(4) Interaction is critical…ask many questions and start discussions.

A portion of core metabolism…



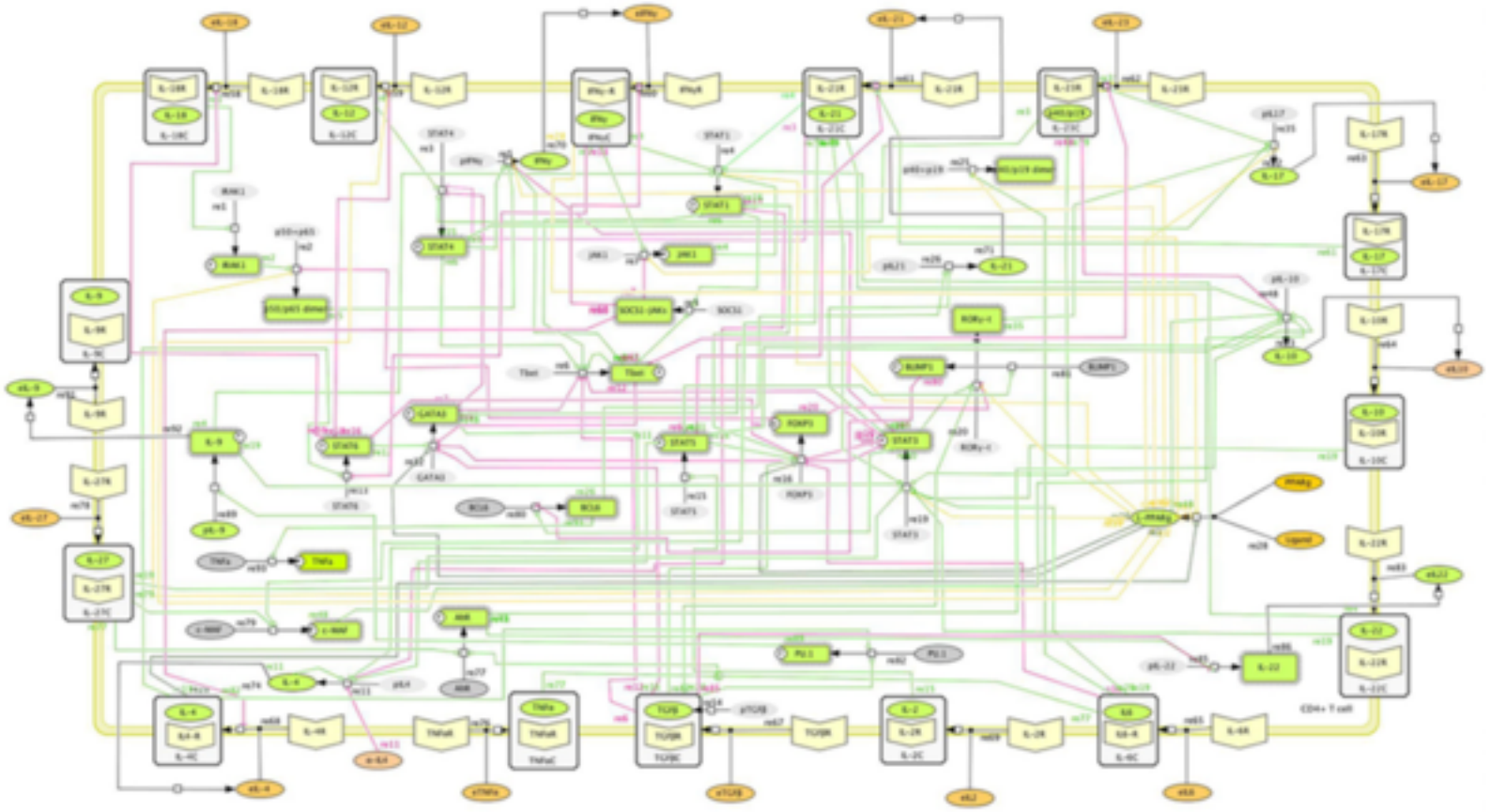
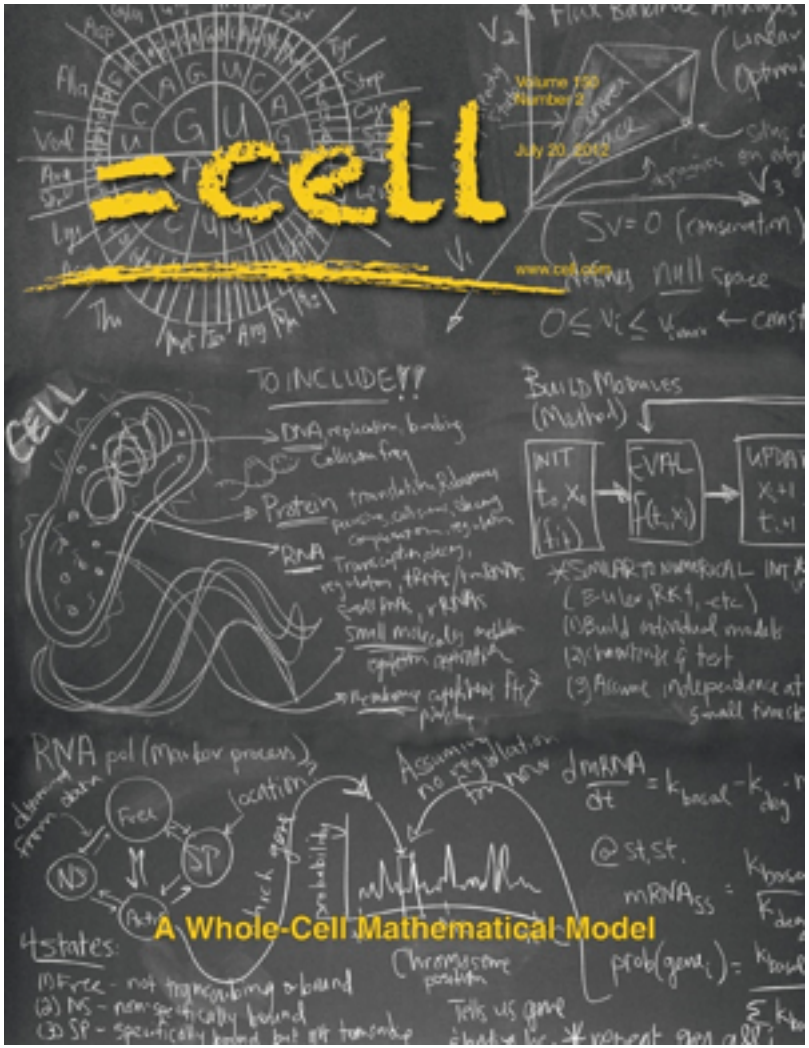


FIGURE 1 | Main intracellular differentiation pathways of a single CD4+ T cell. Systems Biology Markup Language (SBML)-compliant network model of CD4+ T cell differentiation, including cytokines, receptors, and intracellular signaling pathways controlling CD4+ T cell fate and function.

"…the most recent systems biology markup language (SBML)-compliant network…provides a structured understanding on different pathways involved in CD3+ T cell differentiation…."

Does this lead to understanding?

Carbo, Adria, et al. "Computational modeling of heterogeneity and function of CD4+ T cells." Frontiers in cell and developmental biology 2 (2014).



Some have tried to apply the strict principles of reduction-based science….to write down detailed models for each and every reaction.

Does this lead to understanding?

Karr et al. (2012) Cell, 150, 389-401

An important and topical goal is to define the (yet unknown) general laws underlying the behavior and evolutionary origin of *complex systems* in biology

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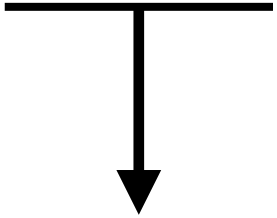

what do we mean by complex?

From Merriam-Webster...

com·plex /käm'pleks/

(1) ....*consisting of many parts*, e.g. a complex piece of machinery...

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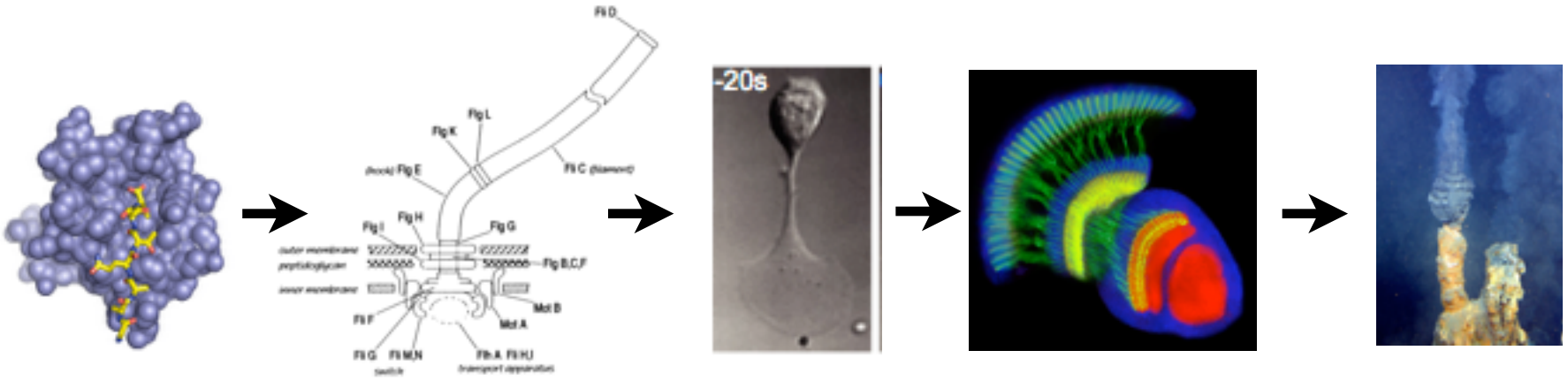

~10^3 - 10^5 atoms

1,000's of parts/reactions

~10^5 neurons
~10^7 synapses

gazillions of individuals/species

From Merriam-Webster...

com·plex /käm'pleks/

(1) ....*consisting of many parts*, e.g. a complex piece of machinery...

But, is the condition of having many parts imply complexity?

A mole of gas has many parts....but we have the ideal gas law and macroscopic properties of this system that can be understood from properties of its parts..

$$PV = nRT$$

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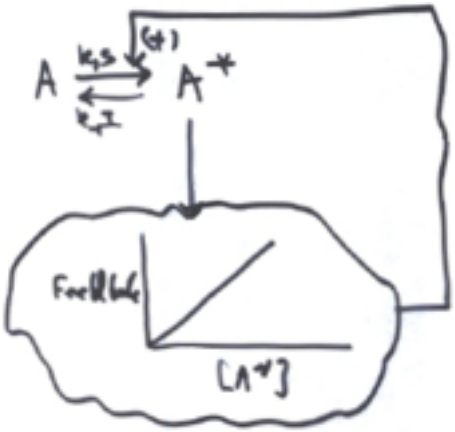
Also as we will see later on, even a ridiculously simple looking reaction with very few parts can exhibit extraordinary complexity…



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So having many parts is neither **necessary** not **sufficient** to specify complexity…

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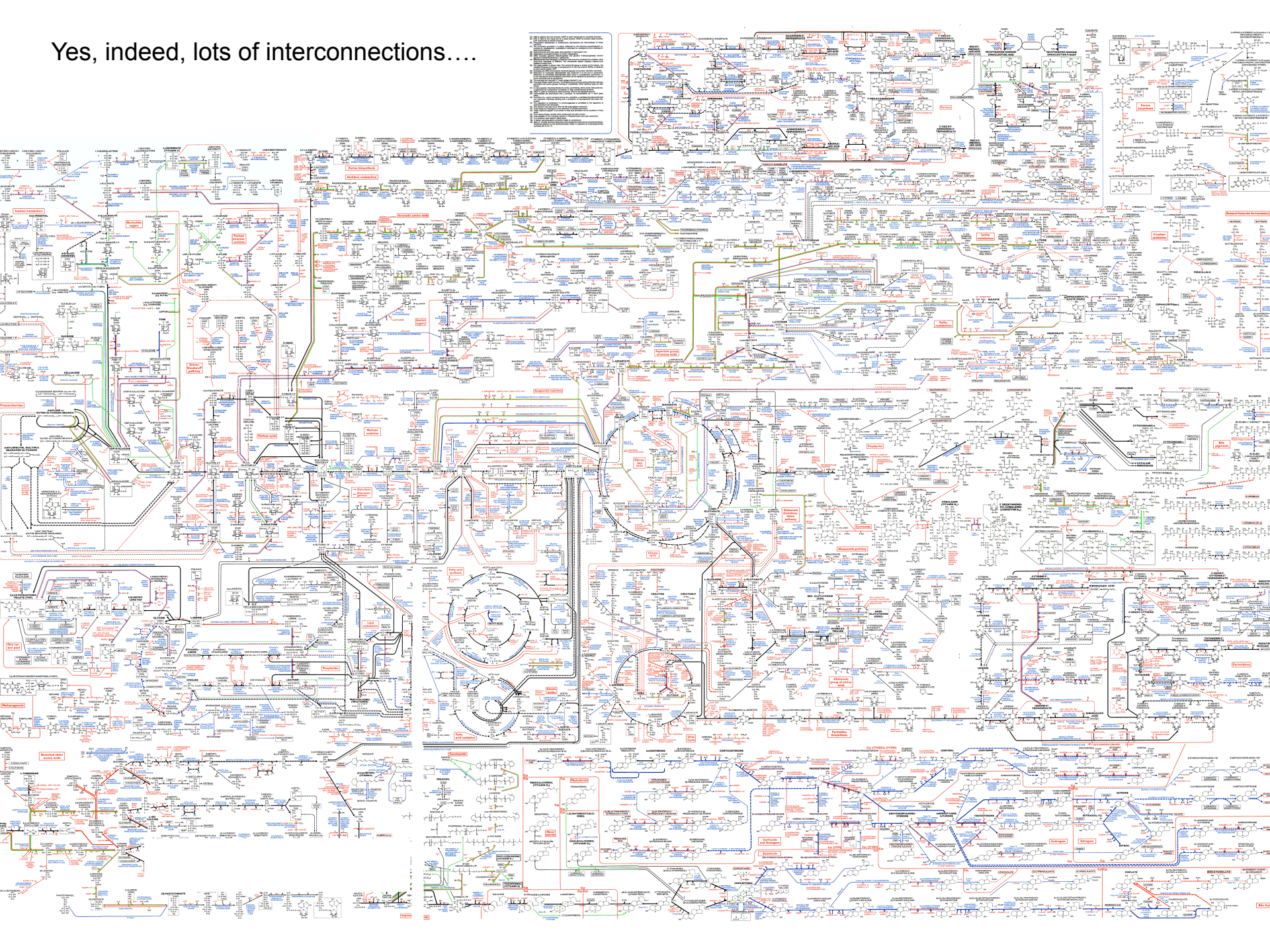
Yes, indeed, lots of interconnections….



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But, does the condition of having many interconnected parts necessarily imply complexity?

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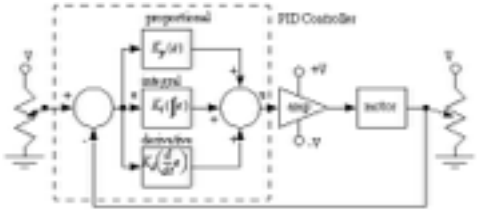

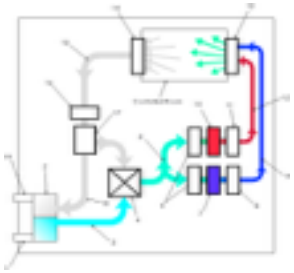

And…we make many very complex circuits with millions of parts and can yet make clear prediction of how such systems behave...satellite control systems, cruise controls of cars, air handling systems, an airplane, this laptop...

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The essence of this simplicity is **linearity** in the connections between system components...

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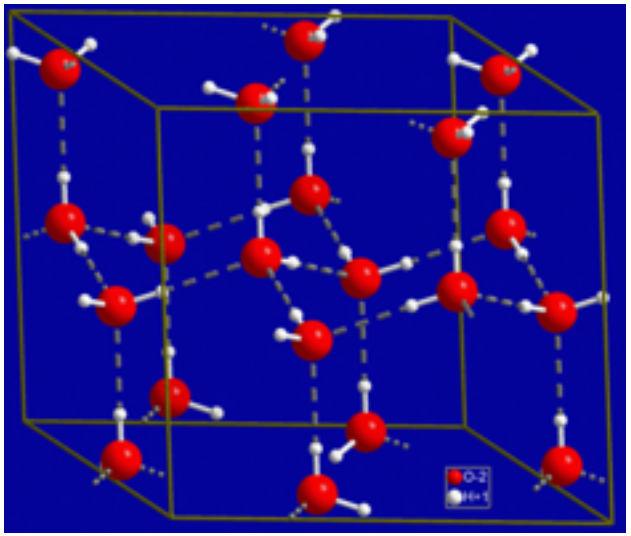

And what about condensed phases like liquid water or ice? An extensive hydrogen bonding network….

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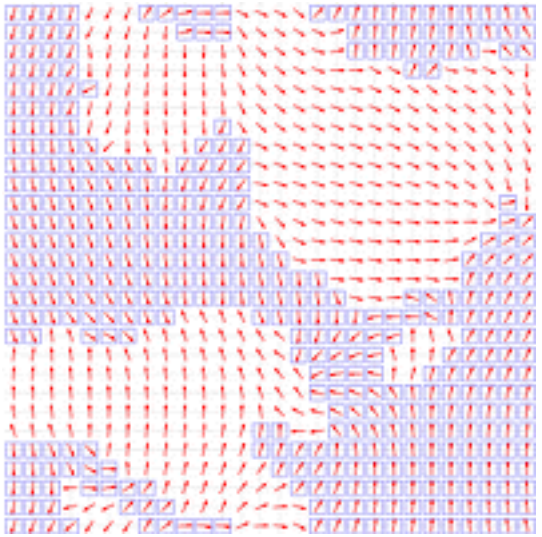

We also have theories for condensed phases of matter such as liquids, solids, and even disordered states such as spin-glasses….and these theories yield general predictive properties of highly interconnected systems….

Li et al., Nature (2012) 483, 336-40

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We also have theories for condensed phases of matter such as liquids, solids, and even disordered states such as spin-glasses....and scientists are discovering new biological principles through applying such theories.

The essence of this simplicity is **homogeneity** in the pattern of interactions....can take averages.

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(1) ....*consisting of many parts*, e.g. a complex piece of machinery...

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(3) ...consisting of parts interconnected so as to make the whole perplexing...

So...what is the essence of it?

Well....complex systems show

heterogeneity of system components such that some parts and connections are much more important than others (can't take averages!), and....

non-linearity, such that the combined activity of components cannot be predicted from properties of the components taken individually. Non-independence of parts and reactions. The whole is NOT a sum of the parts!!

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And, of course….the complexity scales steeply with the number of variables in a system that are engaged non-linearly.

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	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
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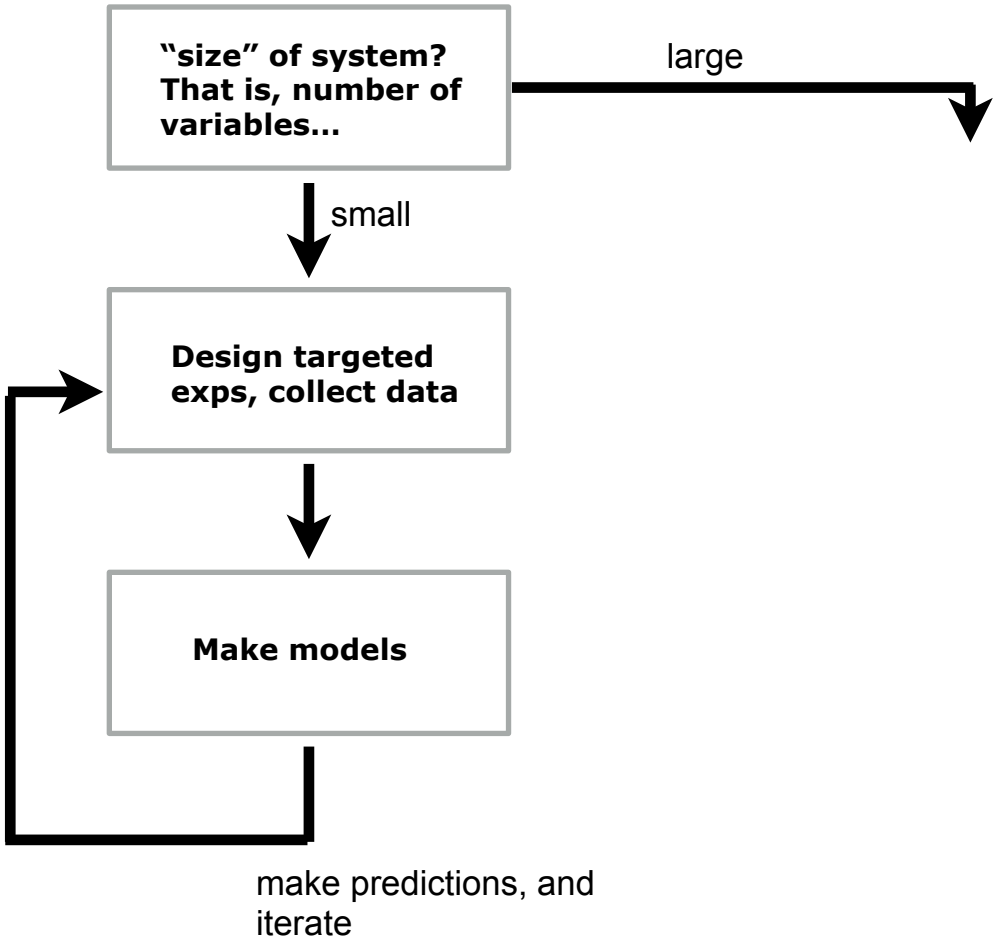
So…how do we proceed in (quantitatively) understanding systems in all these different regimes?



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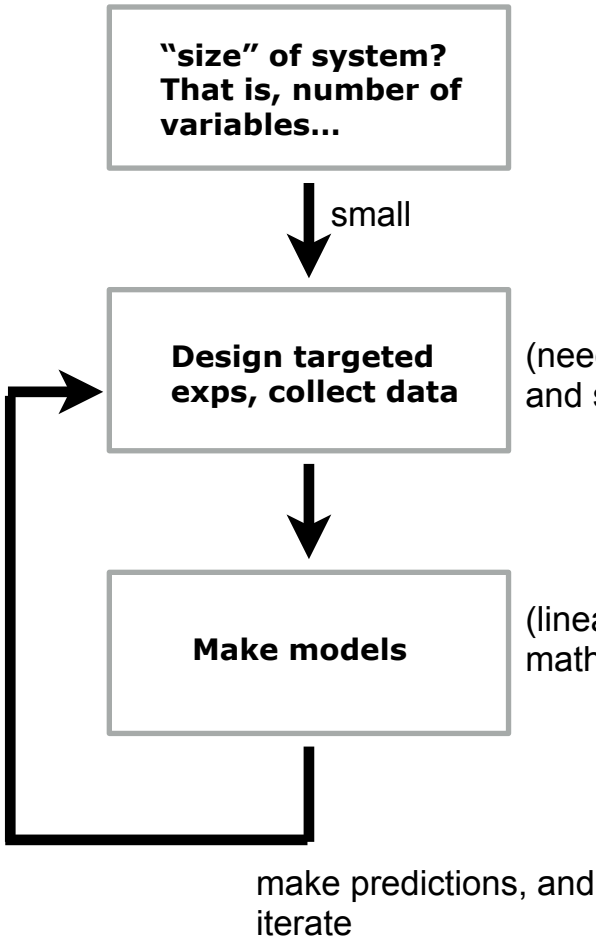
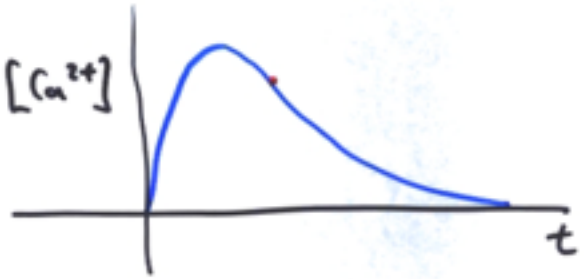


Why make models and what is the process?

① data reduction ... that is, representing 1000's of data points (say a Ca^{2+} trace) in only a few characteristic parameters.



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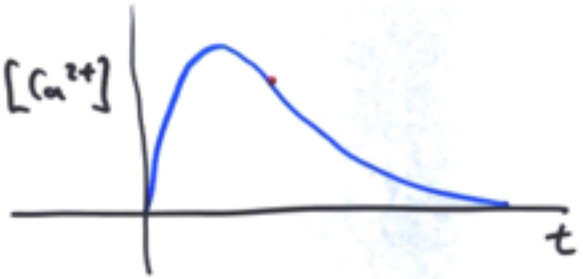
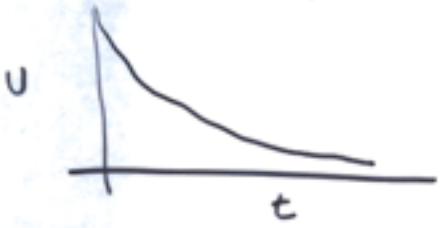


② test a physical model for an observed phenomenon. I collect data on the folding of a protein. Are the data consistent with a two-state equilibrium?

$$U \rightleftharpoons F$$



Why make models and what is the process?

(3) Obtain a mathematical representation that helps predict new experimental results and therefore becomes a tool for guiding experiments. Intuition in "large" problems.

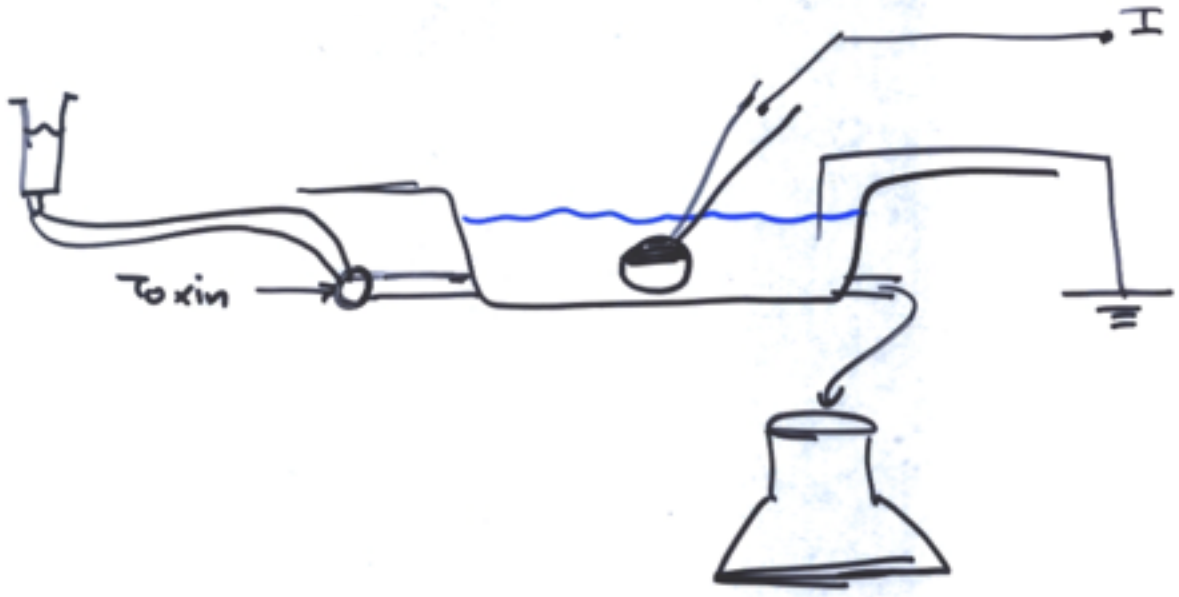
(4) Identify and classify a biological process into sets of common physical mechanisms. Diffusion?
Signal amplifier?
A switch?

Why make models and what is the process?

The five step process of modeling:

1. observe a biological process [collect the data]
2. construct a physical model [$A \xrightarrow{k} B$]
3. abstract it to a mathematical model. [$A(t) = A_0 e^{-kt}$]
4. fit the data, check accuracy of fitting. Does the model explain the data?
5. Fine... but is it predictive?

A simple example for today:



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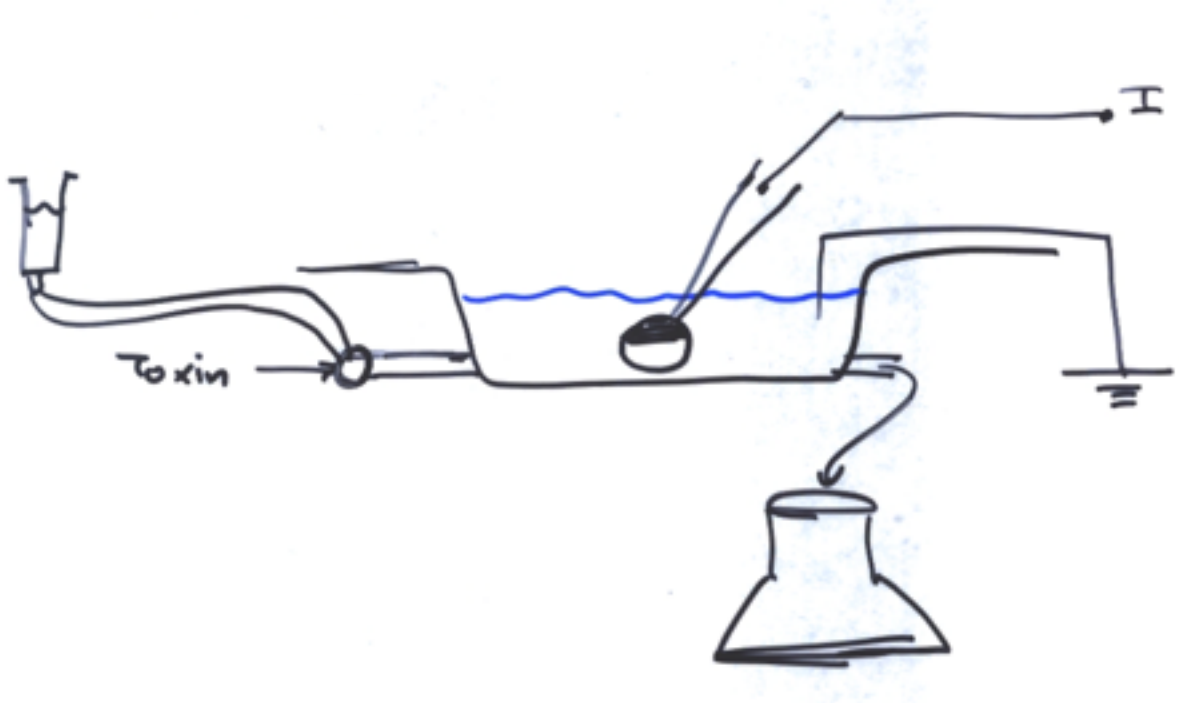

So, we are studying the binding of a toxin molecule that binds to and blocks an ion channel. We want to understand the nature of this reaction.

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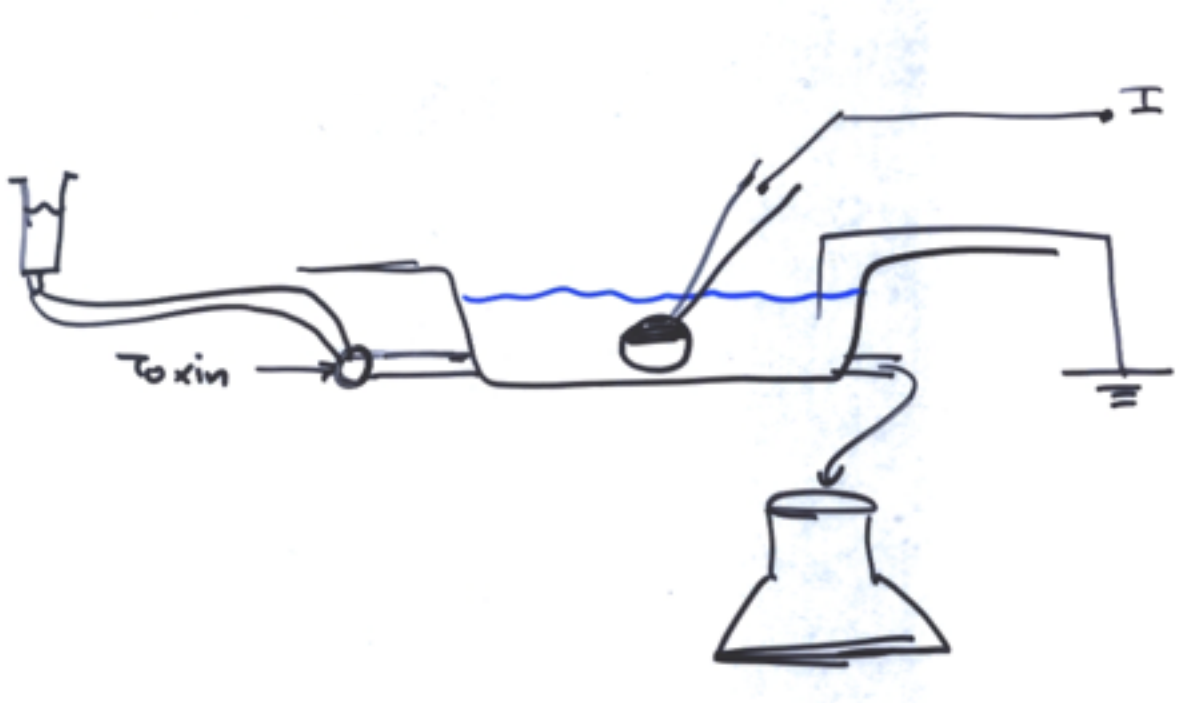
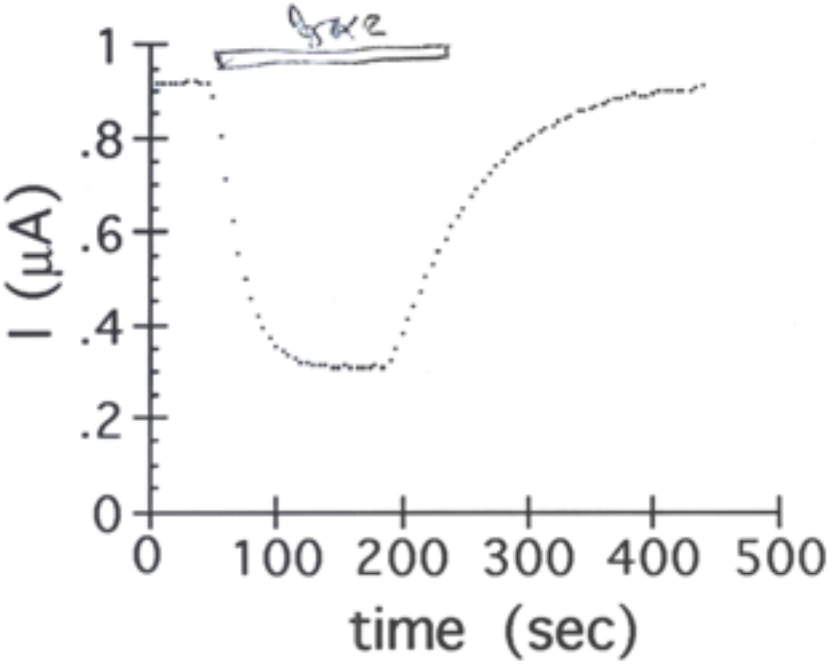


So, we are studying the binding of a toxin molecule that binds to and blocks an ion channel. We want to understand the nature of this reaction.

The experiment….express channels in a Xenopus oocyte, record the channel activity, flow in and wash out the toxin molecules, watch the inhibition of current flow through the channel, record the kinetics.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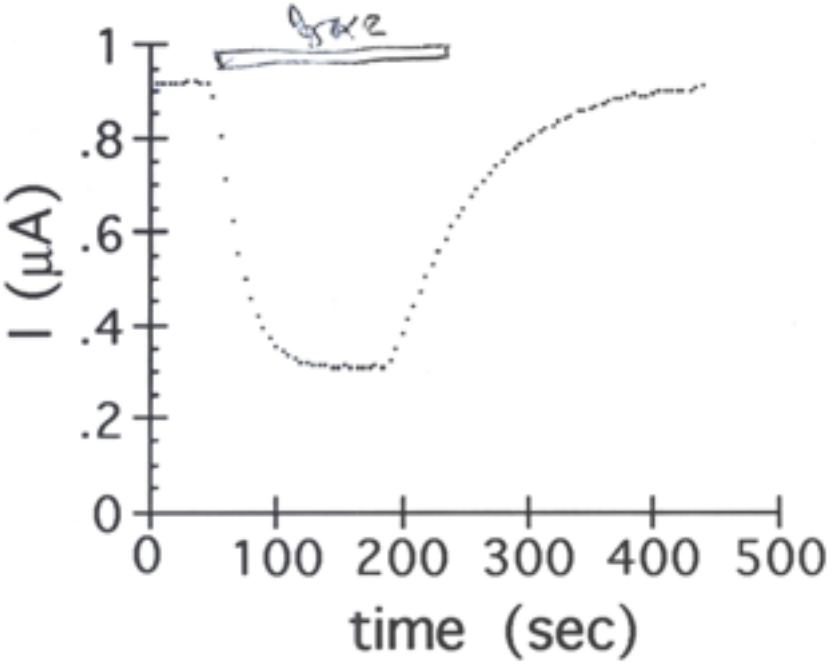
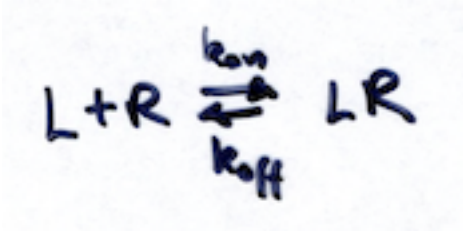
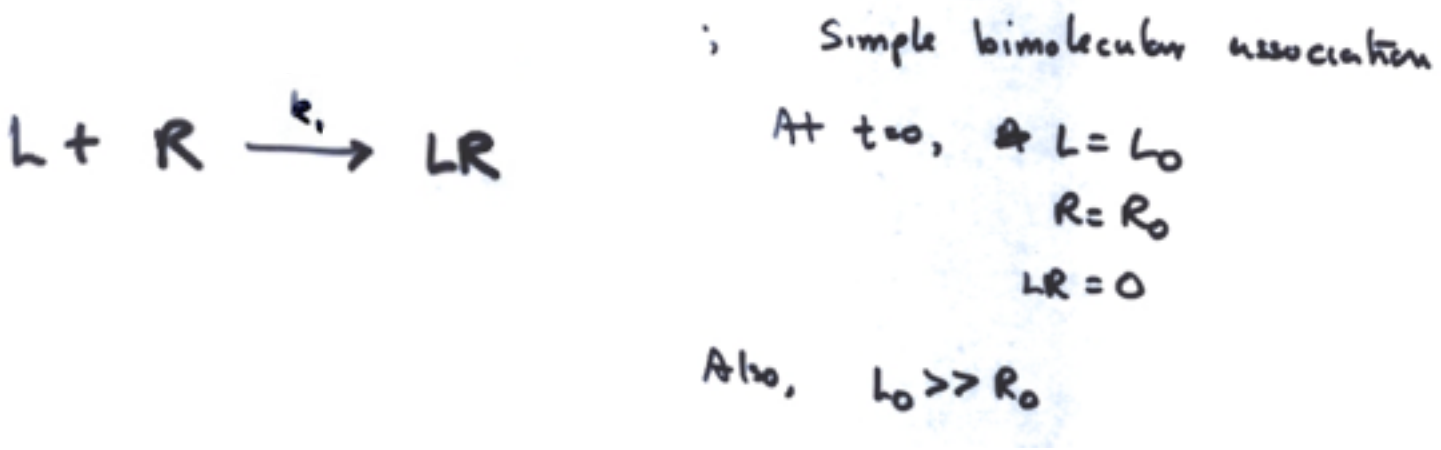


Next step is to make a **physical model**….so we guess that this is a simple bimolecular reaction. L is for the toxin and R is for the channel…



Now to turn this into a **mathematical model**….we write down the chemical kinetics equation and set the initial conditions…



So then…

$$\frac{dR}{dt} = -k_1[L][R]$$

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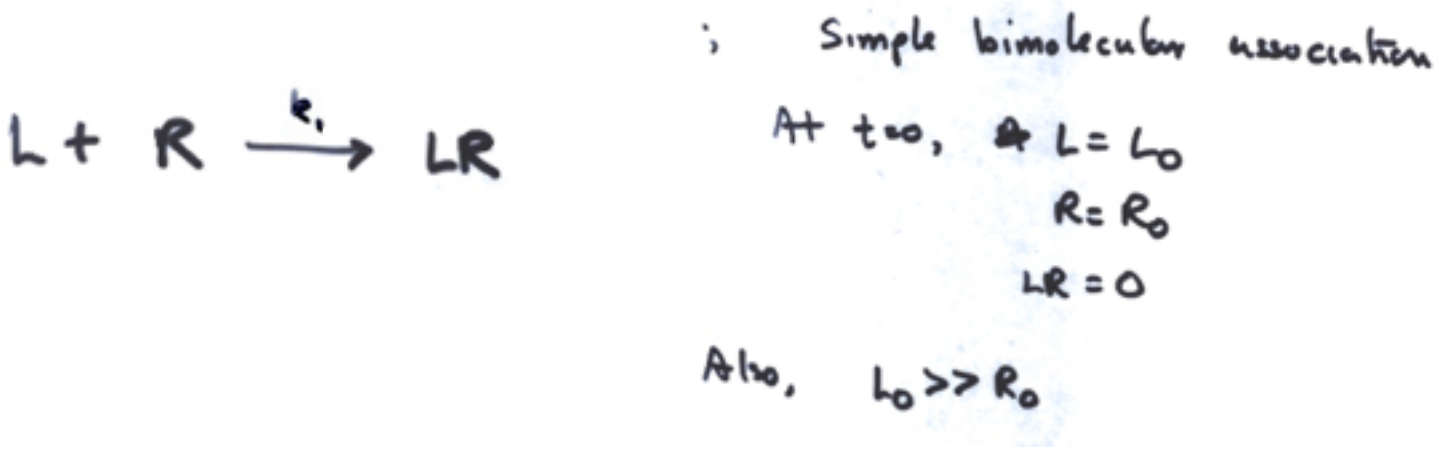

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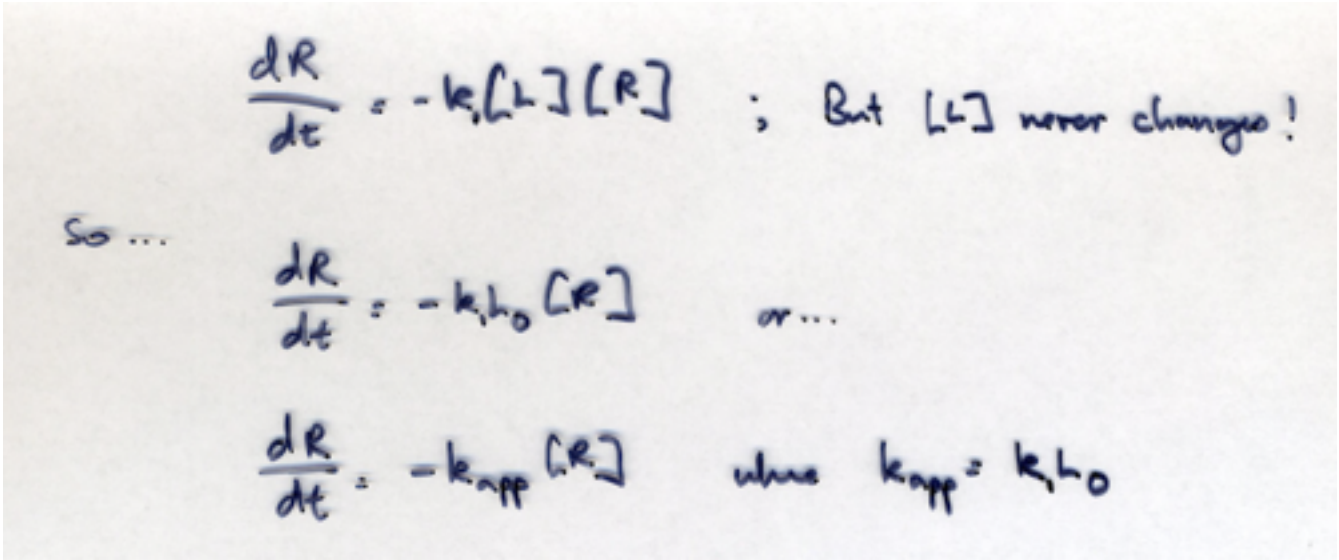

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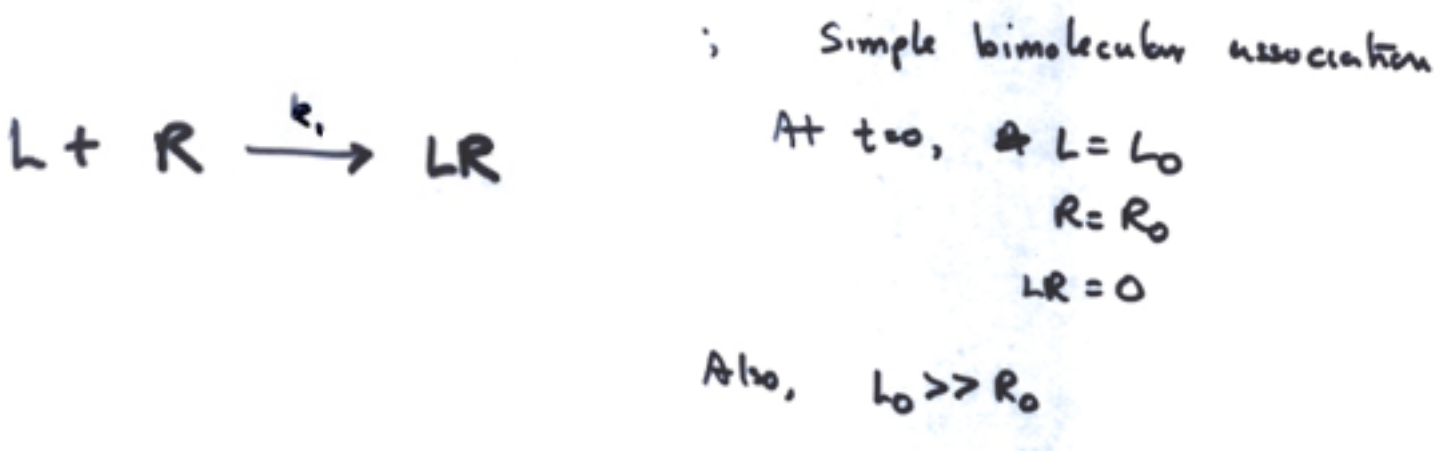

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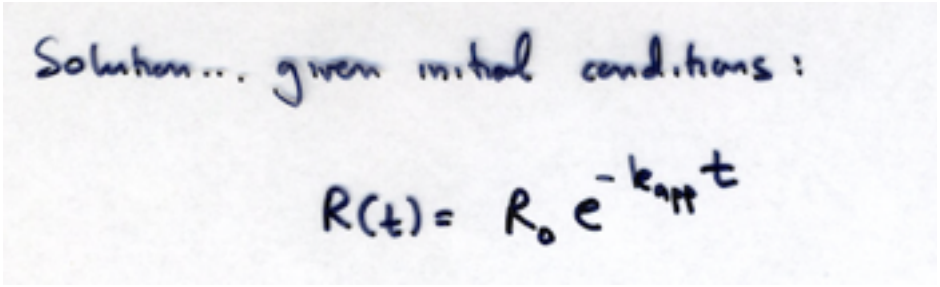
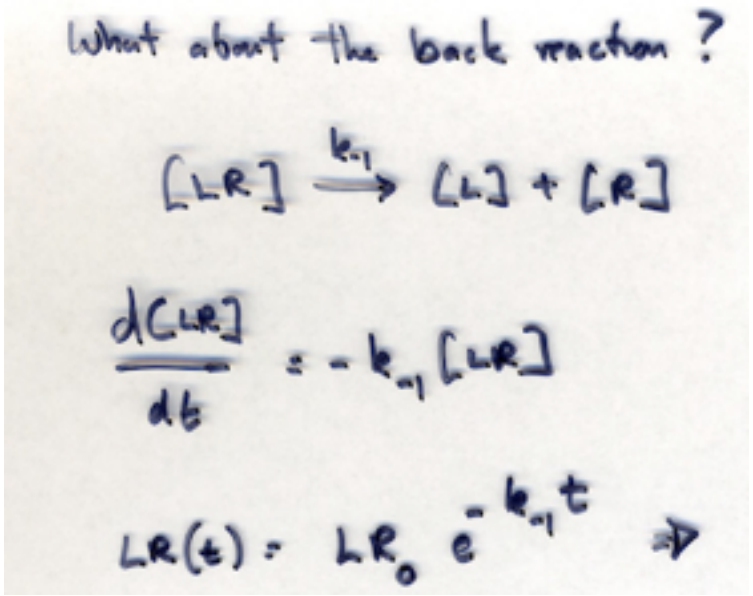


The binding of toxin to the channel should follow single exponential kinetics…



; Simple bimolecular association

At $t = \infty$, $L = L_0$

$R = R_0$

$LR = 0$

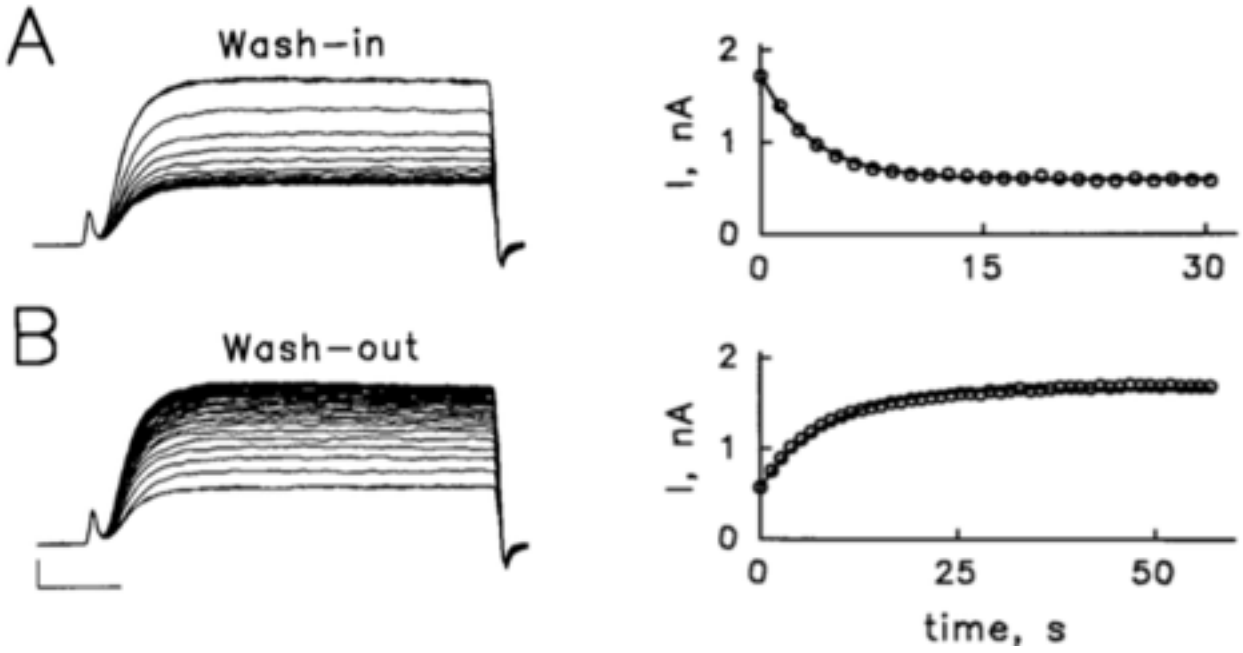
Also, $L_0 >> R_0$

The dissociation of toxin from the channel should also follow single exponential kinetics…

$$R \underset{k_{-1}}{\overset{k_1 L}{\rightleftharpoons}} LR$$

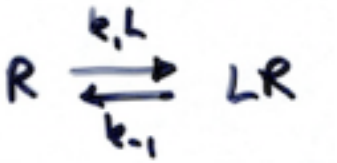
$$R(t) = R_0 e^{-k_{app} t} \quad \text{where} \quad k_{app} = k_1 L_0$$

$$LR(t) = LR_0 e^{-k_{-1} t}$$



Indeed, both toxin binding and release are well-fit by singe exponential functions

Goldstein and Miller, Biophys. J 65, p.1613



$$R(t) = R_0 e^{-k_{app} t} \quad \text{where} \quad k_{app} = k_1 L_0$$

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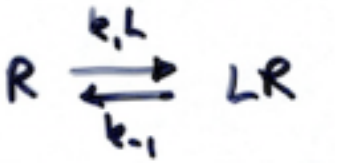
So, the model fits the data well. Good, but does it make new predictions not used in arriving at the model? Yes….

Goldstein and Miller, Biophys. J 65, p.1613



$$R(t) = R_0 e^{-k_{app} t} \quad \text{where} \quad k_{app} = k_1 L + k_{-1}$$

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How should the on-rate and off-rate of toxin binding to the channel depend on the concentration of toxin?

Goldstein and Miller, Biophys. J 65, p.1613

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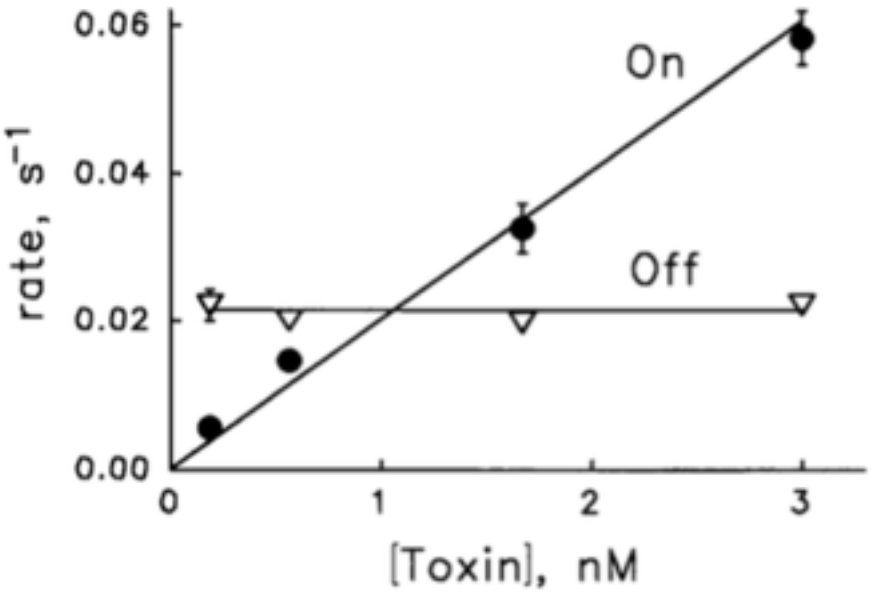

Goldstein and Miller, Biophys. J 65, p.1613

Ok…and finally at equilibrium:

$$R \underset{k_{-1}}{\overset{k_1 L}{\rightleftharpoons}} LR$$

$$\frac{d[LR]}{dt} = k_1 L [R]$$

$$\frac{dR}{dt} = k_{-1}[LR]$$

At equilibrium…

$$k_1 L [R] = k_{-1}[LR] \quad , \text{ but } \quad R + LR = R_{tot}$$

$$k_1 L [R_{tot} - [LR]] = k_{-1}[LR]$$

$$f_B = \frac{[LR]}{R_{tot}} = \frac{L}{\frac{k_{-1}}{k_1} + L} \quad ; \quad K_d = \frac{k_{-1}}{k_1}$$

Goldstein and Miller, Biophys. J 65, p.1613

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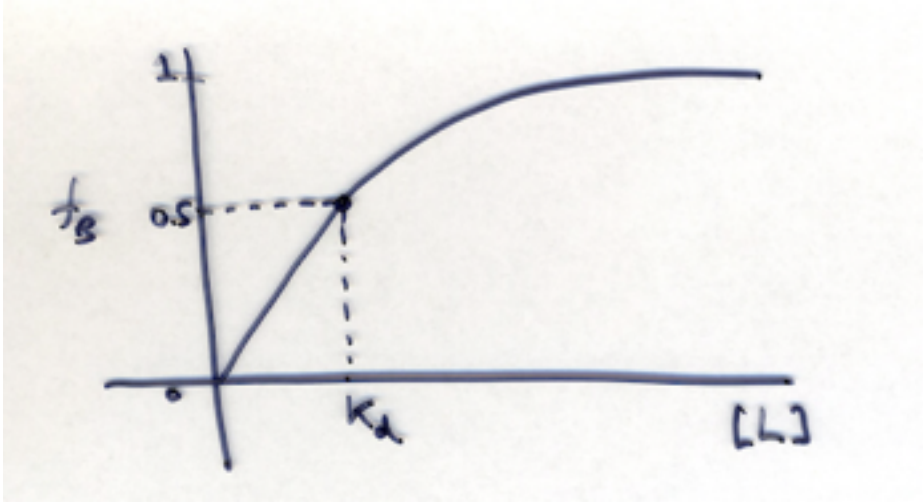

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Goldstein and Miller, Biophys. J 65, p.1613

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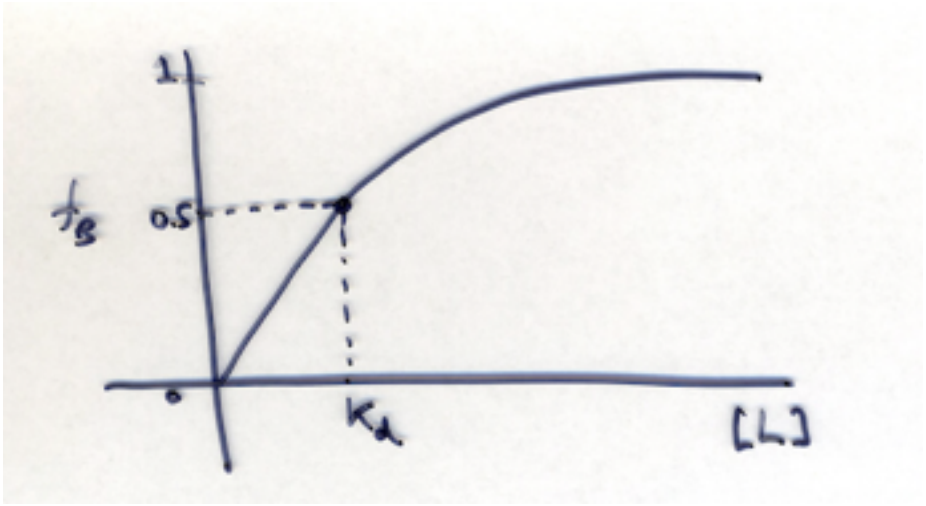

So, the good-old rectangular hyperbola, or "binding isotherm". This gives us an additional check on our model….we should be able to get the dissociation constant (Kd) in two independent ways:

(1) Look at fraction bound as a function of toxin (L) concentration…
(2) Take the ratio of the off-rate and on-rate

These better give us the same number!!

Goldstein and Miller, Biophys. J 65, p.1613

Ok…and finally at equilibrium:

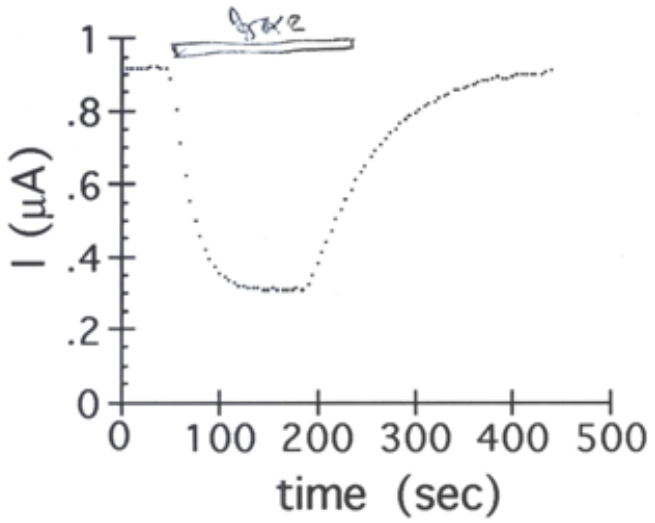

TABLE 1 Blocking parameters for wild-type and mutant charybodotoxins

Toxin	K_i (nM)	$k_{on} \times 10^{-6}$ ($M^{-1}s^{-1}$)	k_{off} (s^{-1})
Multi-pulse protocol			
Wild-type	0.075 ± 0.005	63 ± 5	0.0047 ± 0.0004
S10Q	0.69 ± 0.05	149 ± 18	0.085 ± 0.006
R25Q			
2 K^+ (out)	0.95 ± 0.05	23 ± 2	0.021 ± 0.007

Well….the concentration of toxin at which we get half block is 0.075 nM. And if you compute the ratio of the off and on rates, you get 0.0746 nM.

Pretty good….makes one want to believe the model.

Goldstein and Miller, Biophys. J 65, p.1613

Now just to review….

$$U \xrightarrow{k} U^*$$

we say: $\frac{dU}{dt} = -kU$; but can we derive this rate equation?

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So at $t=0$, we have U_0 molecules. After time Δt, how many molecules of U^* will I have? Well... $k \Delta t \, U_0$

So...

$$U(t+\Delta t) = U(t)\,[1 - k\Delta t]$$

$$= U(t) - U(t)\,k\Delta t$$

$$\frac{U(t+\Delta t) - U(t)}{\Delta t} = -U(t)\,k$$

What happens as $\Delta t \to 0$?

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$$\frac{U(t+\Delta t) - U(t)}{\Delta t} = -U(t) k$$

What happens as $\Delta t \to 0$?

$$\frac{dU}{dt} = -Uk$$

How do we solve this equation?

Solution of a first order differential equation:

the eqn only contains a first derivative.

$$\frac{dU}{dt} = -kU$$

Solve by separation of variables:

How do we solve this equation?

$$\frac{dv}{dt} = -kv$$

$$\frac{1}{v}\,dv = -k\,dt$$

$$\int_{v_0}^{v} \frac{1}{v}\,dv = \int_{0}^{t} -k\,dt$$

$$\ln v \Big|_{v_0}^{v} = -kt \Big|_{0}^{t}$$

$$\ln v - \ln v_0 = -kt$$

$$\ln\left[\frac{v}{v_0}\right] = -kt$$

$$\frac{v}{v_0} = e^{-kt}$$

So…the single exponential decay function.

So, we dealt with the easiest problem…the top left hand corner of the space of problems….

	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
Nonlinear	fixed points bifurcations, multi stability irreversible hysteresis overdamped oscillators	anharmomic oscillators relaxation oscillations predator-prey models van der Pol systems Chaotic systems	systems of non-linear oscillators non-equilibrium thermodynamics protein structure/ function neural networks the cell ecosystems	Nonlinear wave propagation Reaction-diffusion in dissipative systems Turbulent/chaotic flows

adapted from S. Strogatz

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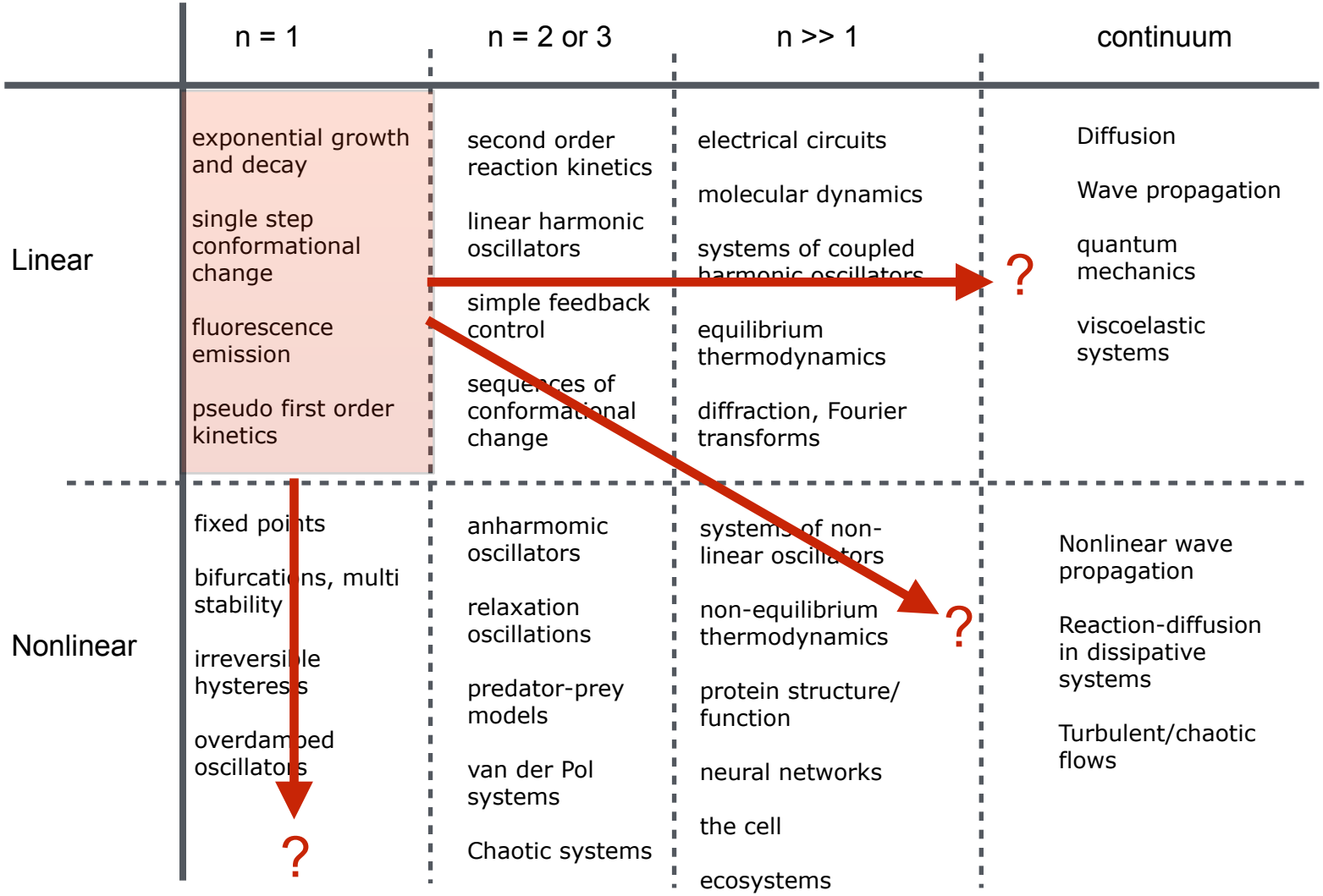

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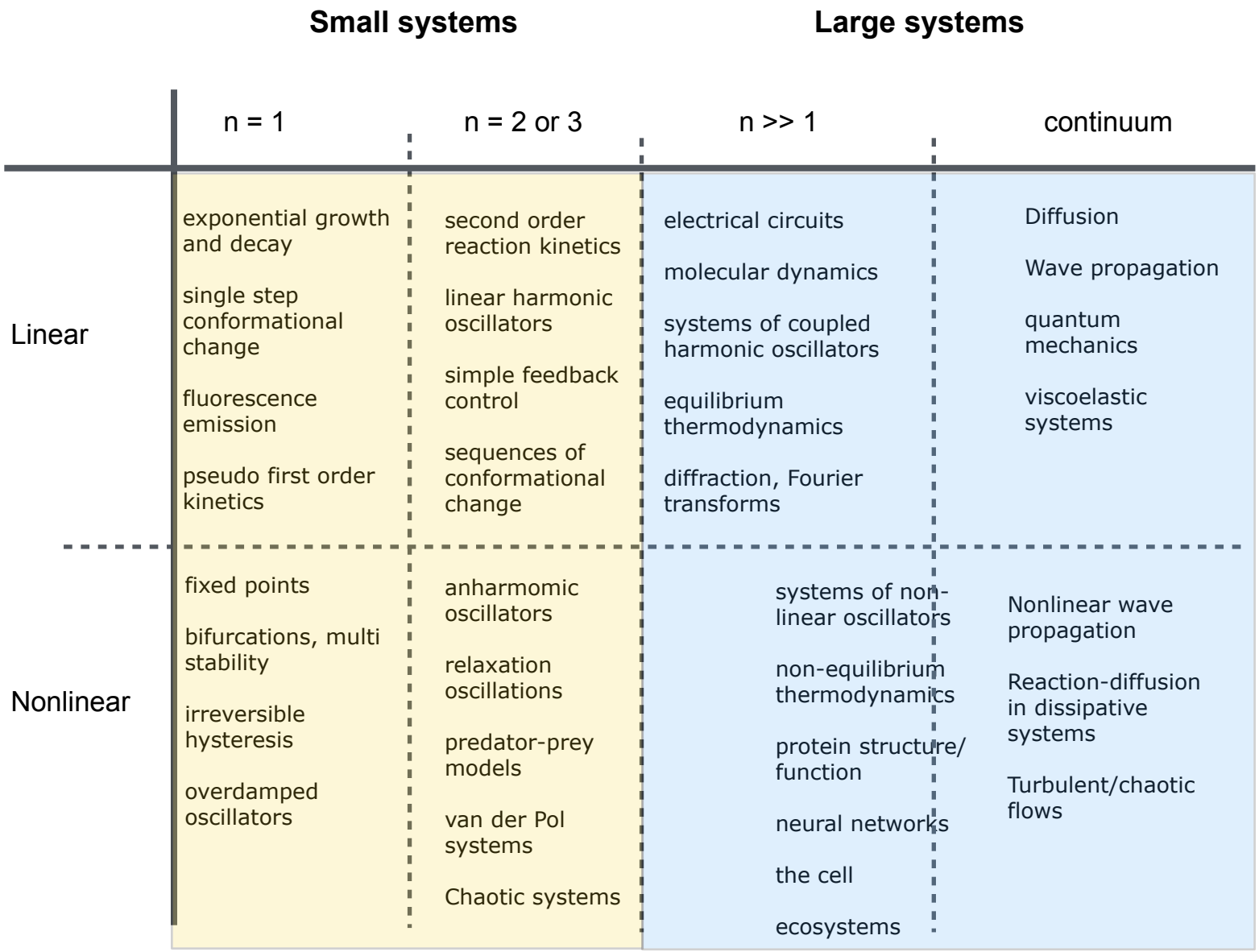

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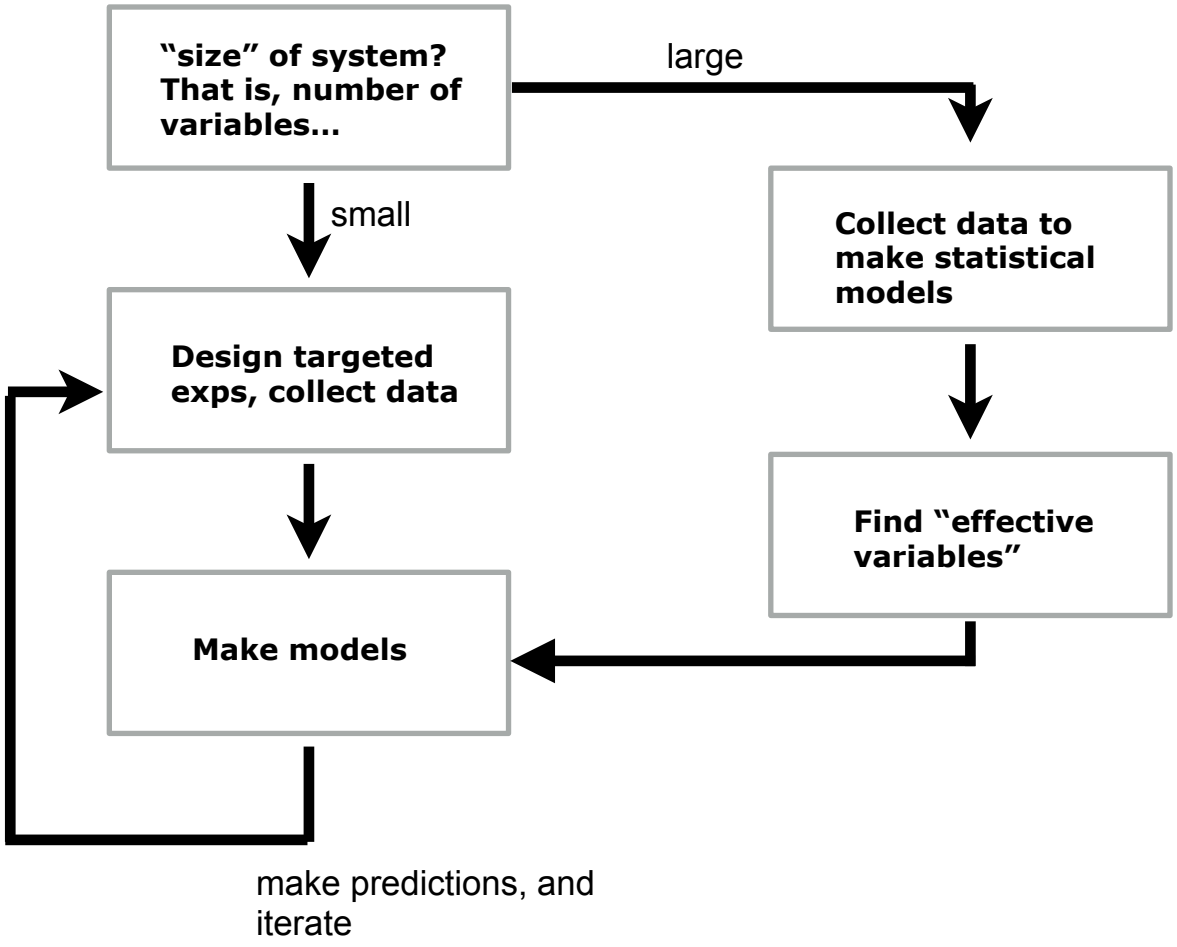
So…how do we proceed in (quantitatively) understanding systems in all these different regimes?



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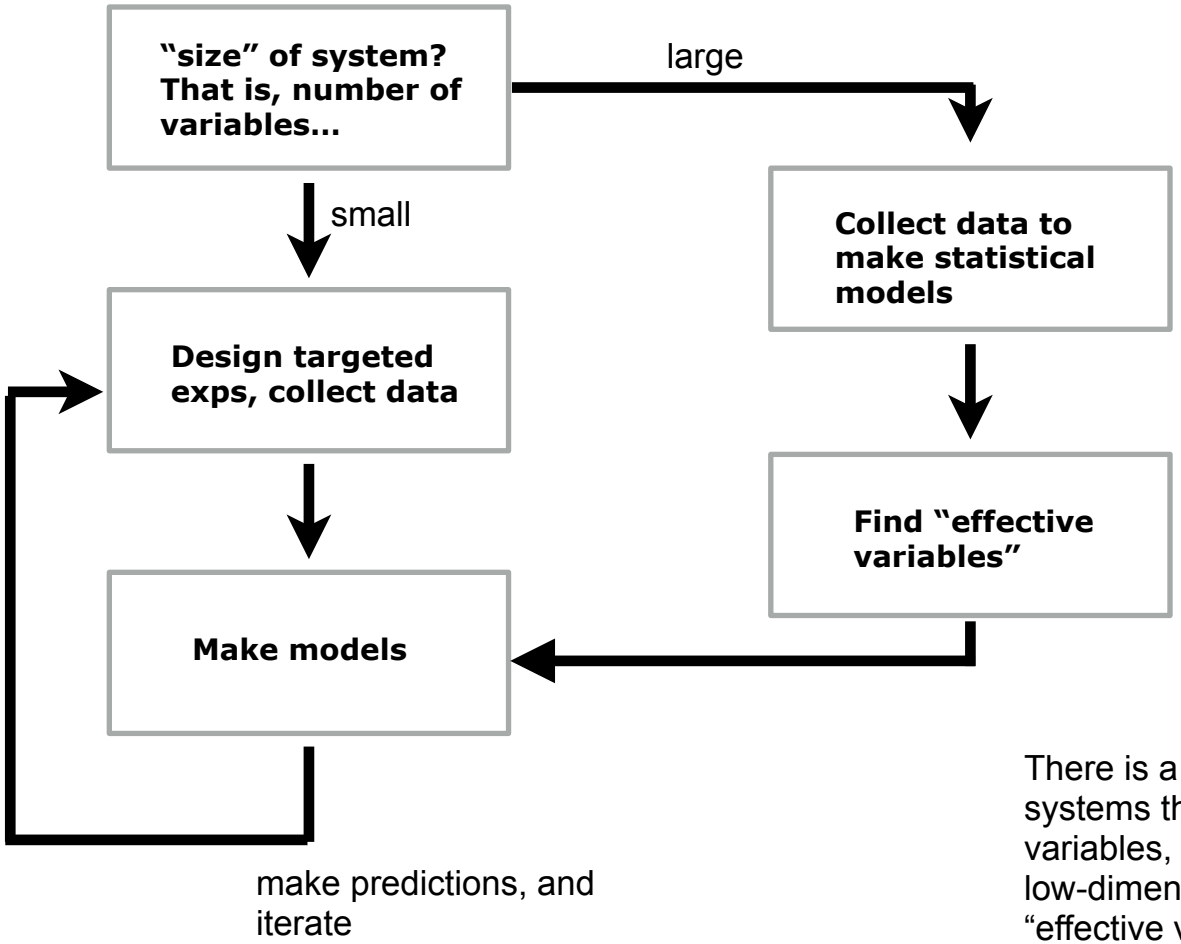
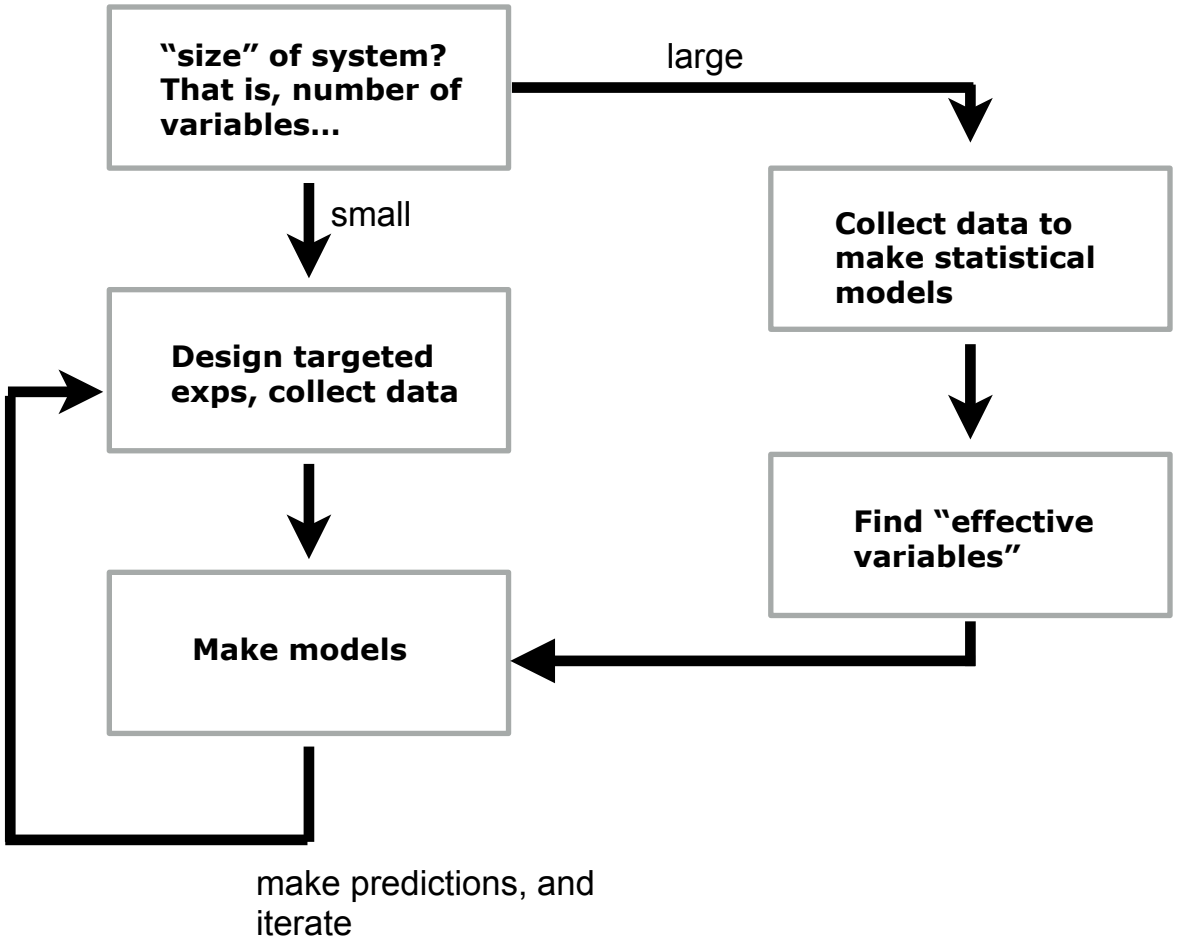


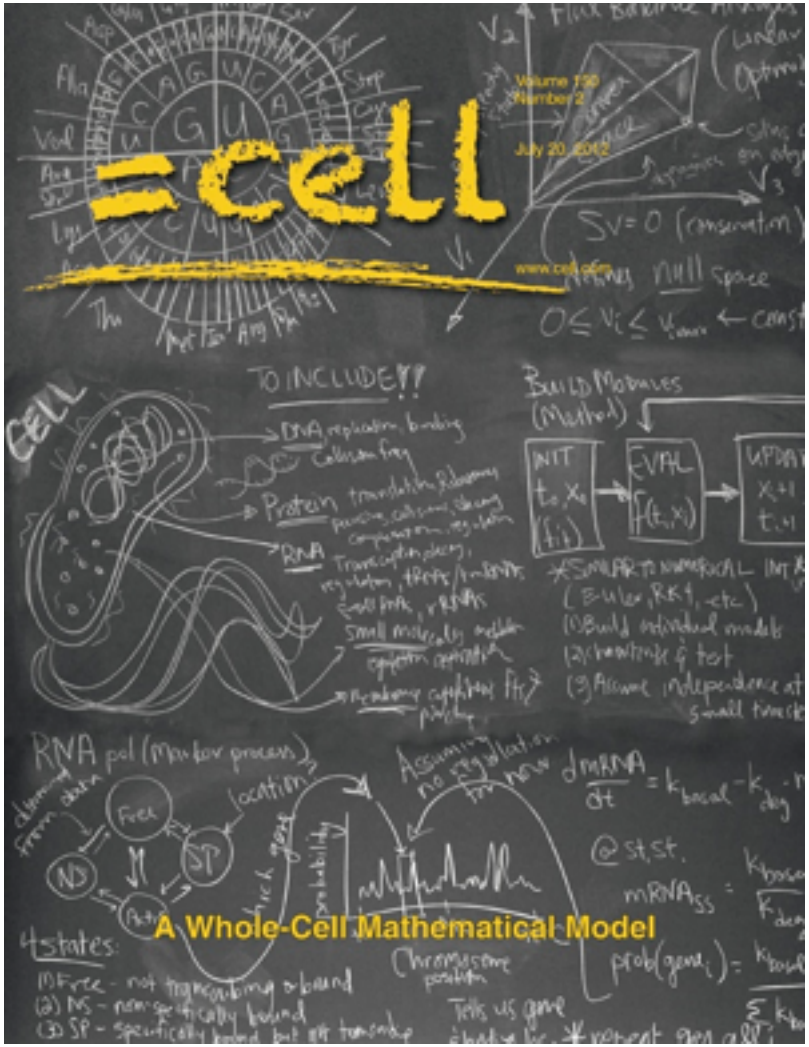
There is a deep hypothesis here that even in systems that seem to have large numbers of variables, the relevant dynamics is ultimately low-dimensional…comprised of just a few "effective variables". The trick for such systems is to find them…

So…how do we proceed in (quantitatively) understanding systems in all these different regimes?



2/20 **Large non-linear systems**…the problem of proteins
2/22 **Epistasis**…genetic and evolutionary principles, fitness landscapes

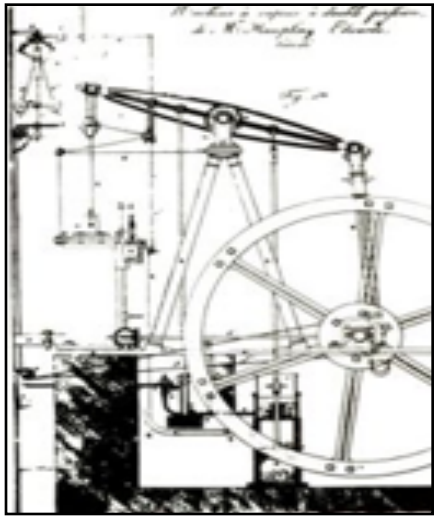
Not everyone in the field of systems biology takes this perspective!

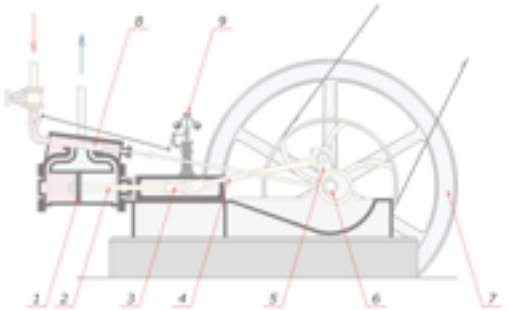


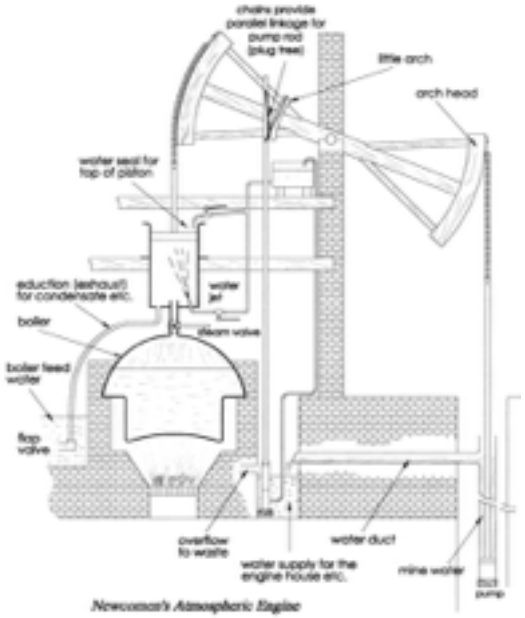
For some, “understanding” means a detailed exposition of every component, reaction, and features of a particular instance of a system.

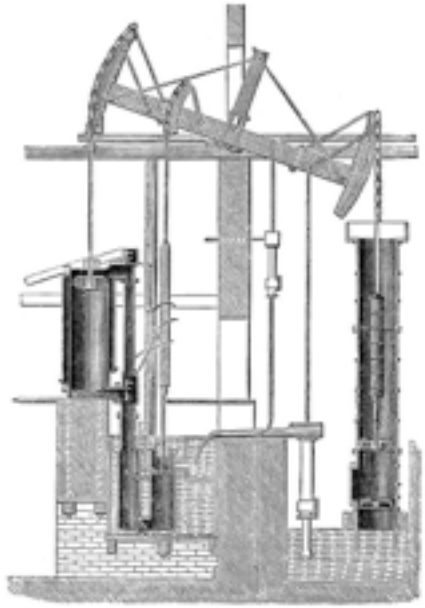
Karr et al. (2012) Cell, 150, 389-401

Consider the status of “understanding” the relationship of heat and work in the early 1900’s....



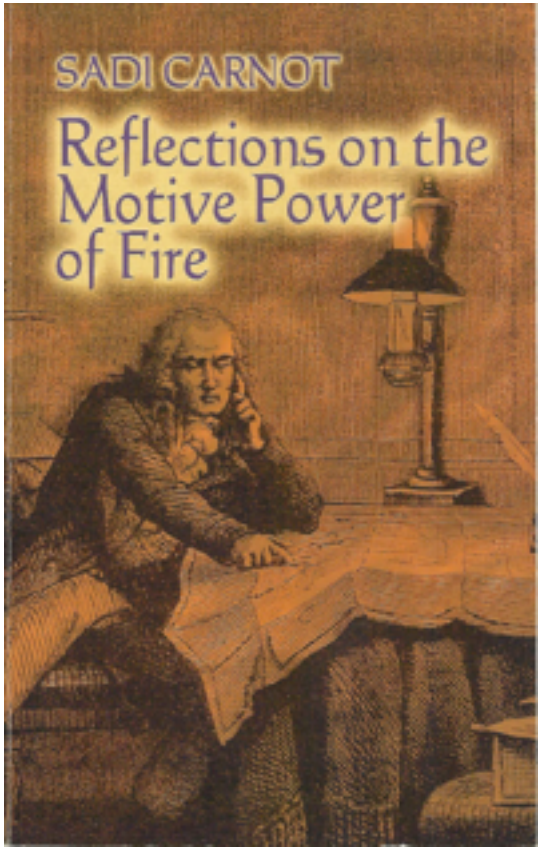





Watt's Single-Acting Pumping-Engine for Mines.

The general approach was a detailed modeling of the Newtonian mechanics of each sort of heat engine....but then....

...came Sadi Carnot...



"..the phenomenon of the production of motion by heat has not been considered from a sufficiently general point of view. We have considered it only in machines the nature...of which have not allowed us to take in the whole extent of application...In such machines, the phenomenon is, in a way, incomplete. It becomes difficult to recognize its principles and study its laws..."

"In order to consider in the most general way the principle of the production of motion by heat, it must be considered independently of any mechanism or any particular agent. It is necessary to establish principles applicable....to all imaginable heat engines, whatever the working substance and whatever the method by which it is operated..."

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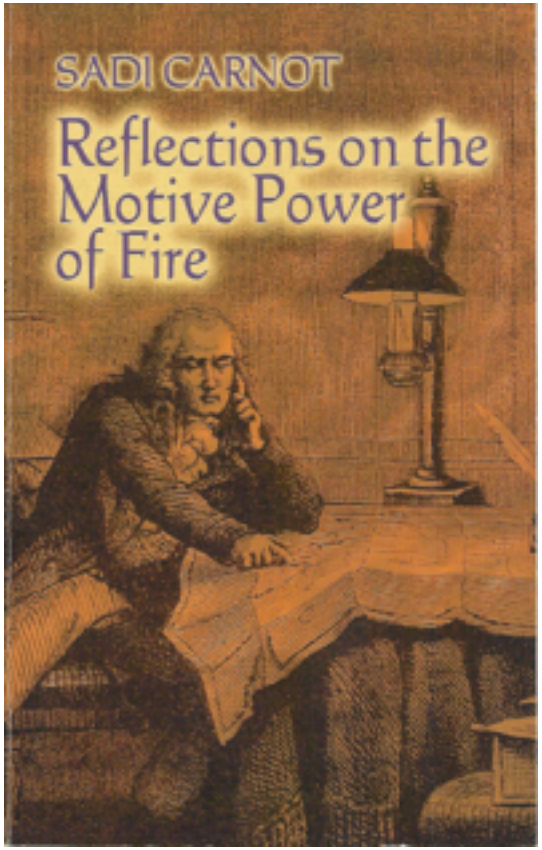

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What emerged were the laws of thermodynamics....

So...