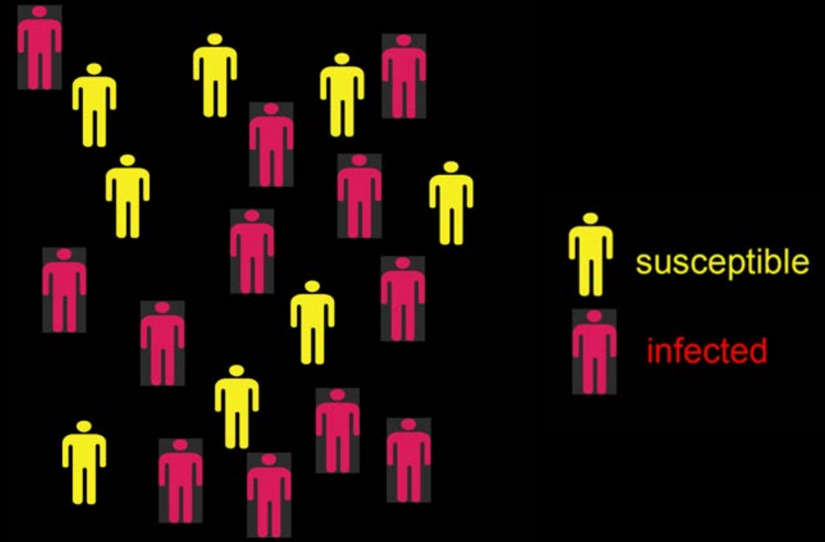
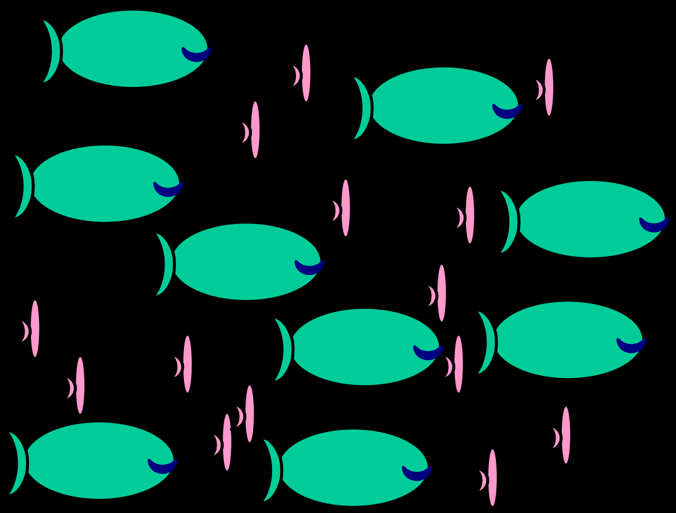
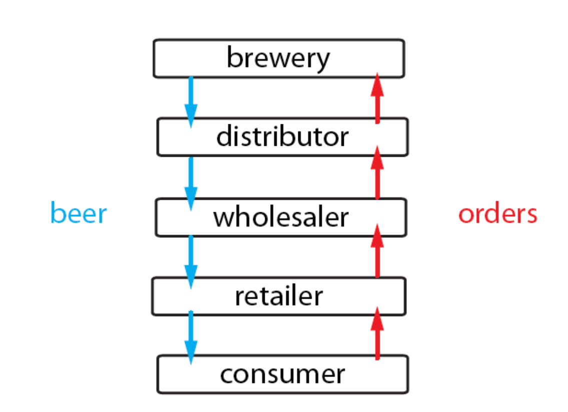
Teaching Dynamics to Biology Undergrads





Alan Garfinkel
Professor of Medicine
and Integrative Biology and Physiology
UCLA



OLSUME Oct 10 2023

HHMI

AAMC
Tomorrow's Doctors, Tomorrow's Cures®

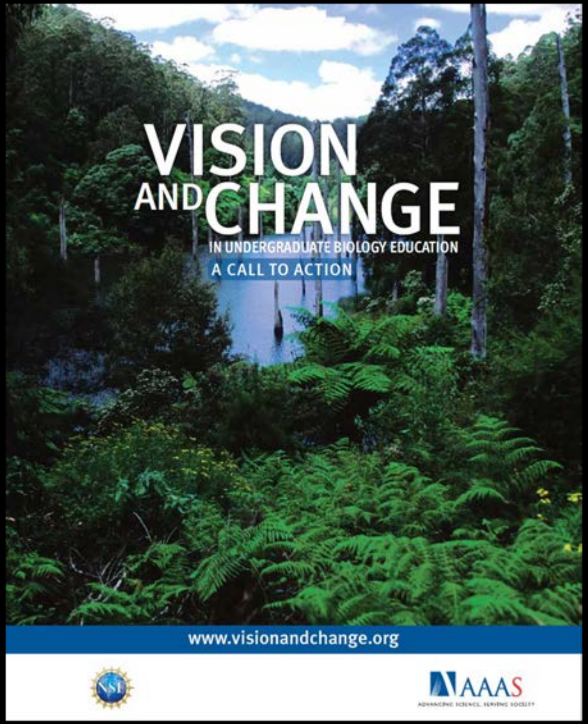
2009

Scientific Foundations for Future Physicians

"Undergraduate Competencies"

"Quantify and interpret changes in dynamical systems

- positive or negative feedback.
- explain how feedback mechanisms lead to damped oscillations in glucose levels. …
- Use the principles of feedback control to explain how specific homeostatic and reproductive systems maintain the internal environment and identify (1) how perturbations in these systems may result in disease and (2) how homeostasis may be changed by disease."



NSF
AAAS

2011

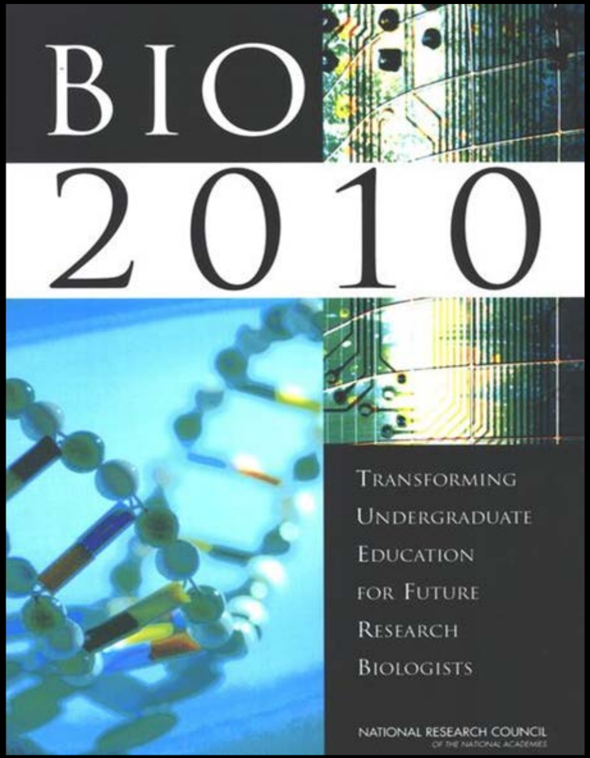
"Studying biological dynamics requires a greater emphasis on modeling, computation, and data analysis tools.

- the dynamic modeling of neural networks helps biologists understand emergent properties in neural systems.

- Systems approaches to examining population dynamics in ecology also require sophisticated modeling.

Alan Garfinkel UCLA

what kind of math do we need to study feedback loops?



National Academy of Sciences

"Mathematical/computational methods should be taught, but on a need-to know basis….

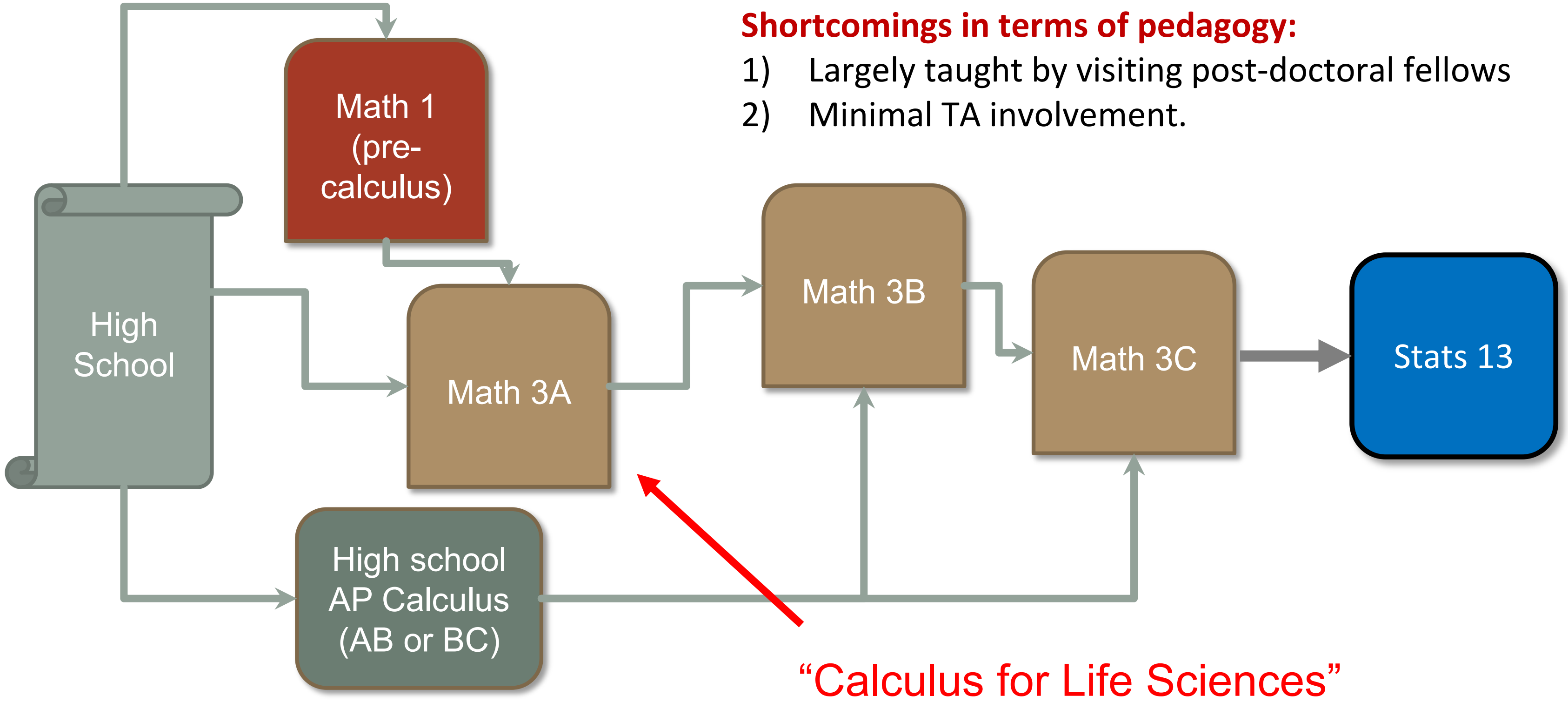
The emphasis should not be on the methods per se, but rather on how the methods elucidate the biology.

*…**ordinary differential equations** (made tractable and understandable via Euler's method without any formal course in differential equations required)… "*

Shortcomings of current Math department offerings

Shortcomings in terms of content:
1) Lack of biologically relevant examples and mathematical approaches.
2) No computational lab.

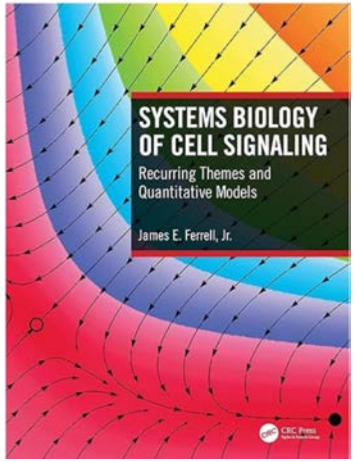
Shortcomings in terms of pedagogy:
1) Largely taught by visiting post-doctoral fellows
2) Minimal TA involvement.



Deans Blaire Van Valkenburg, Victoria Sork
UCLA

Life Sciences want:

- multivariable non-linear differential equations
- as models for biological phenomena
- studied through computer simulation and dynamical systems theory (equilibrium points, etc.)



our Instructors (research postdocs) cannot teach this.
our Grad students cannot TA this.

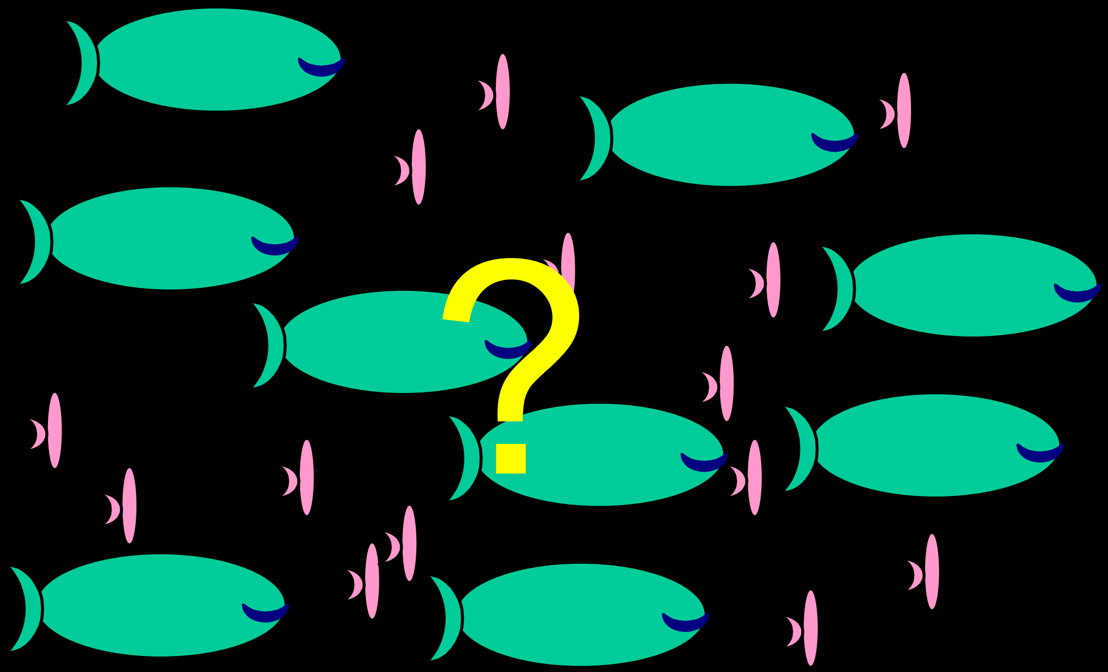
Do not agree with our emphasis on dynamics and modeling.

Strongly question whether the class would prepare students for Physics.

(to the Senior Dean for Life Sciences): “Victoria, computers play no role in mathematics”

UCLA LS30

- <u>freshman</u> biology students
- <u>no prerequisite</u>
- replaces "Calculus for Life Sciences"
- currently enrolling ~2000 students/yr



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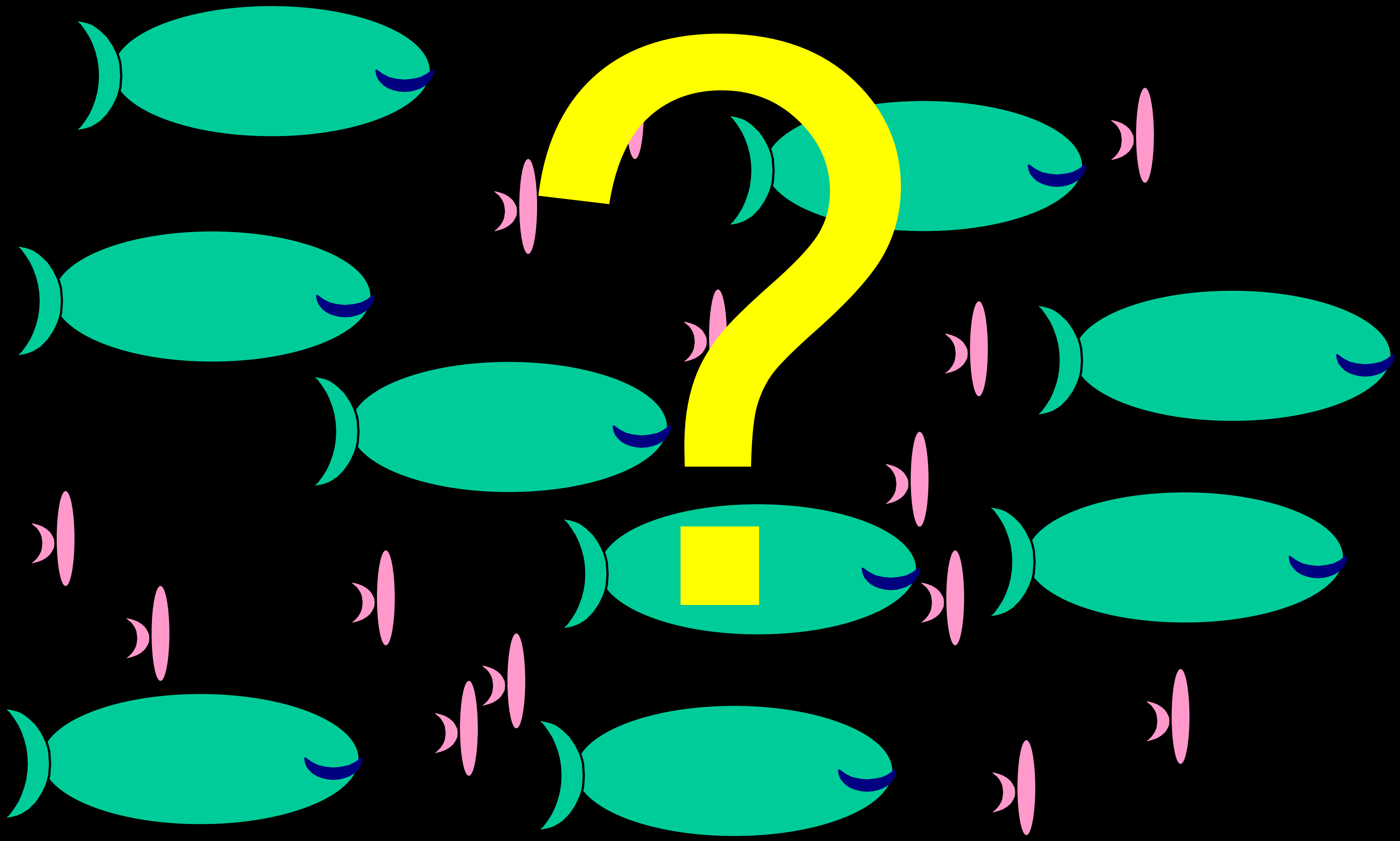

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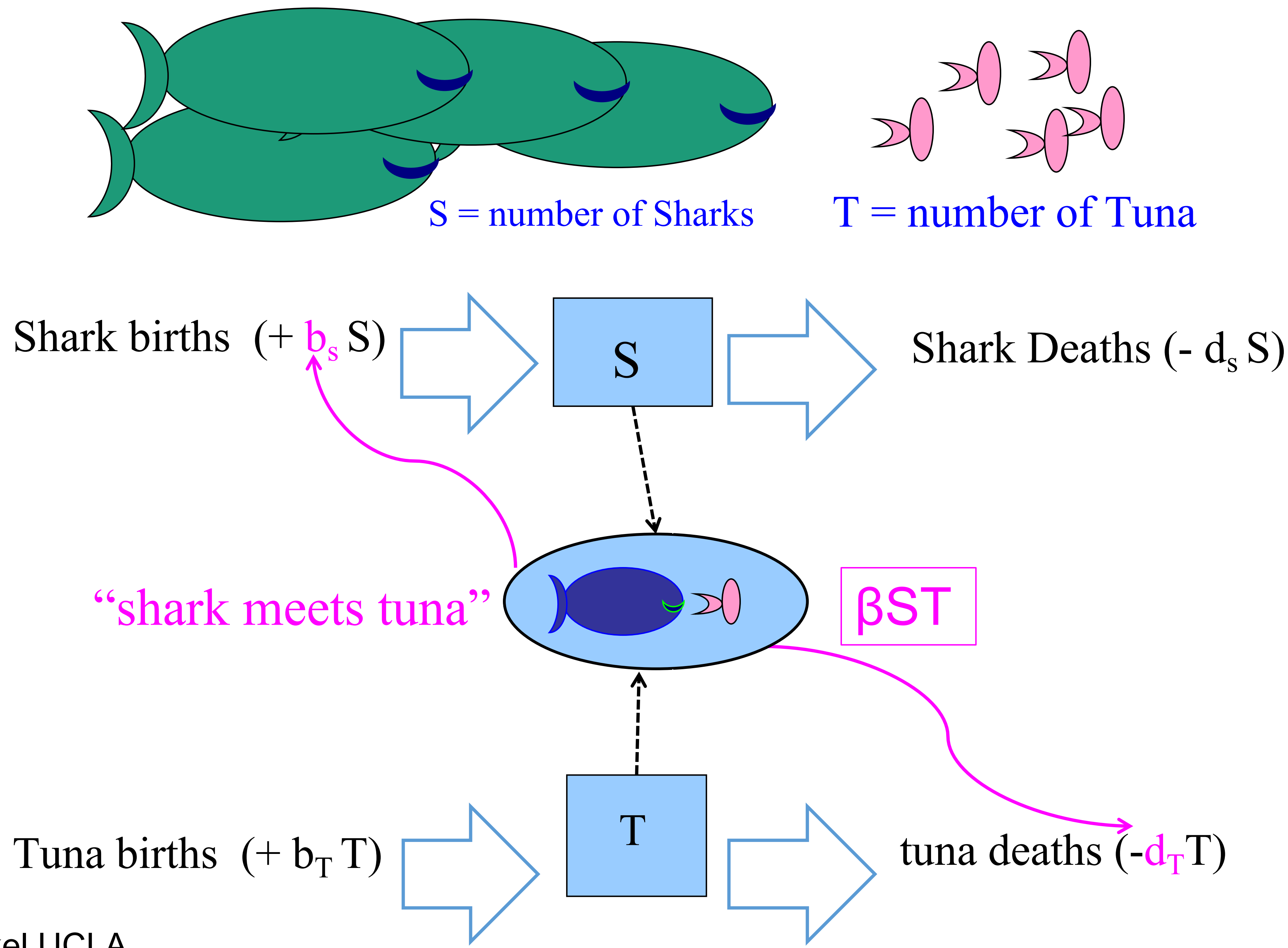
Why do we need mathematical modeling?

because you can’t figure out the behavior of a feedback system by “intuition”

Alan Garfinkel UCLA

How to make a model

Alan Garfinkel UCLA



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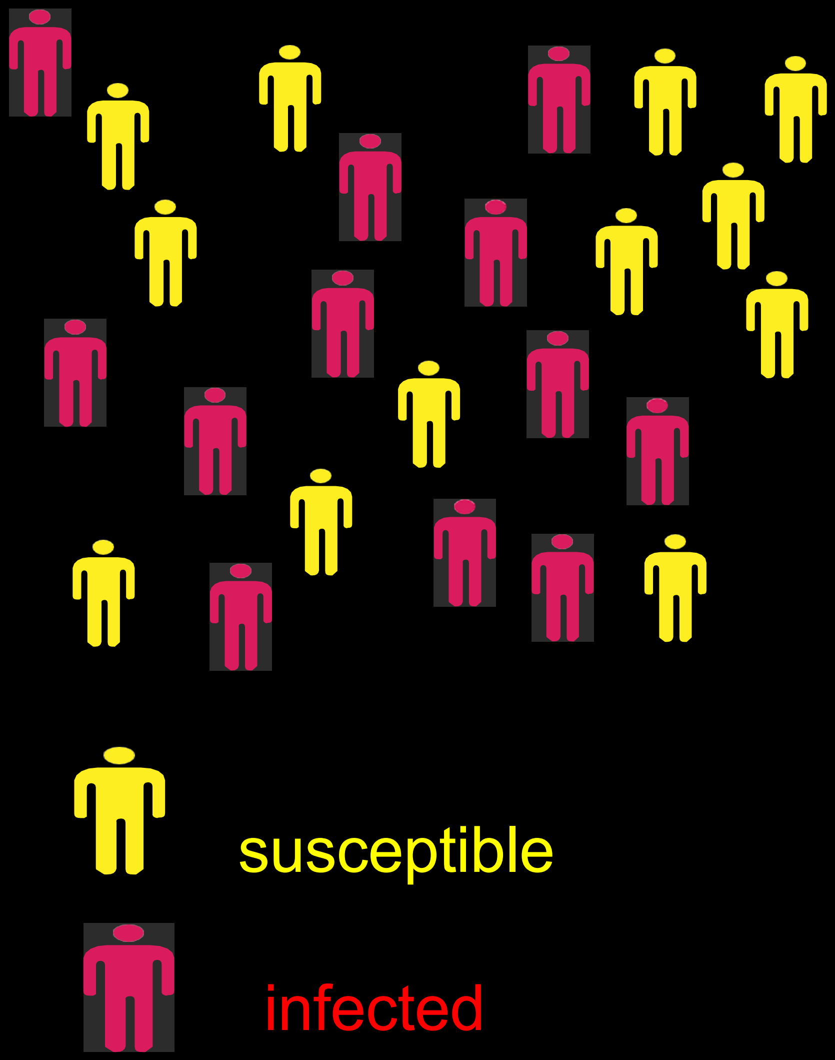
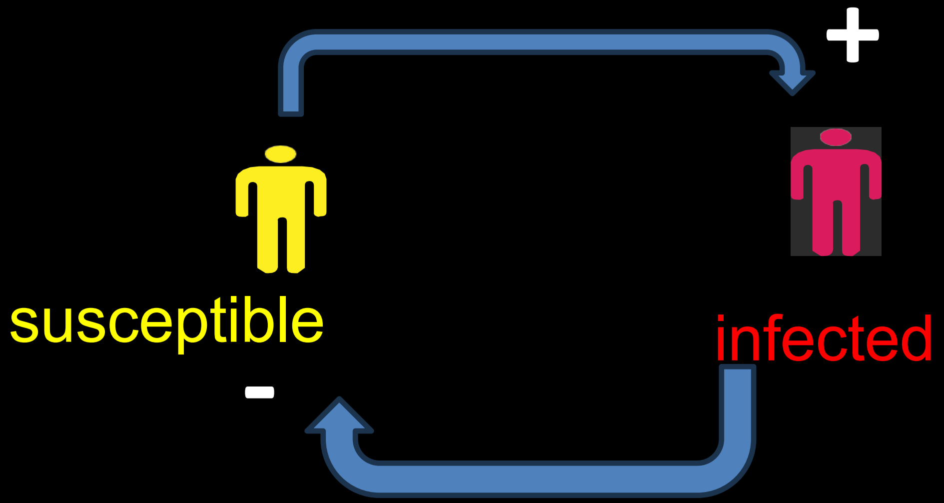
Epidemiology: feedback loops





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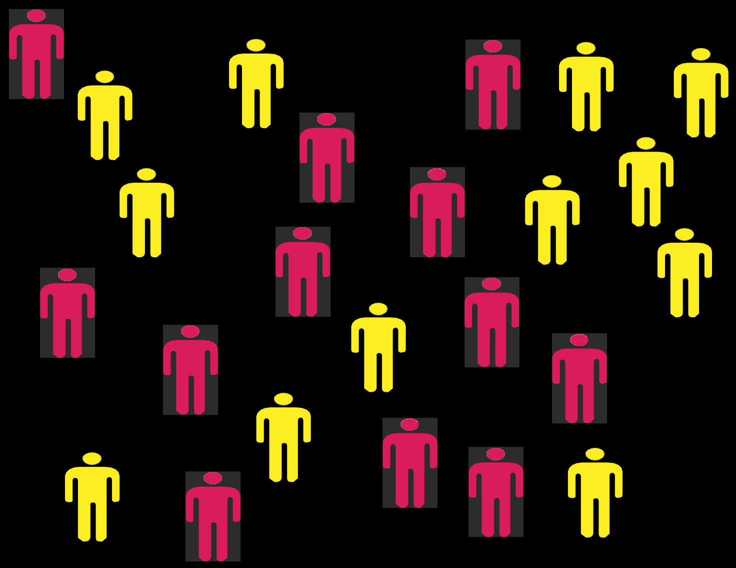
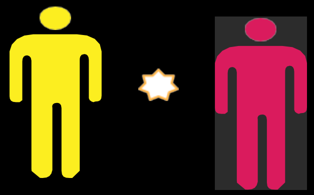
Epidemiology

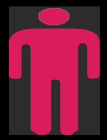


$$S' = b - mS - \beta SI$$
$$I' = -mI - dI + \beta SI$$

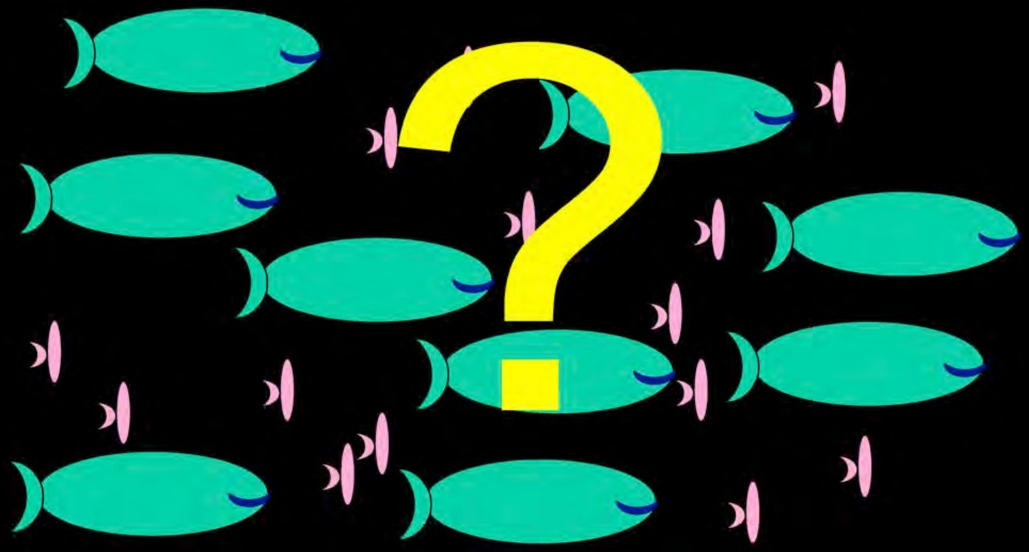


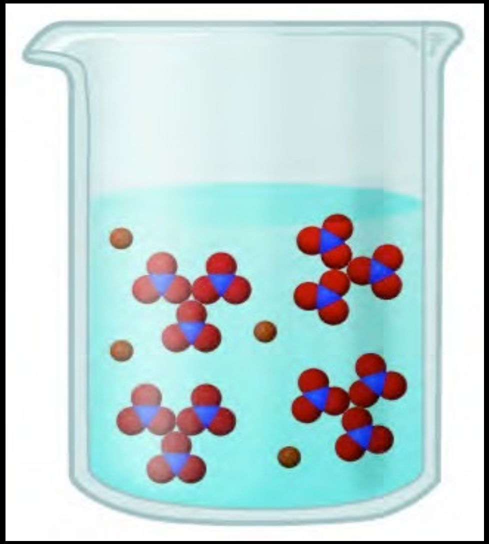
$$\beta * S * I$$


susceptible


infected

How is shark-tuna model like a chemical reaction?

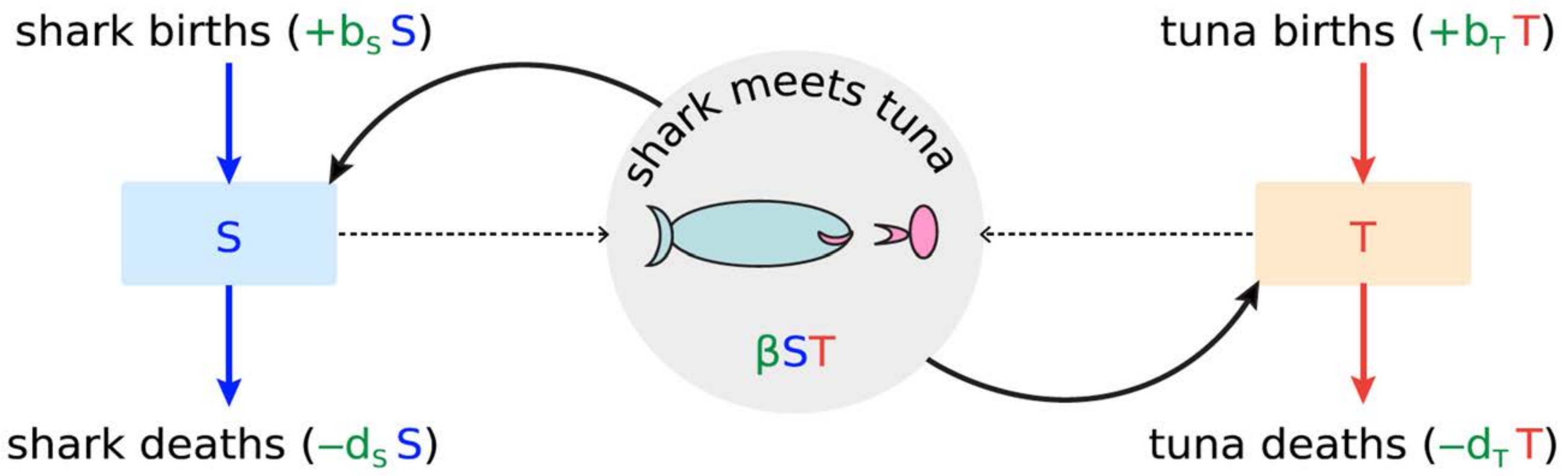




$$S + T \xrightarrow{\beta} 2S$$
$$S \xrightarrow{d} D$$
$$T \xrightarrow{b} 2T$$

$$A + B \xrightarrow{k} C$$

$$A' = -kAB$$
$$B' = -kAB$$
$$C' = +kAB$$



"Change Equation"

"the change in S" $S' = +b_S S \quad -d_S S \quad +k\beta ST$

shark birth — shark death — shark eats tuna

"the change in T" $T' = +b_T T \quad -d_T T \quad -\beta ST$

tuna birth — tuna death — shark eats tuna

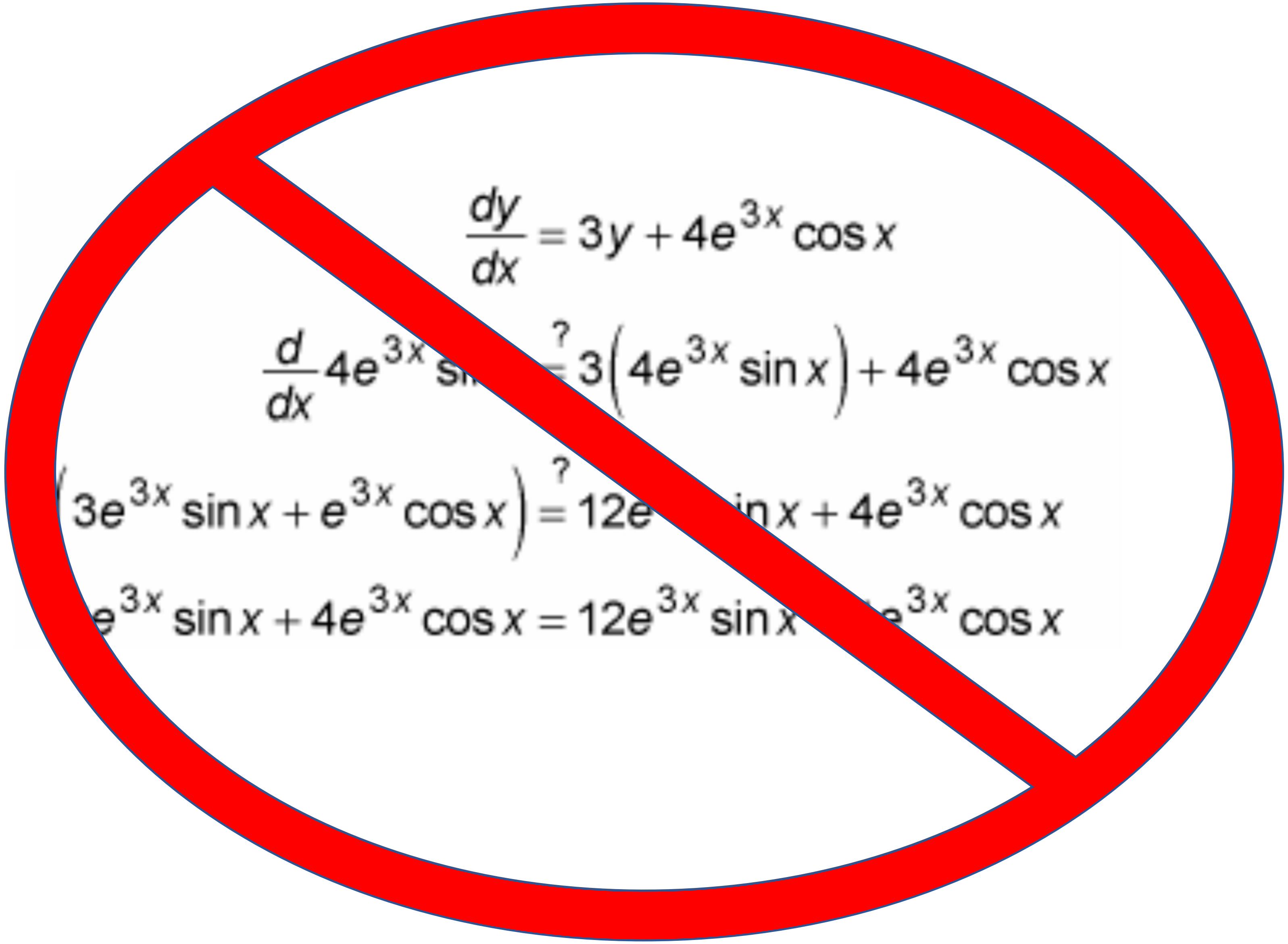
Alan Garfinkel UCLA

Garfinkel, A., S. Bennoun, E. Deeds and B. Van Valkenburgh (2022). "Teaching Dynamics to Biology Undergraduates: the UCLA Experience." Bulletin of Mathematical Biology

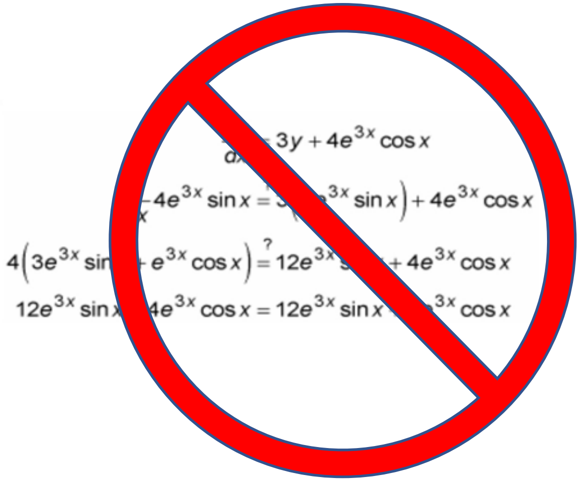
What do we do with a change equation?

"the change in S"	$S' =$	$+b_S S$	$-d_S S$	$+k\beta ST$
		shark birth	shark death	shark eats tuna
"the change in T"	$T' =$	$+b_T T$	$-d_T T$	$-\beta ST$
		tuna birth	tuna death	shark eats tuna

No symbolic manipulations!



The Shark-Tuna equations



$$S' = -d_S S + k\beta ST$$

$$T' = b_T T - \beta ST$$

<u>have no</u> analytic **solution**

Calculus: Fail

Alan Garfinkel UCLA

All the procedural tricks that constitute the standard approach to "Calculus" go out the window on the first day of real life

- infinitesimal limits and series; limit laws
- trigonometric identities
- procedural rules for differentiating famous functions
- L'Hopital's rule
- integrals as anti-derivatives
- Integration by parts
- integration by substitution of variables
- …..

Calculus from Hell

Q: What is a derivative?

A: "yeah, I took calculus. Like, the derivative of X^2 is 2X. You put the exponent in front of the variable, and then you have to drop the exponent by 1"

Michael C. Reed

DUKE UNIVERSITY

1987!!!

The first problem on the exam was to differentiate $x^{\sin x}$ and I said, "*That* is what is wrong with calculus."

Why should I spend all my time worrying about how to differentiate stupid looking functions like that? No function like that has ever occurred in the history of physics.

Well, it sounds like a joke, but it's not a joke. It means that the teaching of calculus has developed into a series of technical hurdles for students to go past, one after the other, bearing very little relation to what they're supposed to get out of the course.

$$S' = -d_S S \quad +k\beta ST$$

shark death — shark eats tuna

$$T' = +b_T T \quad -\beta ST$$

tuna birth — shark eats tuna

The "change equation" is a machine for spitting out the change instructions (change vectors) (S_0', T_0') for any given state (S_0, T_0)

"If you are at (S_0, T_0) head in the direction of the change vector (S_0', T_0'), at a speed equal to the length of the change vector"

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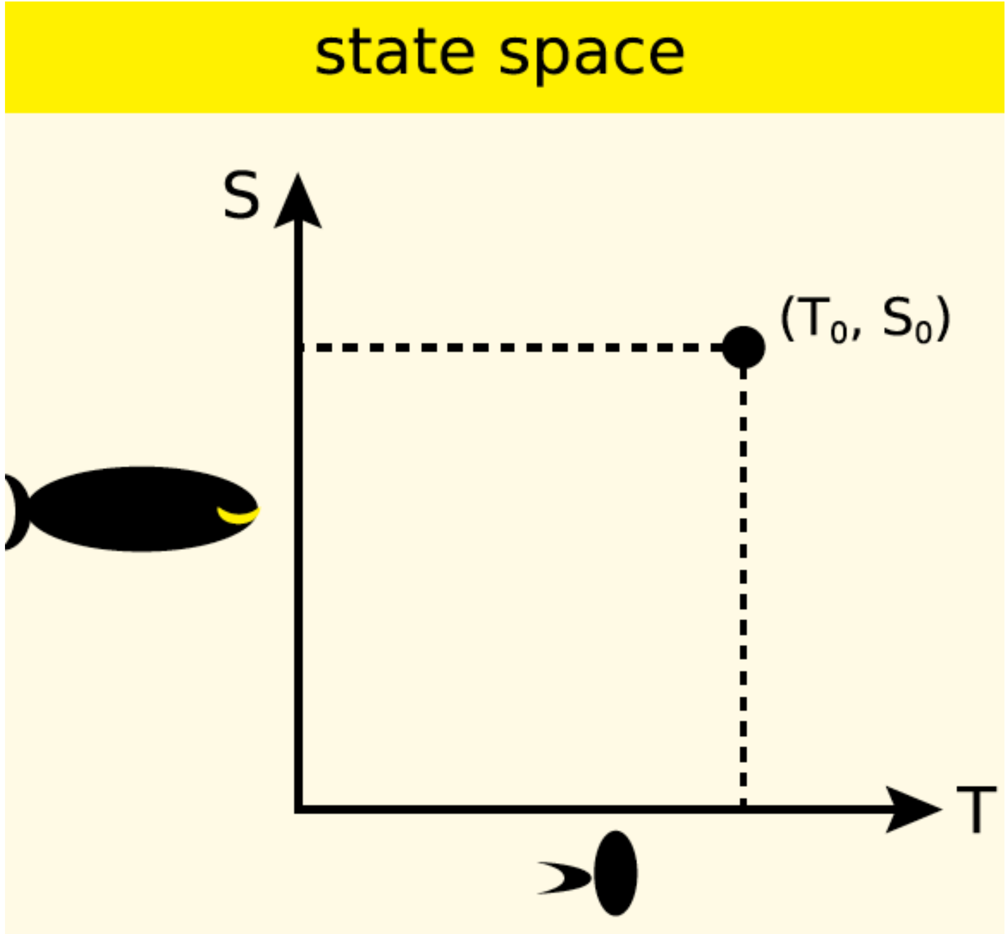
key concept #1: state space



The system state (T_0, S_0) is a point in (T, S) state space

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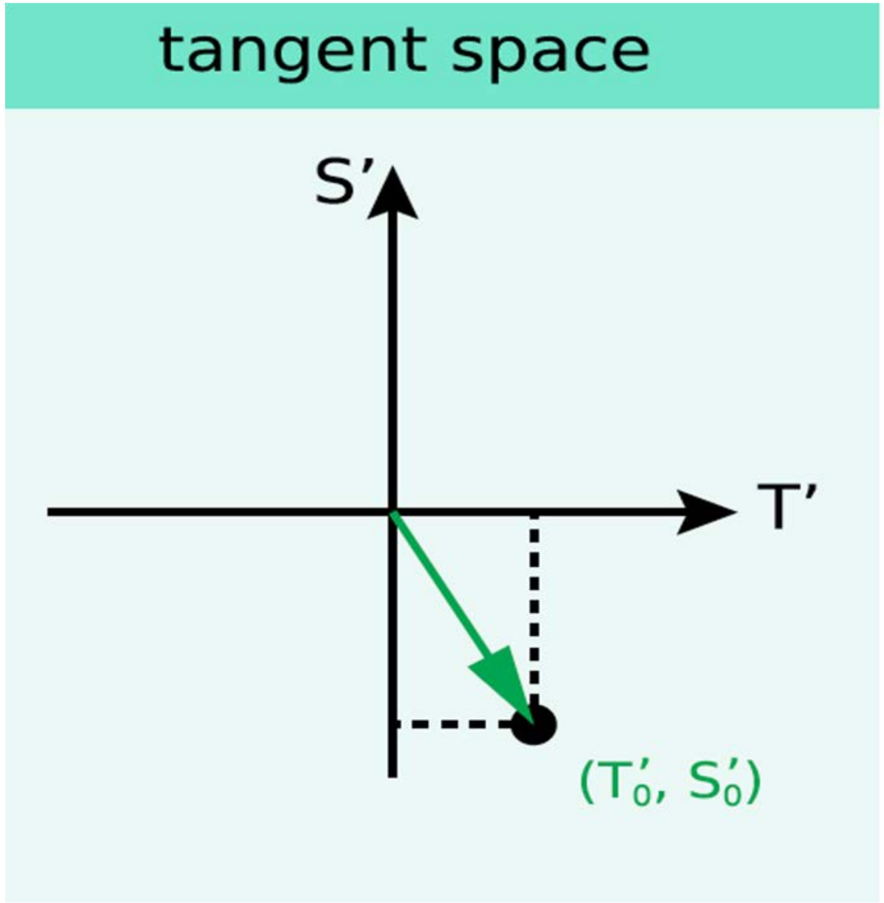
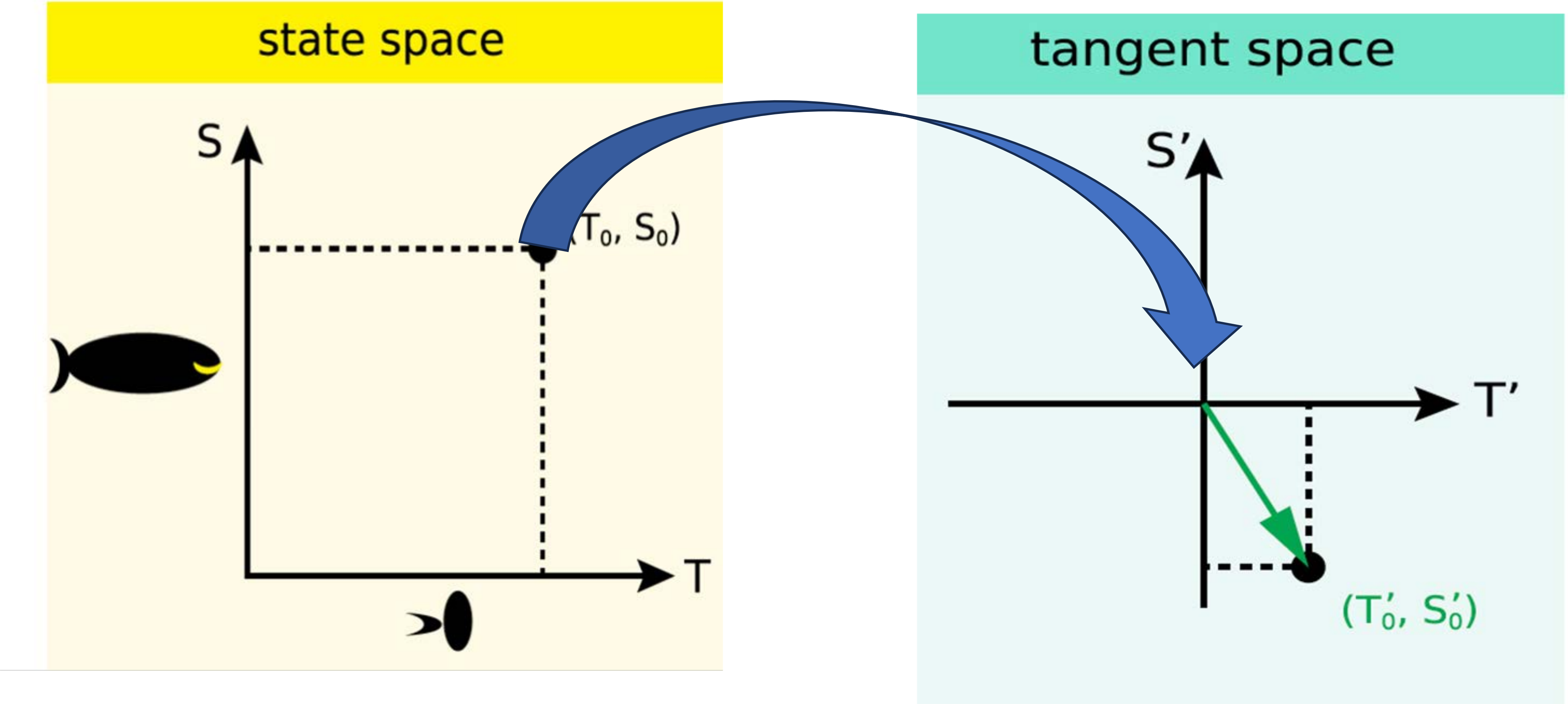
key concept # 2: change vector space



A point in tangent space is a change vector (T_0', S_0')

key concept #3: A “change equation” is a vectorfield



A *vectorfield* is a function from state space into tangent space

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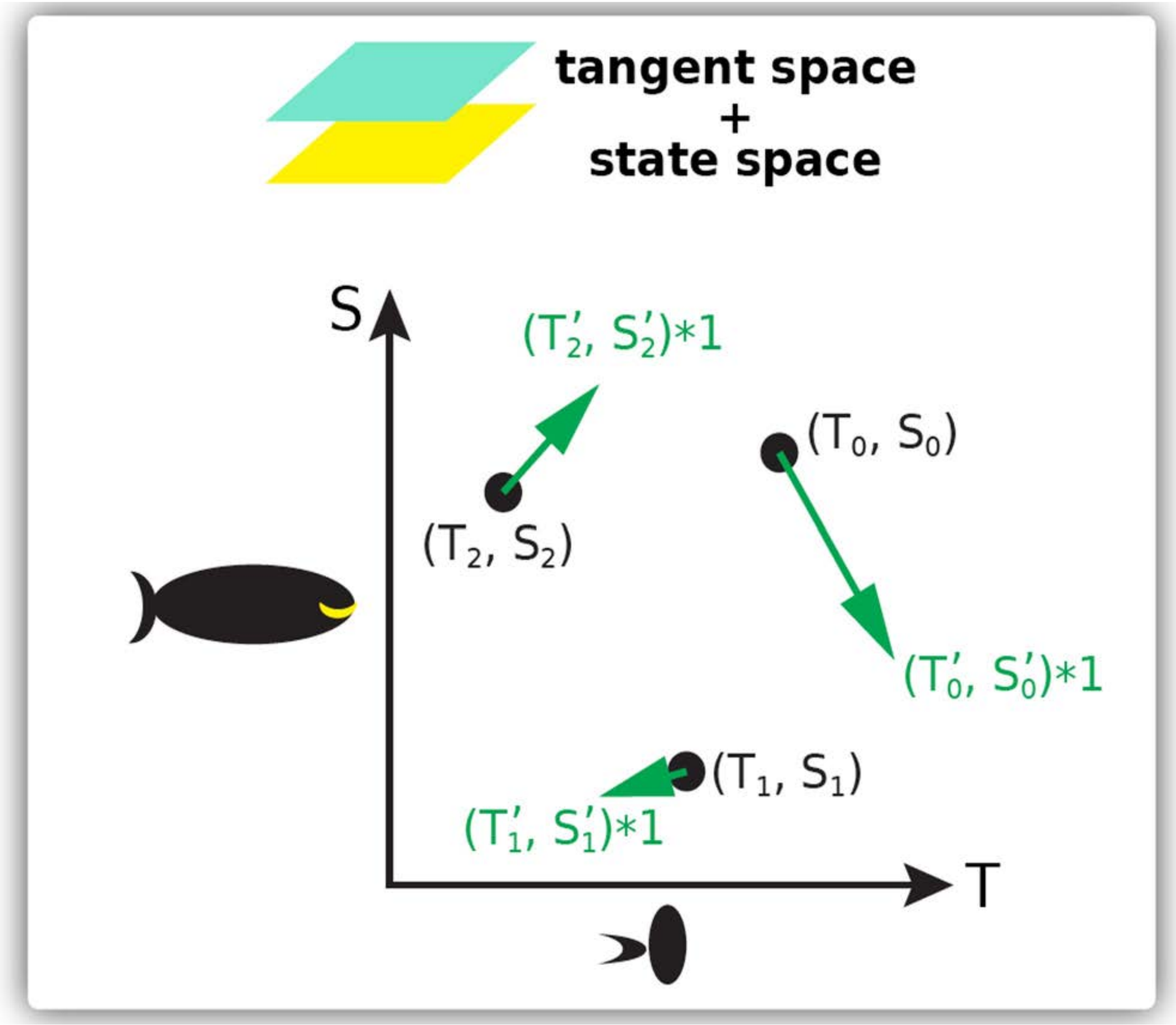
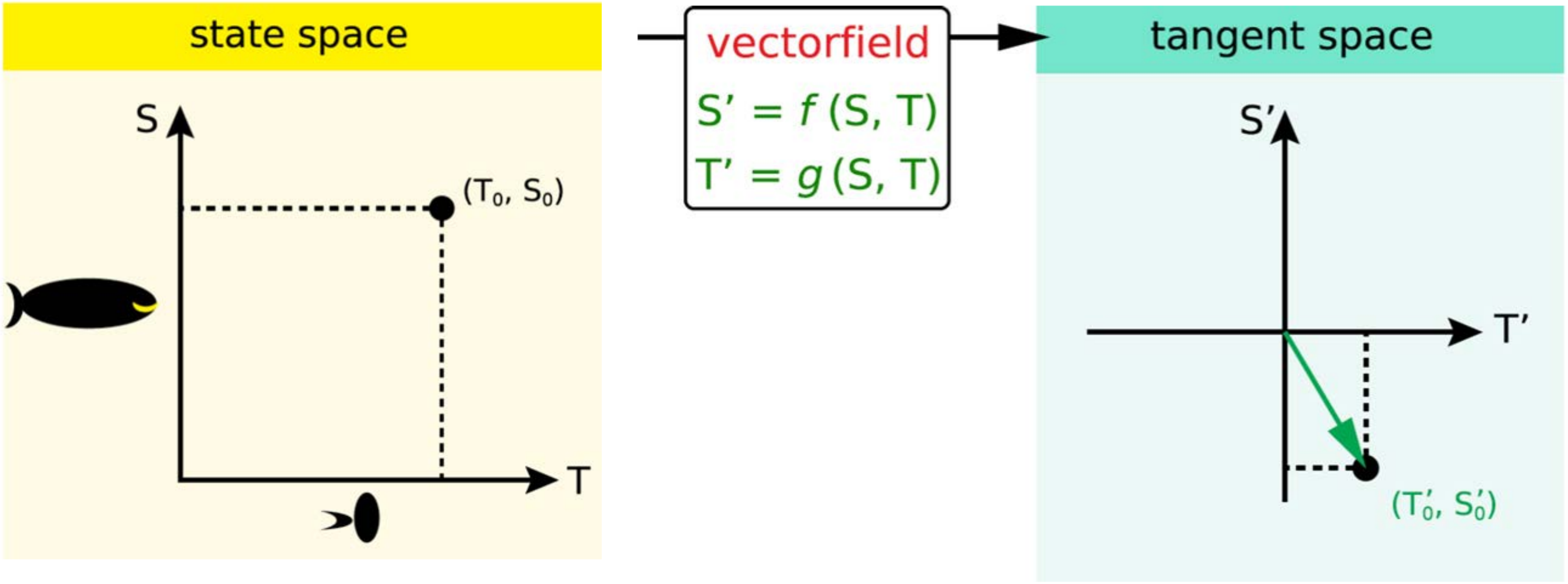
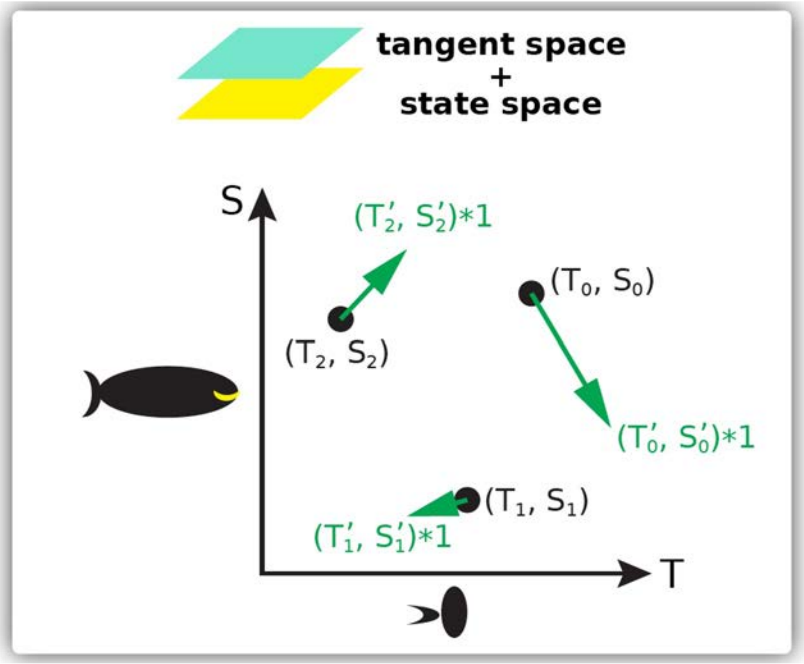
Writing the appropriate change arrows right on state space



Multiply (T_0', S_0') by 1t (t has units of time) and put it right on the point (T_0, S_0)



A *vectorfield* is a function from state space into tangent space



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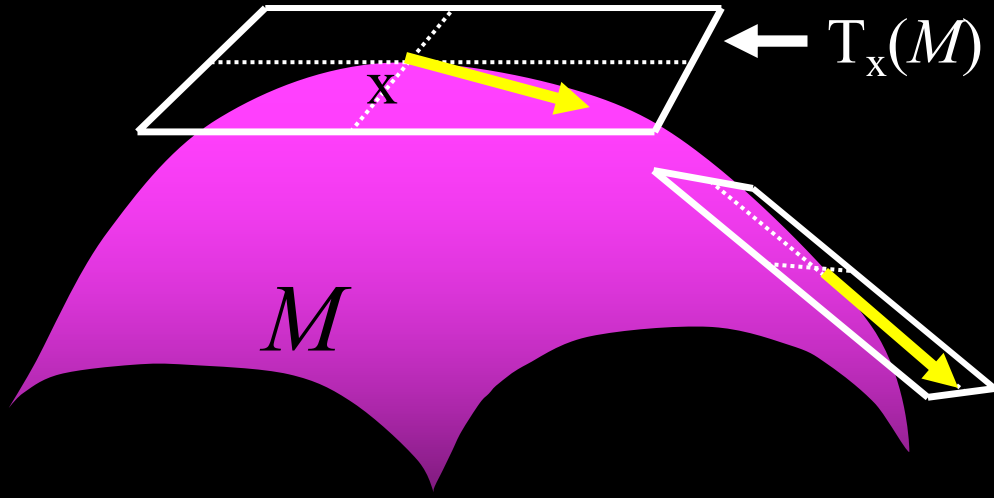

For each x εM, $T_x(M)$ is tangent space at x

$$T(M) = \left\{ T_x(M) \,\middle|\, x \,\varepsilon\, M \right\} \qquad \pi\!: T(M) \longrightarrow M$$

differential equation (vector field) V is **a cross-section of the tangent bundle**

$$\mathbf{V} : M \longrightarrow T(M)$$

$$\pi \circ \mathbf{V} = 1_M$$

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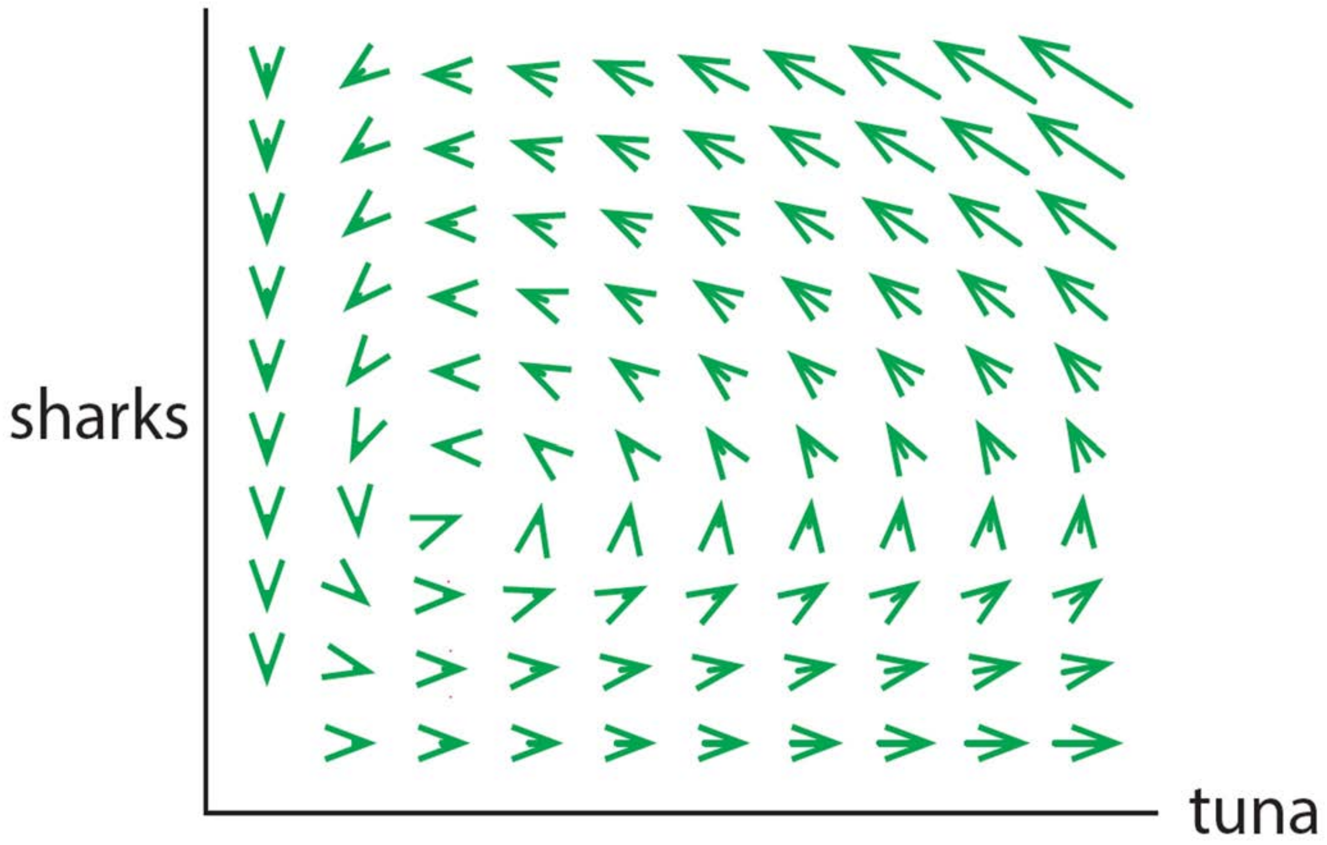

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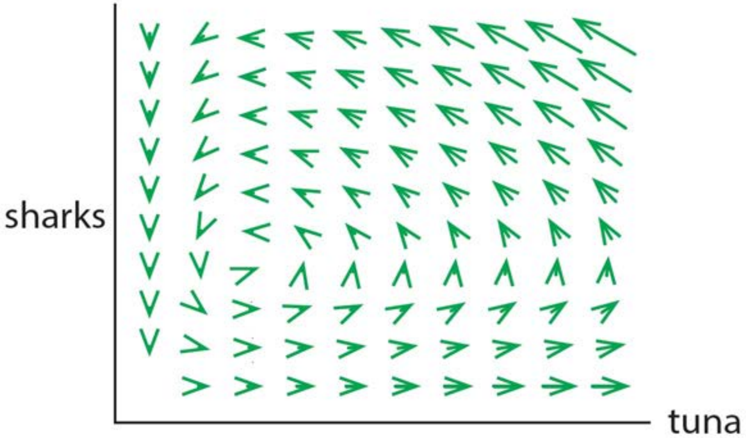
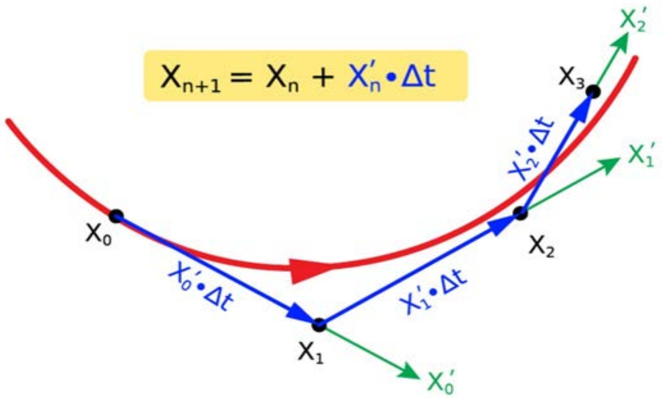
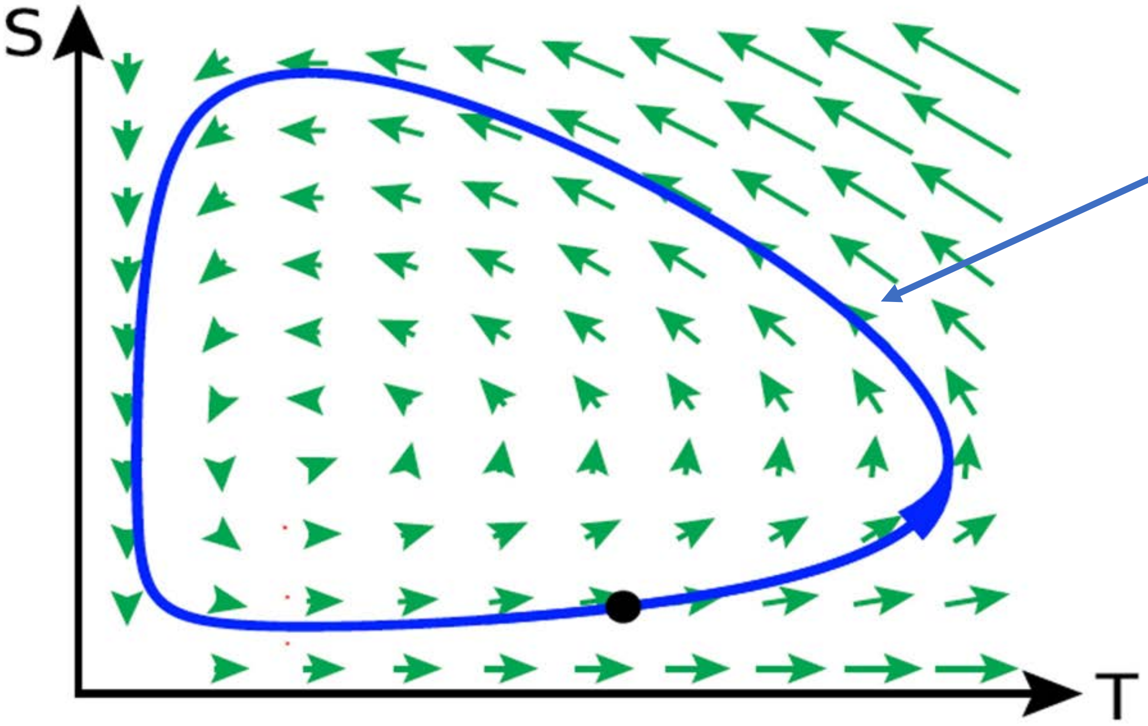




Euler's method



There is no equation for the blue curve

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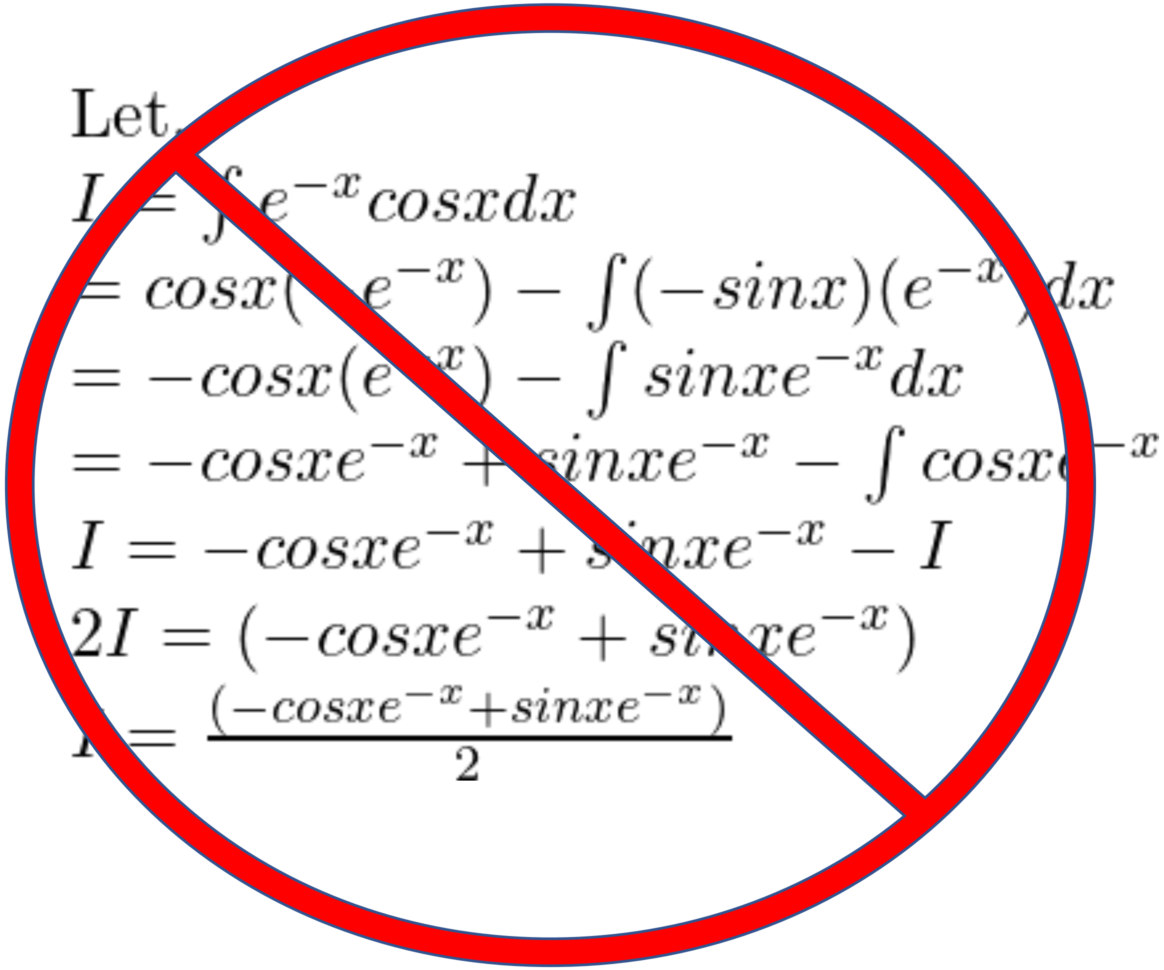
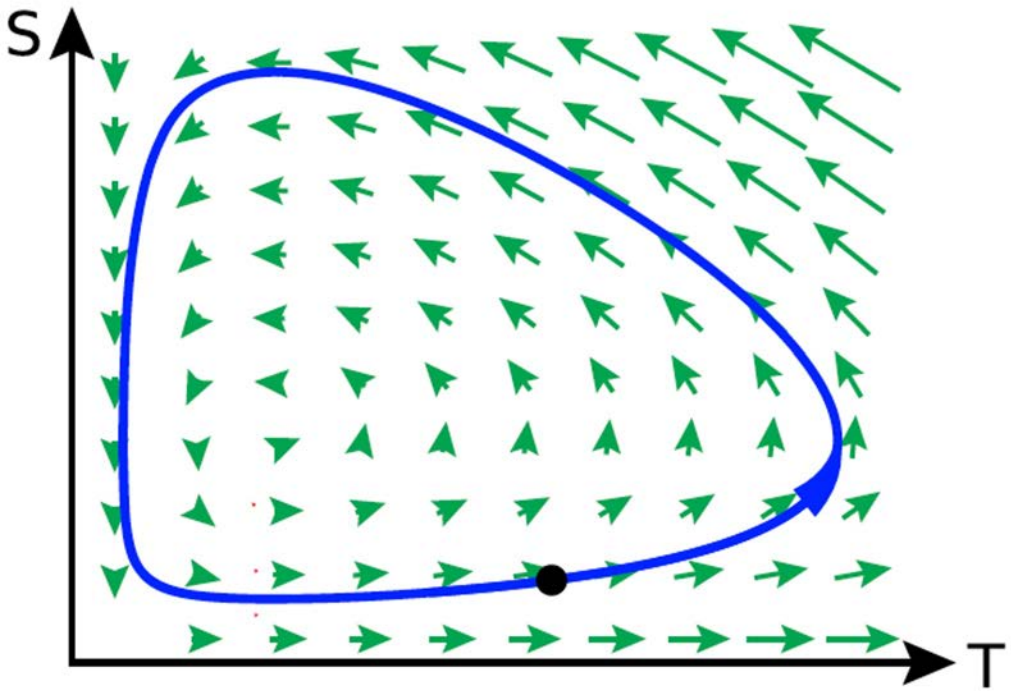
"I'm integrating a differential equation"





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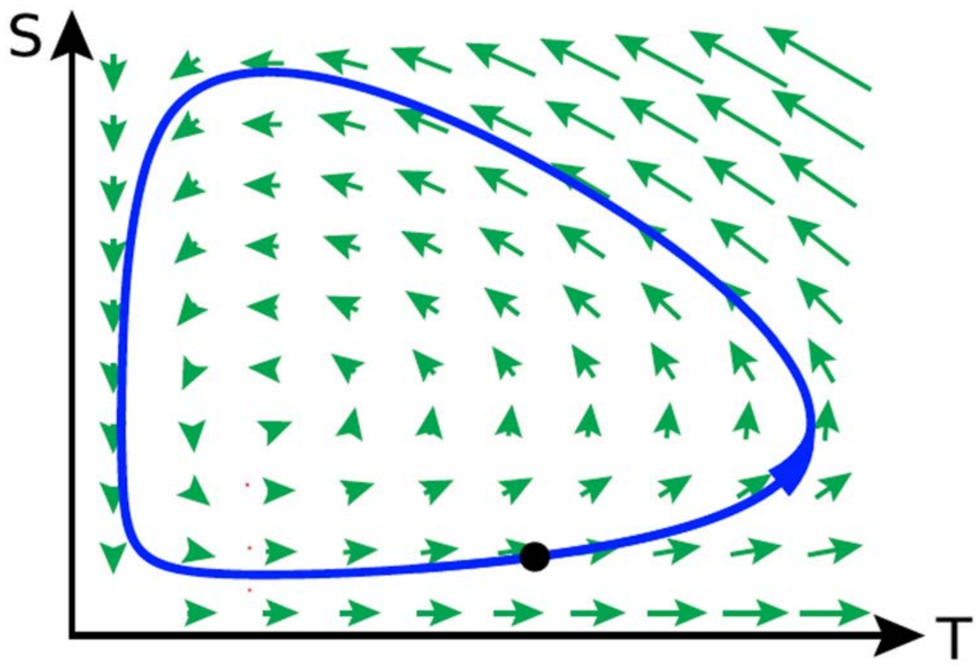
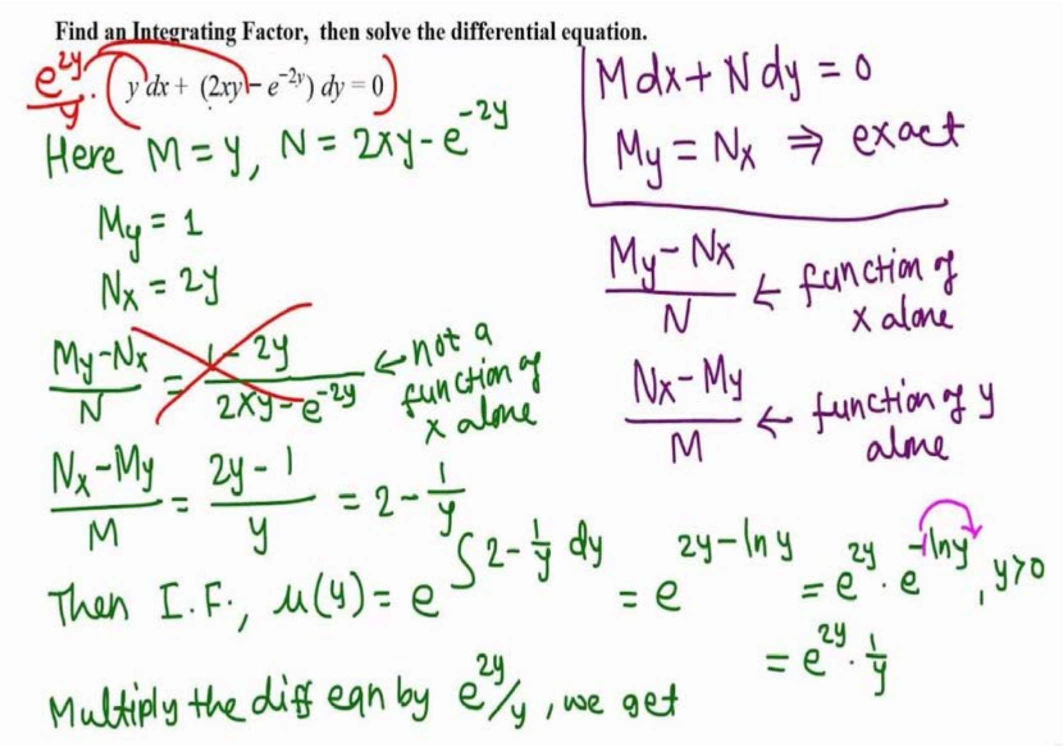
Python

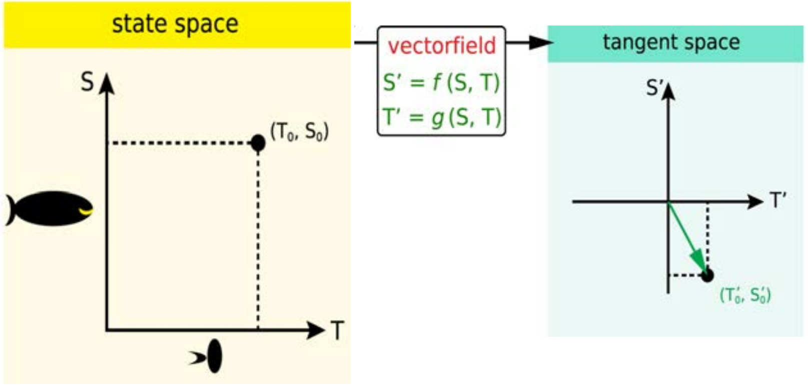
```
import numpy as np
import matplotlib.pyplot as plt

n = 10
t, s = np.linspace(0, 2, n), np.linspace(0, 2, n)
T, S = np.meshgrid(t, s)
fT = T - T*S
fS = T*S - S

plt.quiver(t, s, fT, fS, color ='g') # plot vector field
plt.streamplot(t, s, fT, fS,          # draw a trajectory
               start_points=[[1.8,1.2]], color="b")
```



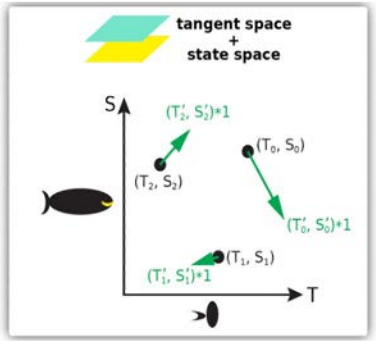
19th century



20th century



A *vectorfield* is a function from state space into tangent space



👉 **The 20th century concept is better pedagogy!**

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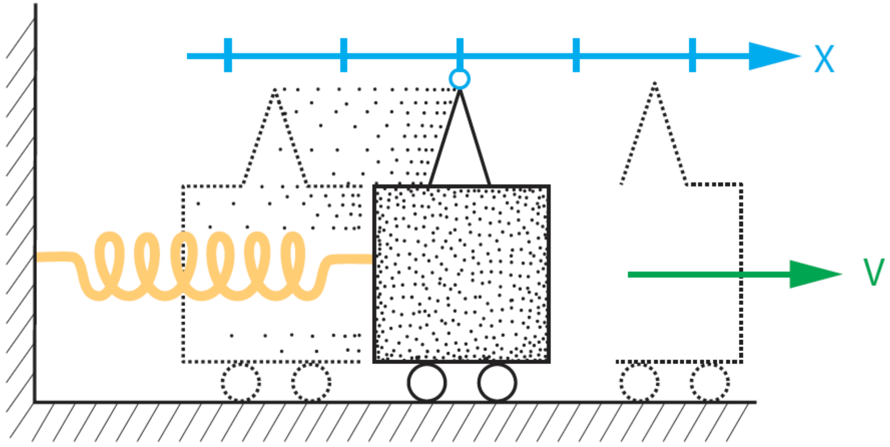
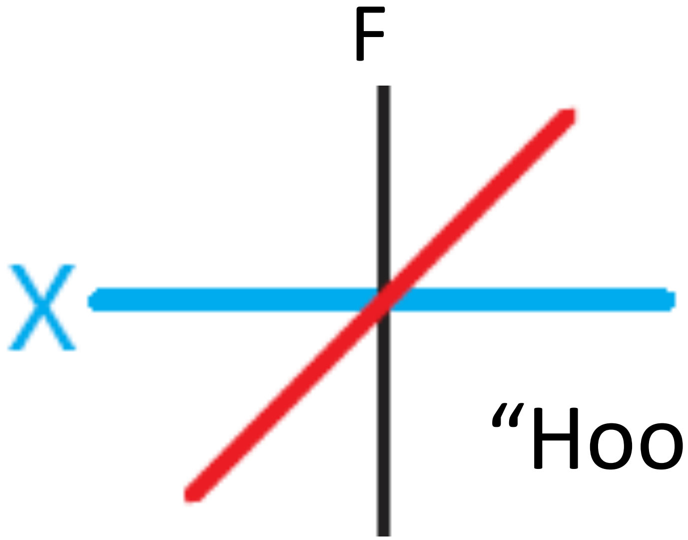


$X' = V$

$V' = -F$ (= Force)

(better way of thinking about "F = ma")

What is F in this case?
"Spring Force"



"Hooke's Law"

$X' = V$

$V' = -X$

X(t) = cos (t)
Y(t) = sin (t)

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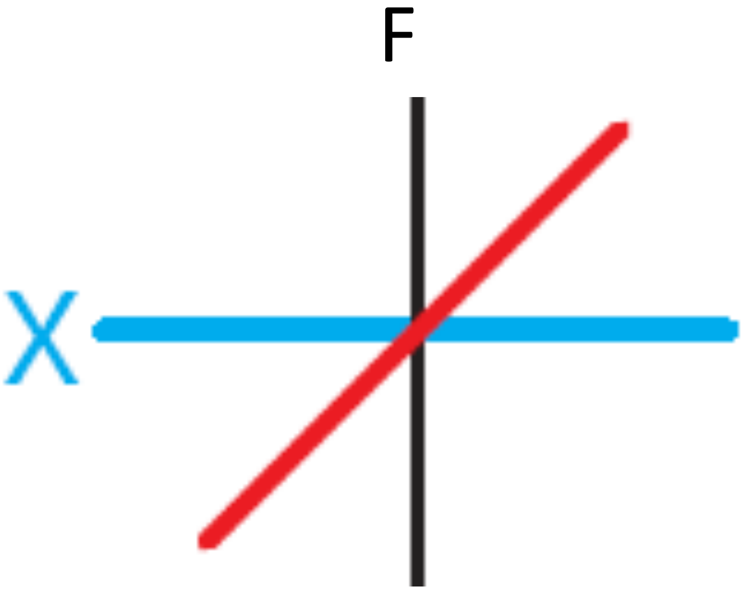
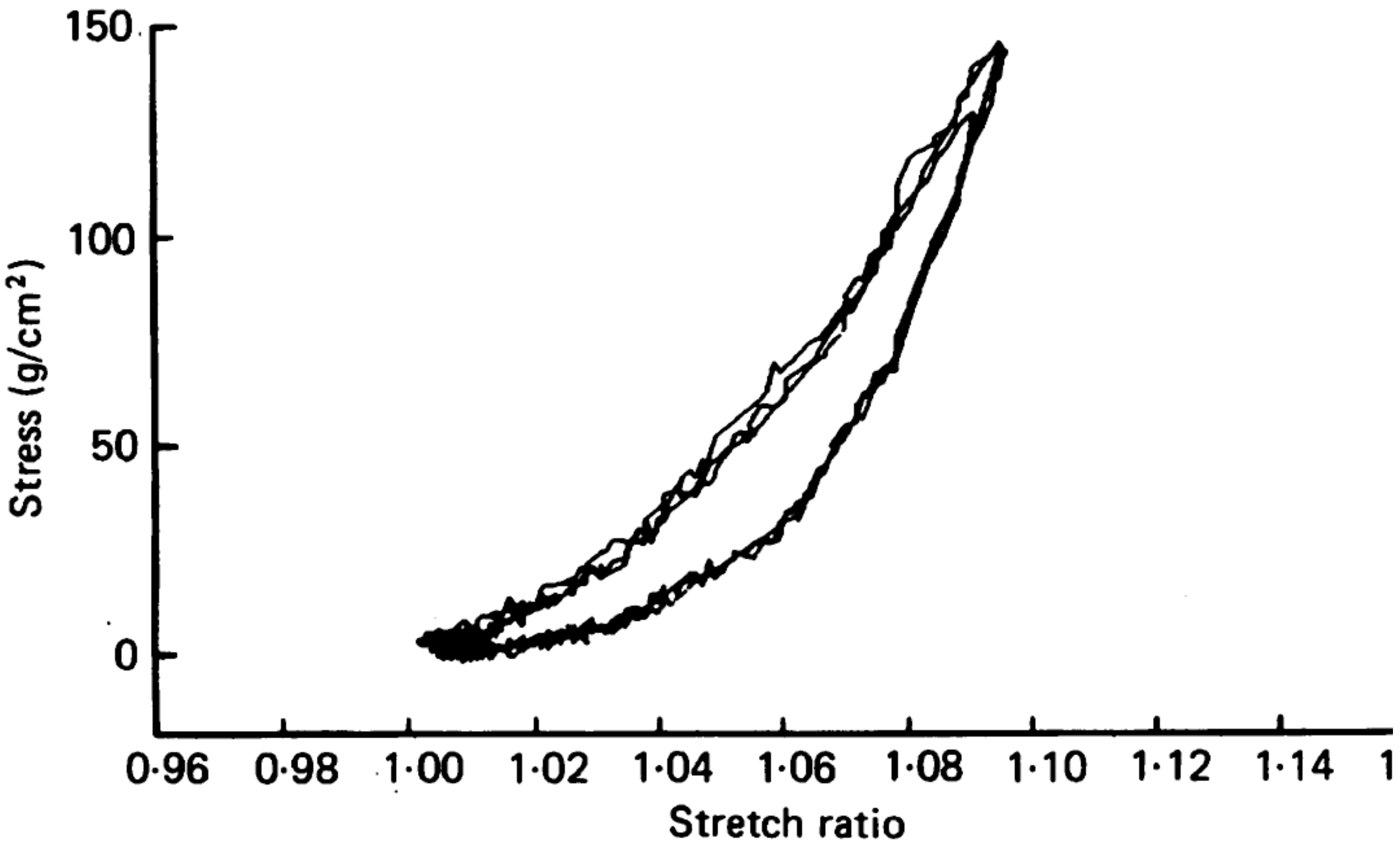


"Hooke's Law"

is false in biology!

The biological 'spring' (muscle, bone, cell membrane, etc.) is **nonlinear**



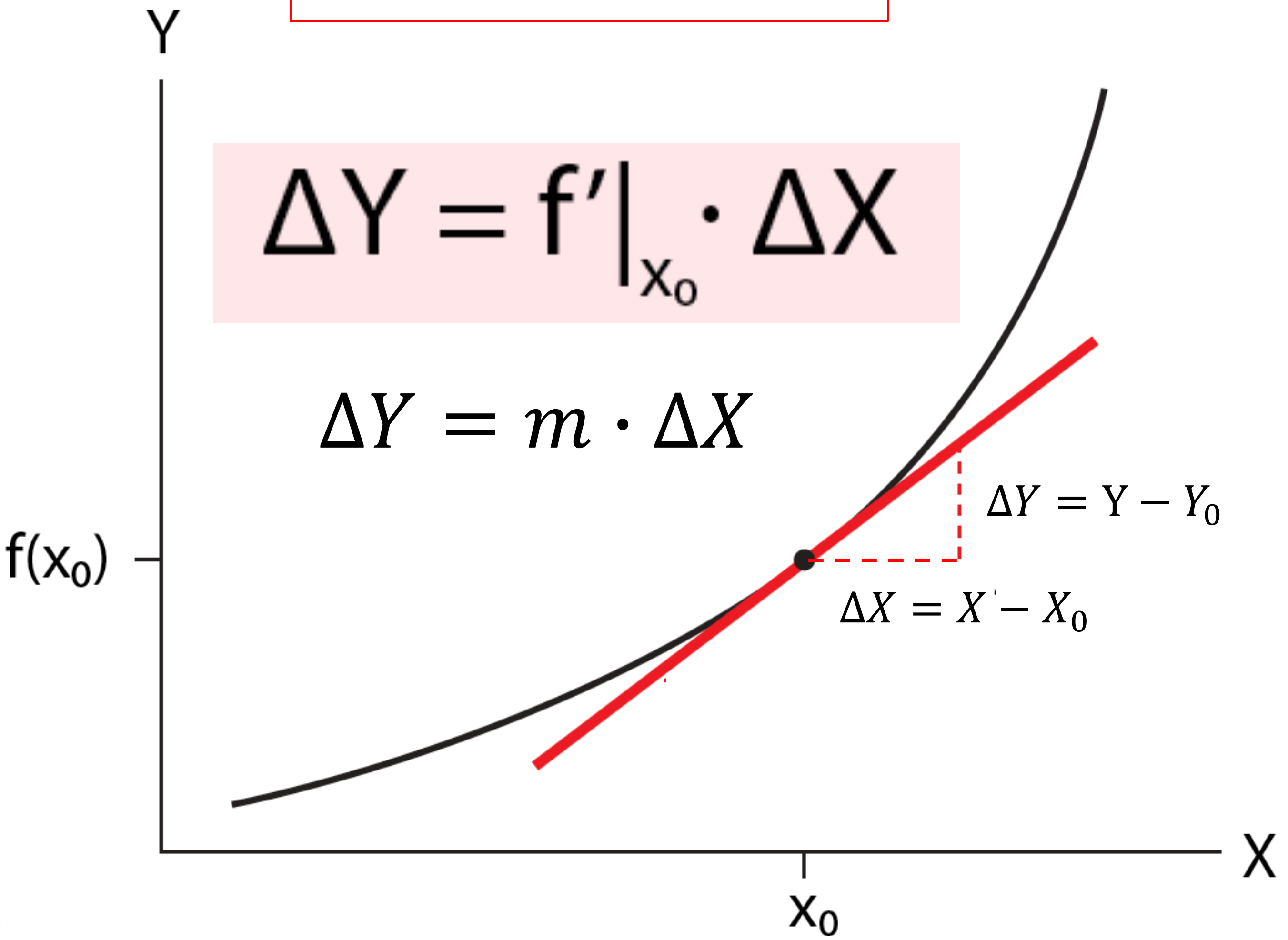
J. Physiol. (1983), **339**, *pp.* 615–630
With 7 text-figures
Printed in Great Britain
615

PASSIVE BIAXIAL MECHANICAL PROPERTIES OF ISOLATED CANINE MYOCARDIUM

BY LINDA L. DEMER* AND FRANK C. P. YIN†
From the Departments of Biomedical Engineering and Medicine†,*
Johns Hopkins Medical Institutions, Baltimore, MD 21205, U.S.A.

Alan Garfinkel UCLA

The Derivative



The derivative is the linear approximation to the function at a point

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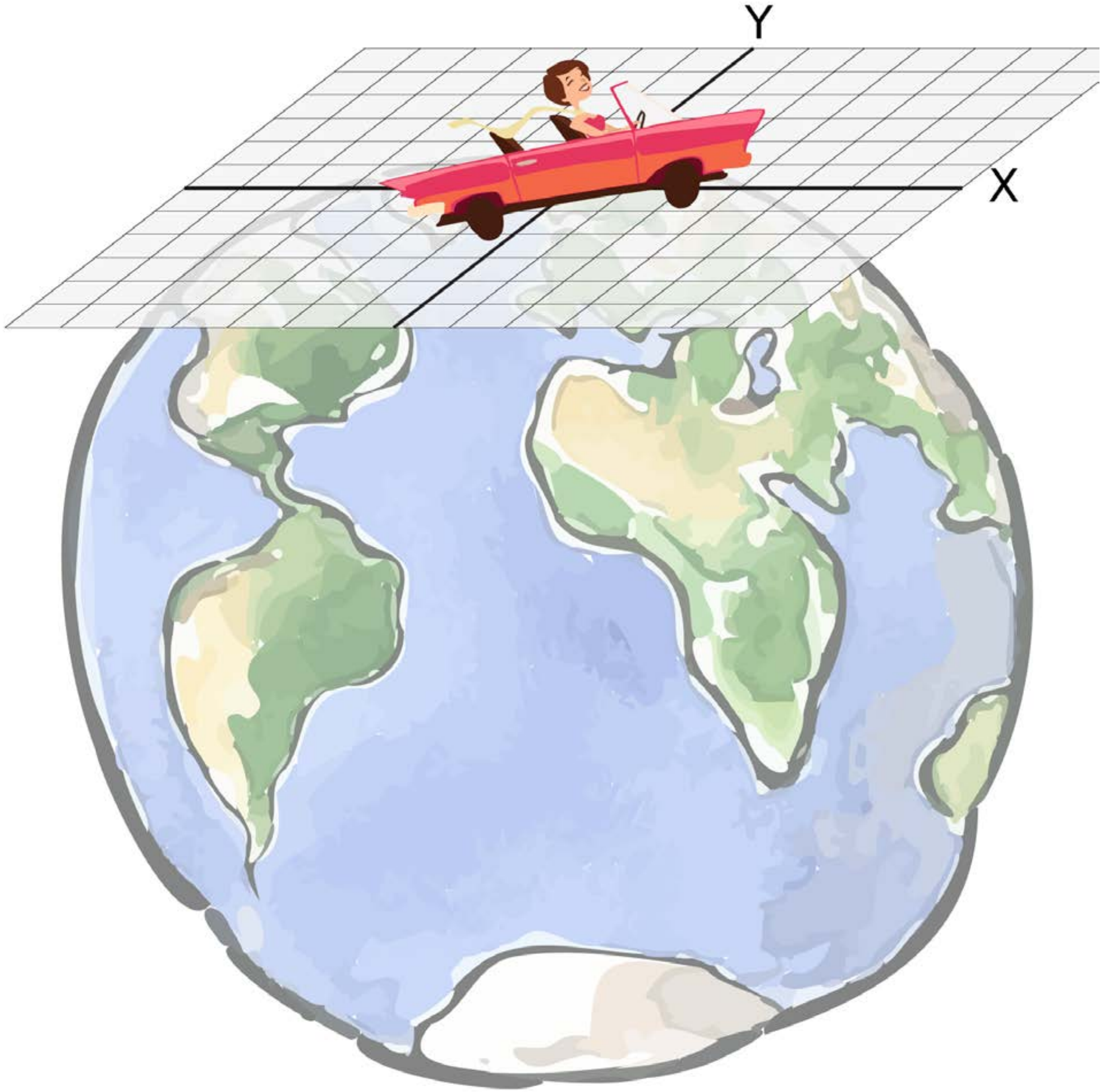
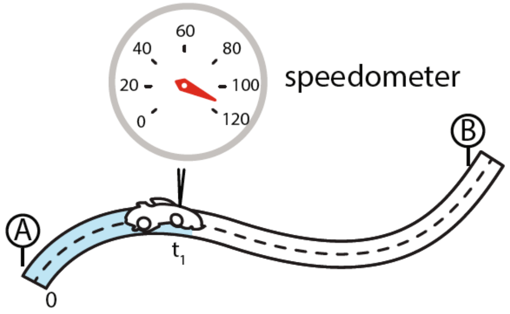
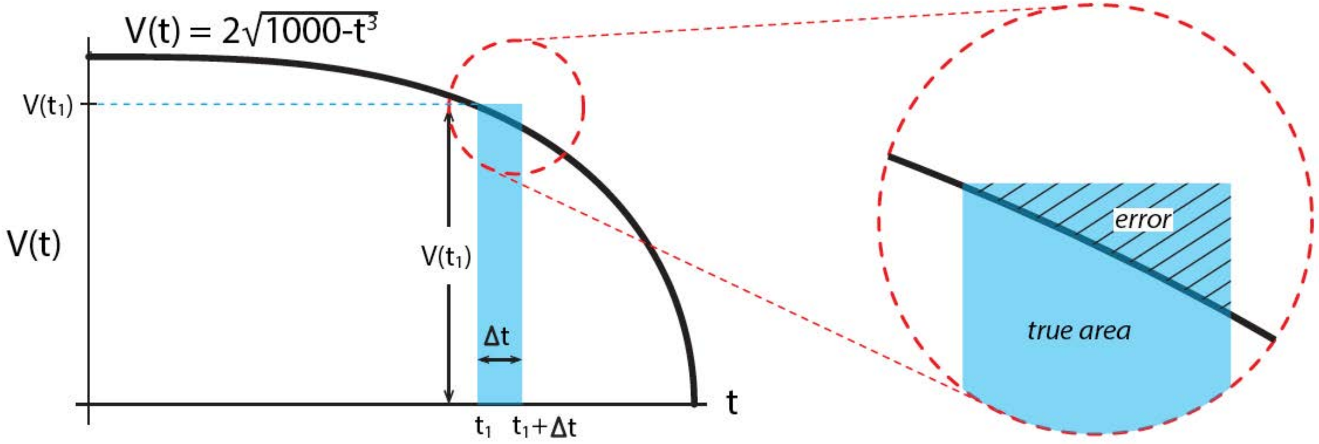


$$J = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}$$

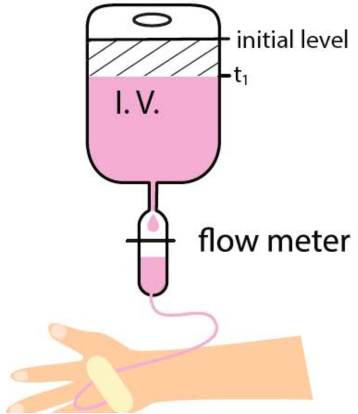
Alan Garfinkel UCLA

integration





distance = velocity × time

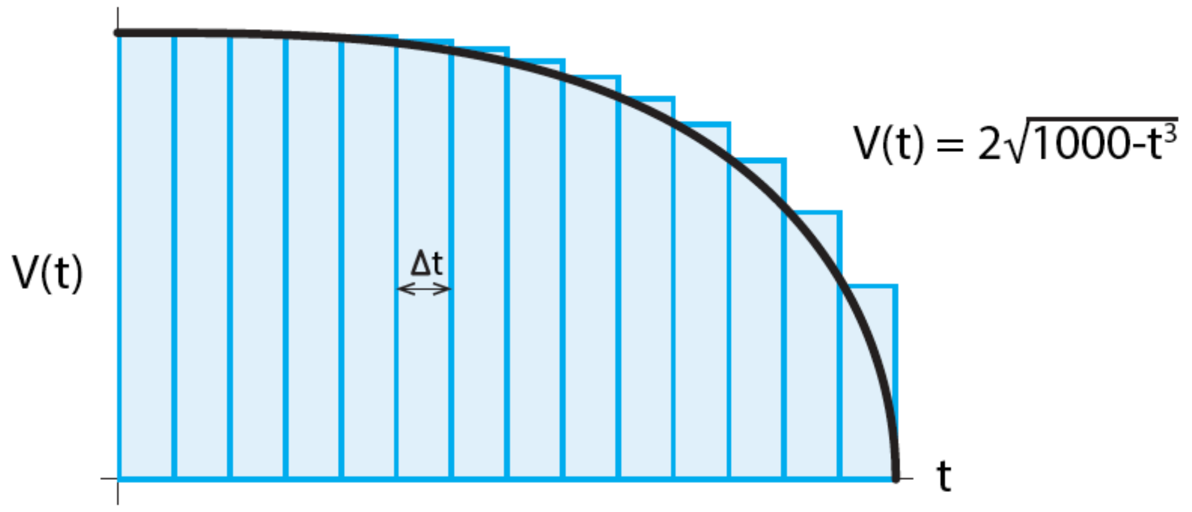


distance	=	velocity	×	time
⇳		⇳		⇳
$V(t_1)\cdot\Delta t$	=	$V(t_1)$	×	Δt
⇳		⇳		⇳
area	=	height	×	width

flow = flow rate X Δt

Alan Garfinkel UCLA

Integration: “add up the little rectangles”



$$X(t) \approx X(0) + \underset{k=0}{\overset{k=n}{\textbf{Sum}}}\, V(k \cdot \Delta t) \cdot \Delta t$$

$$X(t) = X(0) + \lim_{\Delta t \to 0} \sum_{k=0}^{k=n} V(k \cdot \Delta t) \cdot \Delta t$$

$$X(t) = X(0) + \int_0^t X' \cdot dt$$

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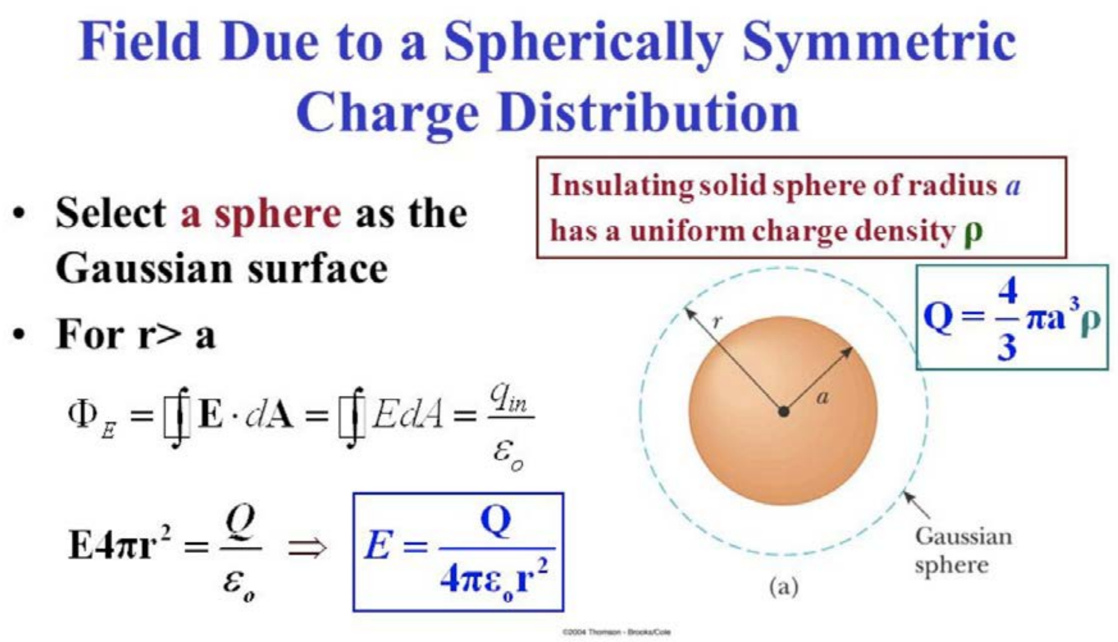
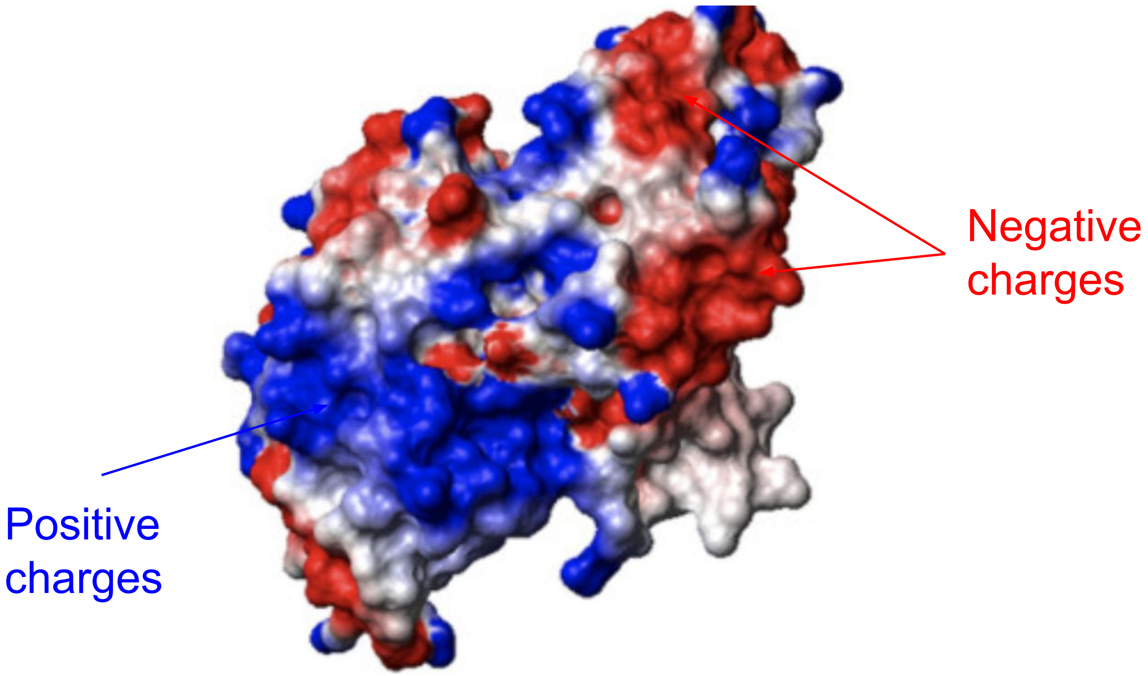


Uniform charge density?

Perfect Sphere?

Use Calculus!

Glyceraldehyde Phosphate Dehydrogenase



Actual molecule?

Add up the little rectangles

(with a computer)

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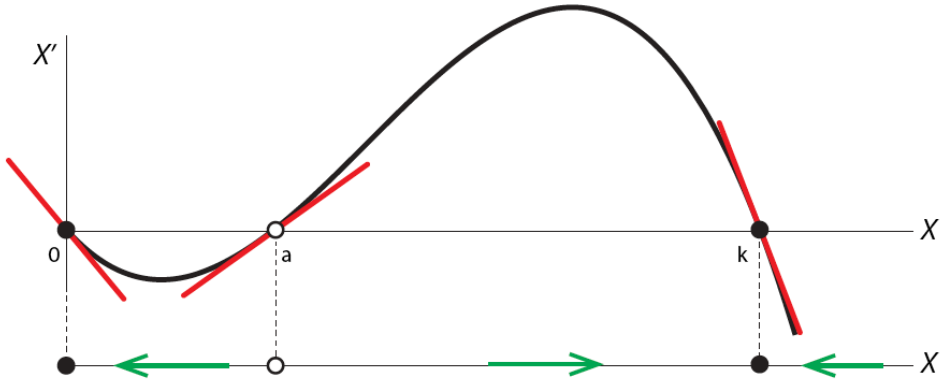
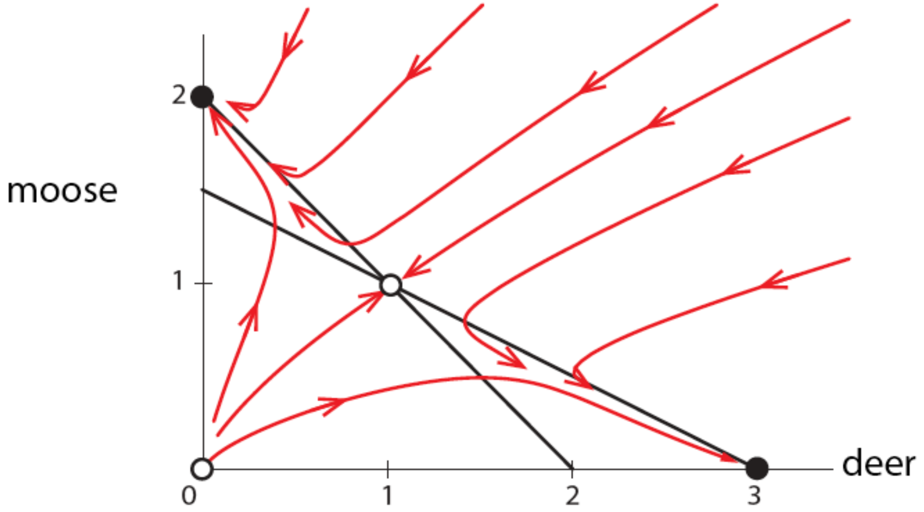
Equilibrium Points



$$X' = rX(1 - \frac{X}{k})(\frac{X}{a} - 1)$$

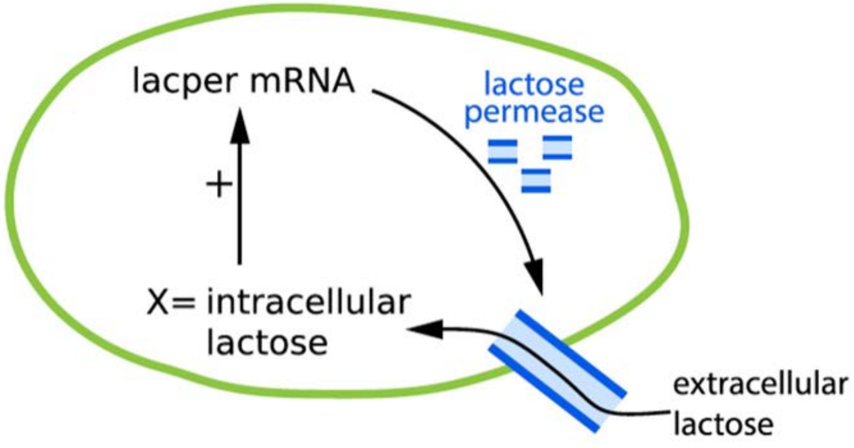


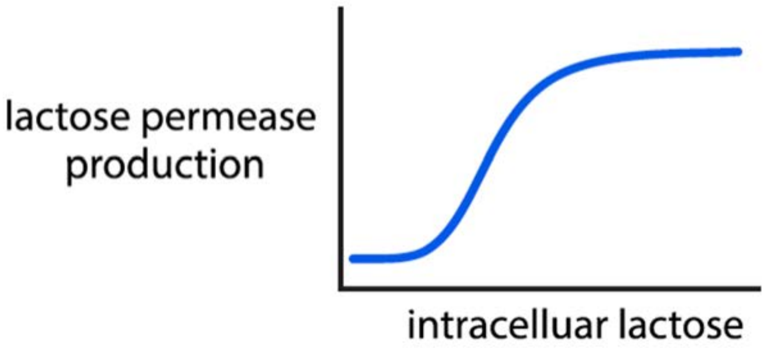
$$D' = 3D - 2MD - D^2$$
$$M' = 2M - DM - M^2$$

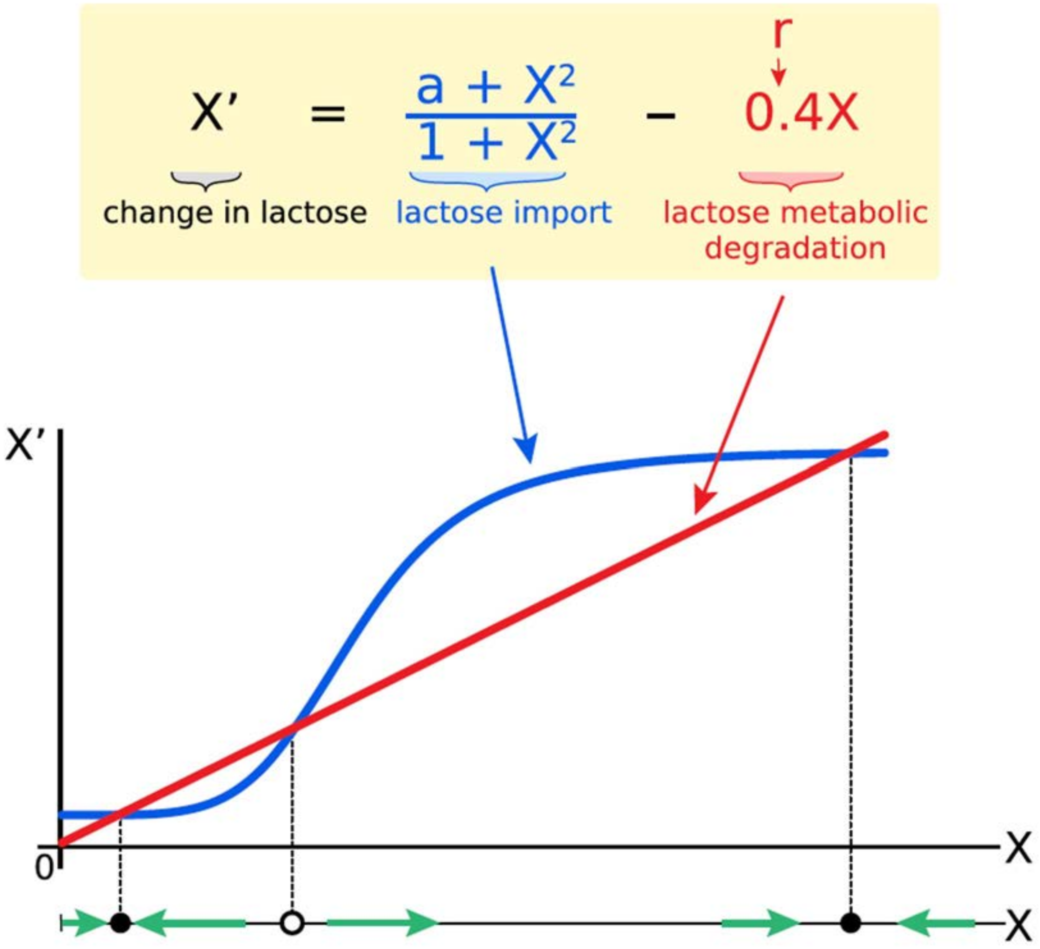
Stability of Equilibrium Points

- simulation
- linearization (Hartman-Grobman Theorem)

“Biological Switch” = bistable dynamical system







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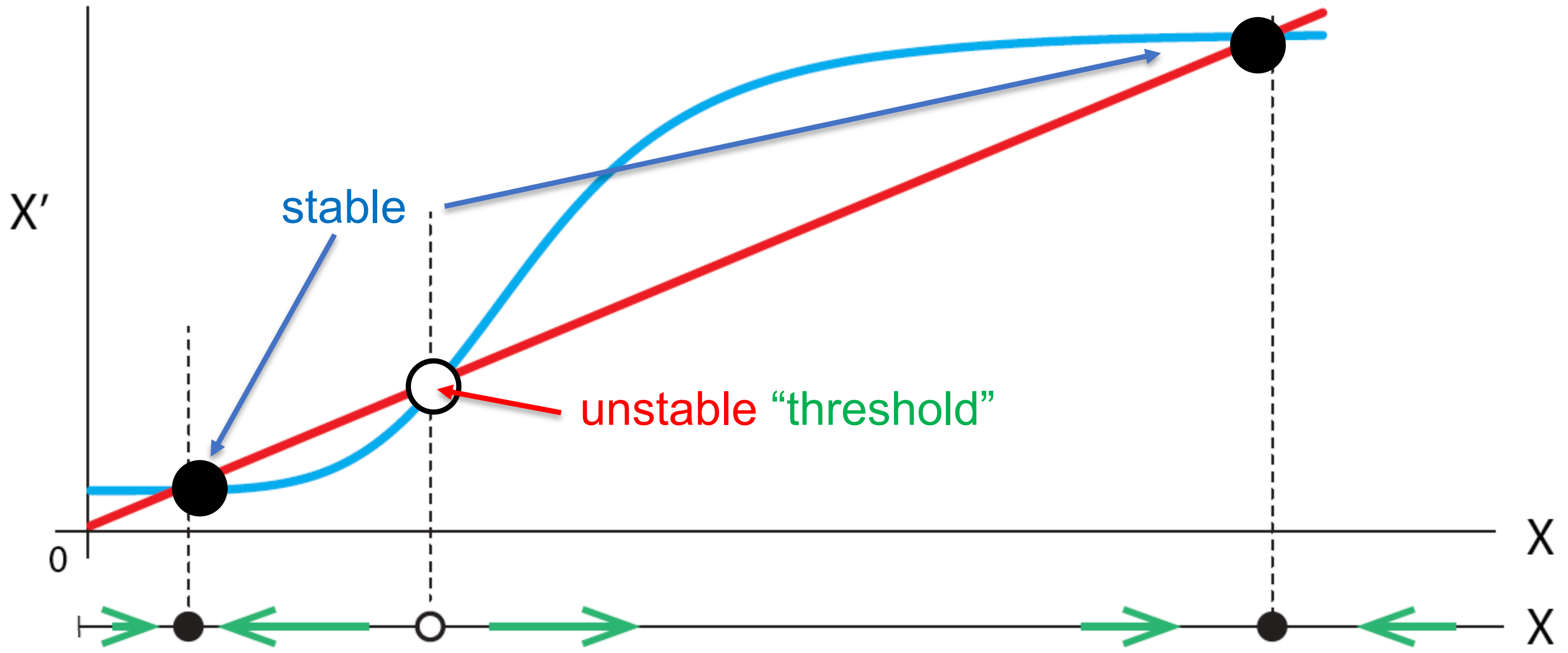

“Biological Switch” = bistable dynamical system

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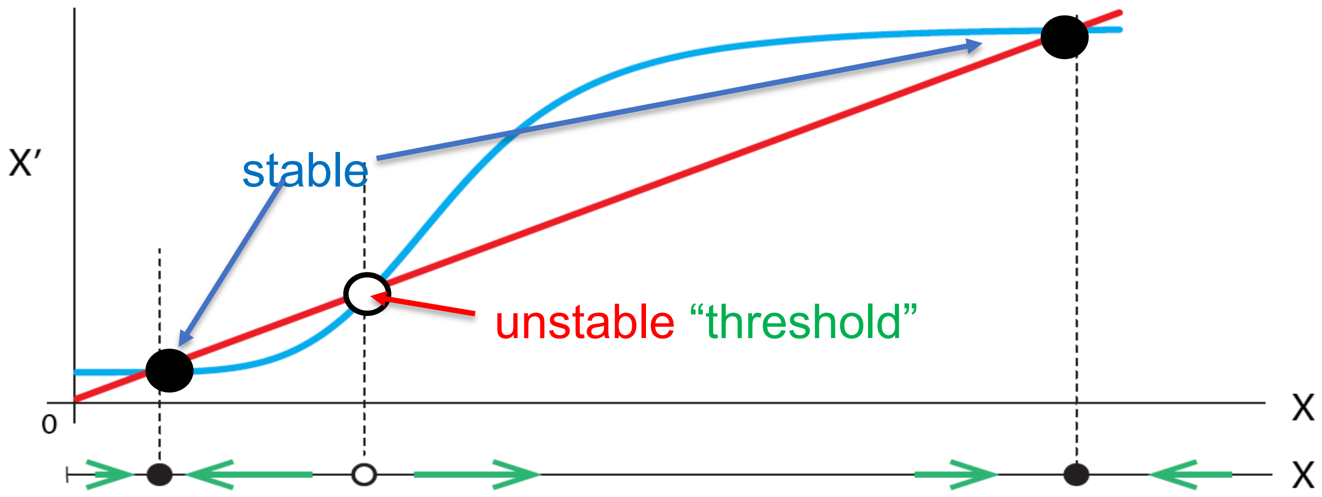
“Threshold” ??

“If X > X_T, then do Y_1 else do Y_2”



Bifurcations: **Qualitative Changes** in Equilibrium Structure as Parameters Vary

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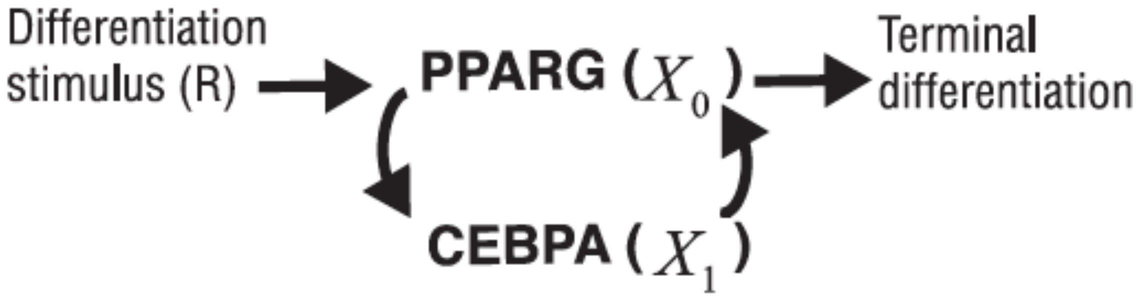
"These pre-adipocytes differentiate through a bistable switch mechanism with a single threshold for activation in each cell that involves positive feedback between two key transcription factors, CCAAT/enhancer binding protein a (CEBPA) and peroxisome proliferator-activated receptor g (PPARG)"

rosiglitizone



$$\frac{dX_0}{dt} = \varepsilon_0 * R * \left(1 + \alpha * \frac{X_1^3}{1 + X_1^3}\right) - X_0$$

$$\frac{dX_1}{dt} = \varepsilon_1 * X_0 - X_1$$

Teruel, *Science* 2014

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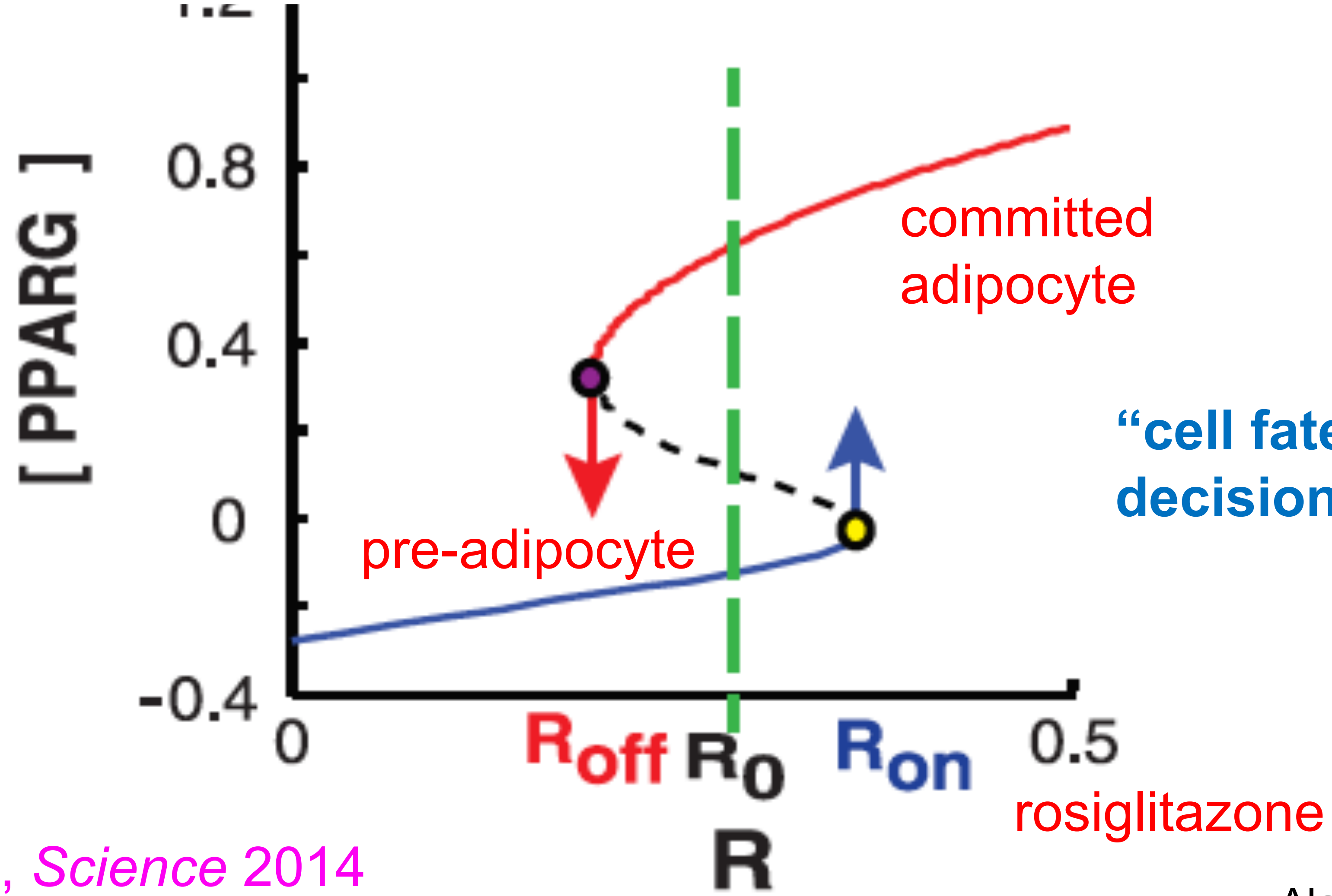
“These pre-adipocytes differentiate through a bistable switch mechanism with a single threshold for activation in each cell that involves positive feedback...



“cell fate decision”

Teruel, *Science* 2014

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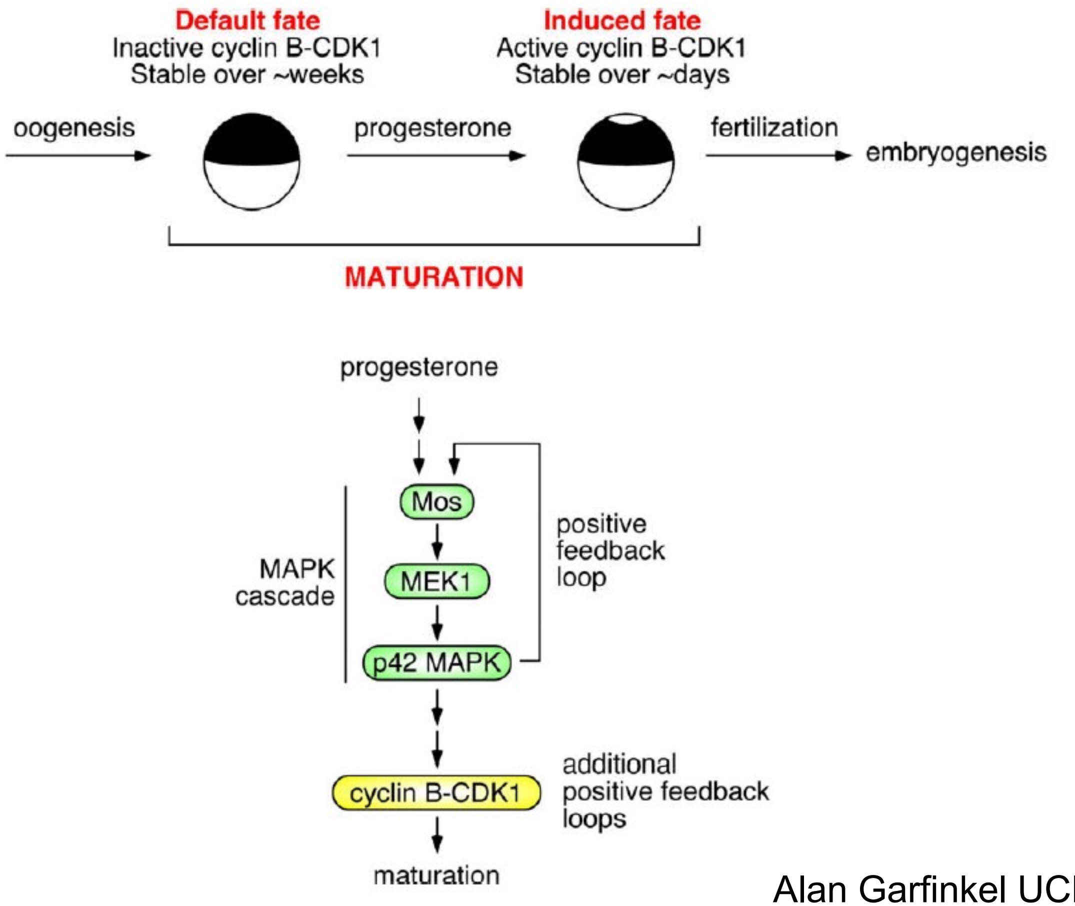
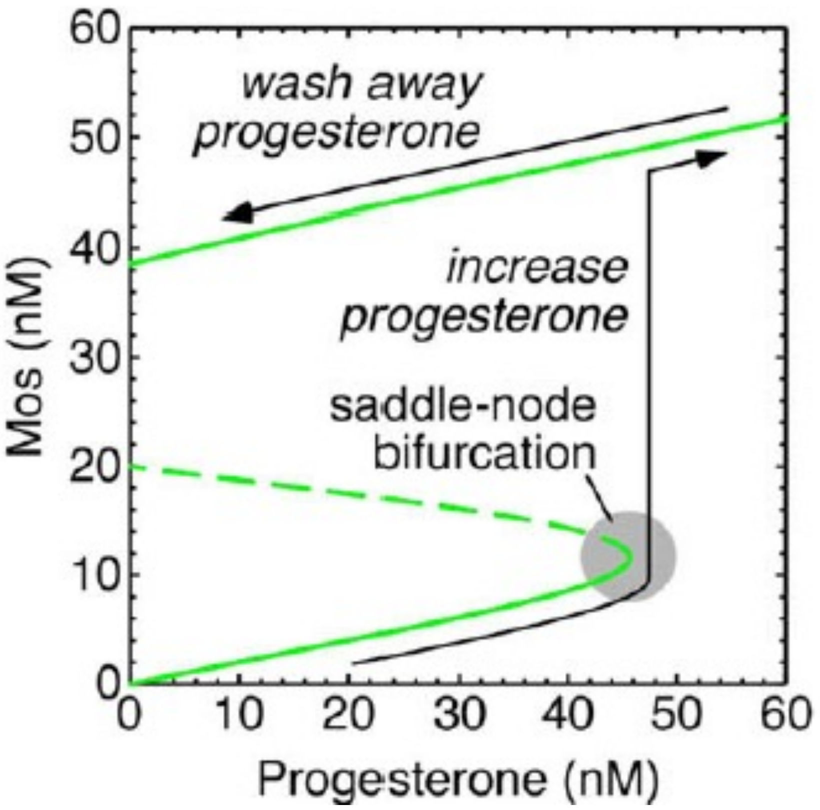
Simple, realistic models of complex biological processes: Positive feedback and bistability in a cell fate switch and a cell cycle oscillator

James E. Ferrell Jr. *, Joseph R. Pomerening, Sun Young Kim, Nikki B. Trunnell, Wen Xiong, Chi-Ying Frederick Huang, Eric M. Machleder

Department of Chemical and Systems Biology, Stanford University School of Medicine, Stanford, CA 94305-5174, USA





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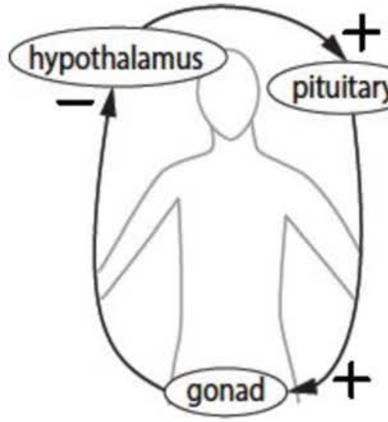
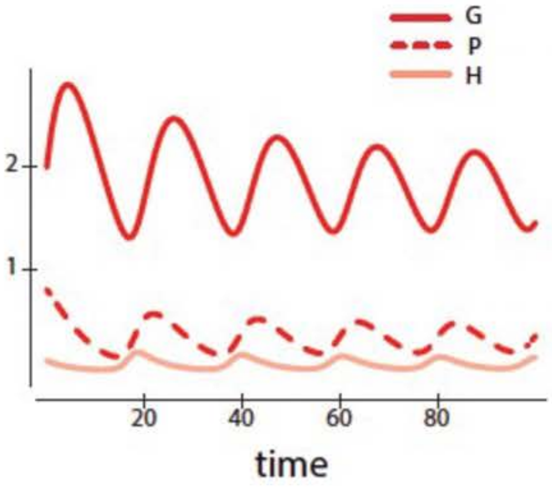
Hopf bifurcation: a system begins to oscillate as a parameter passes a critical point

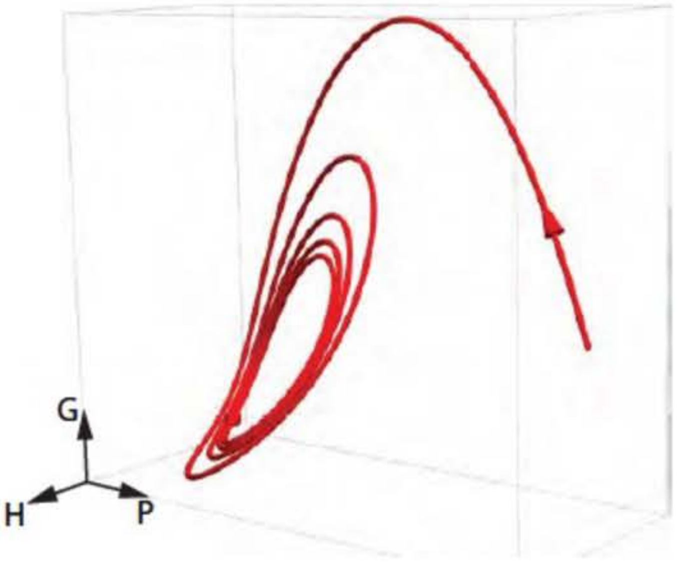


$$H' = \frac{1}{1+G^n} - k_1 H$$

$$P' = H - k_2 P$$

$$G' = P - k_3 G$$





if n > 8, system exhibits stable oscillations

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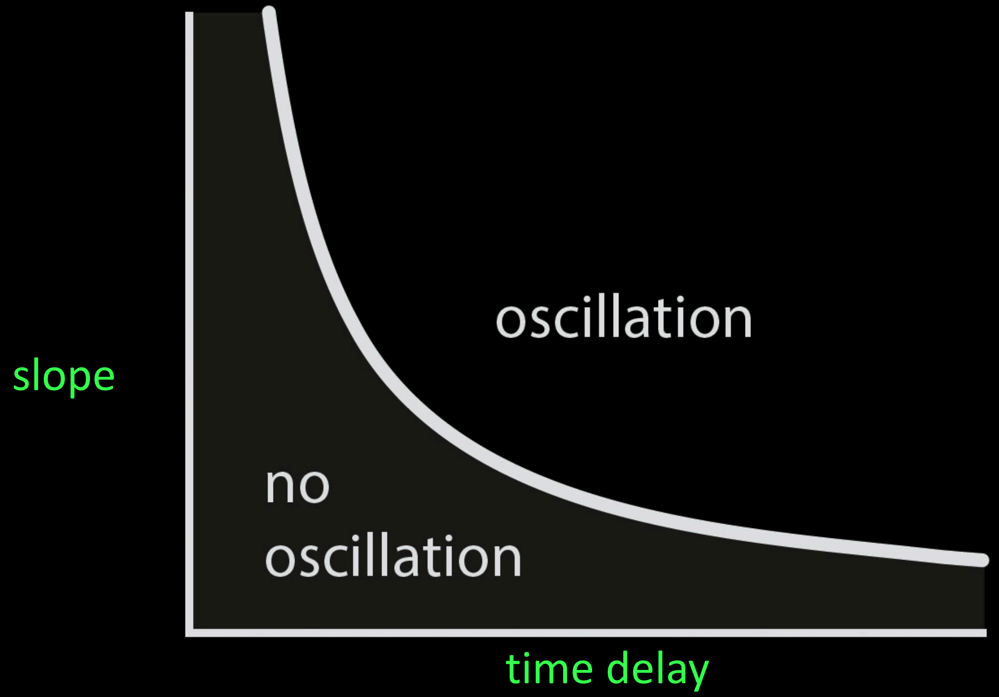
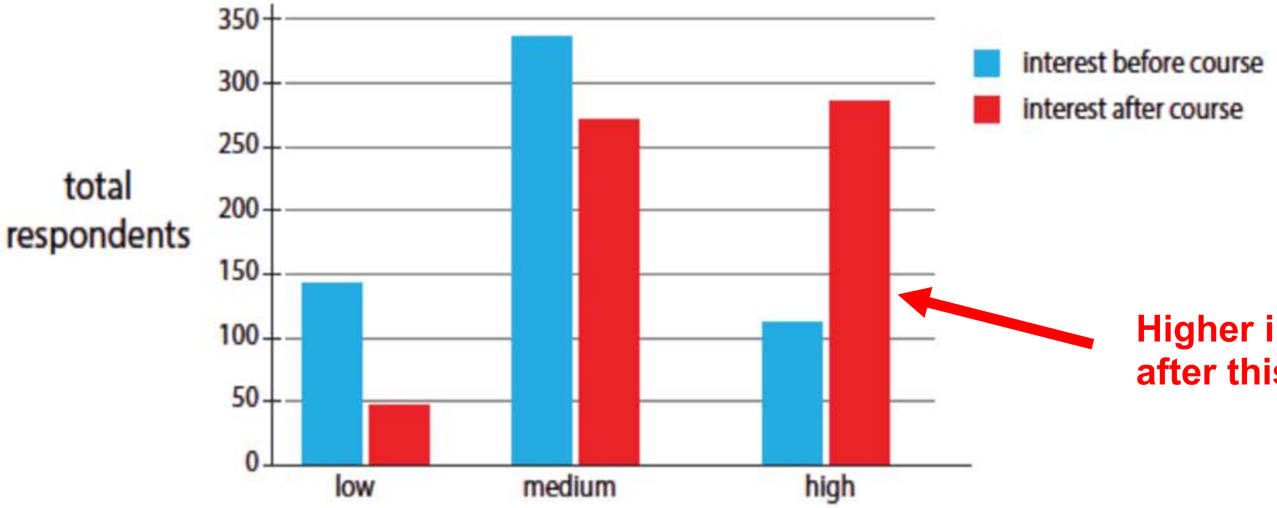
Lesson

- Steeply-sloped (highly sensitive) negative feedback
- time delays

unstable behavior



Student Outcomes

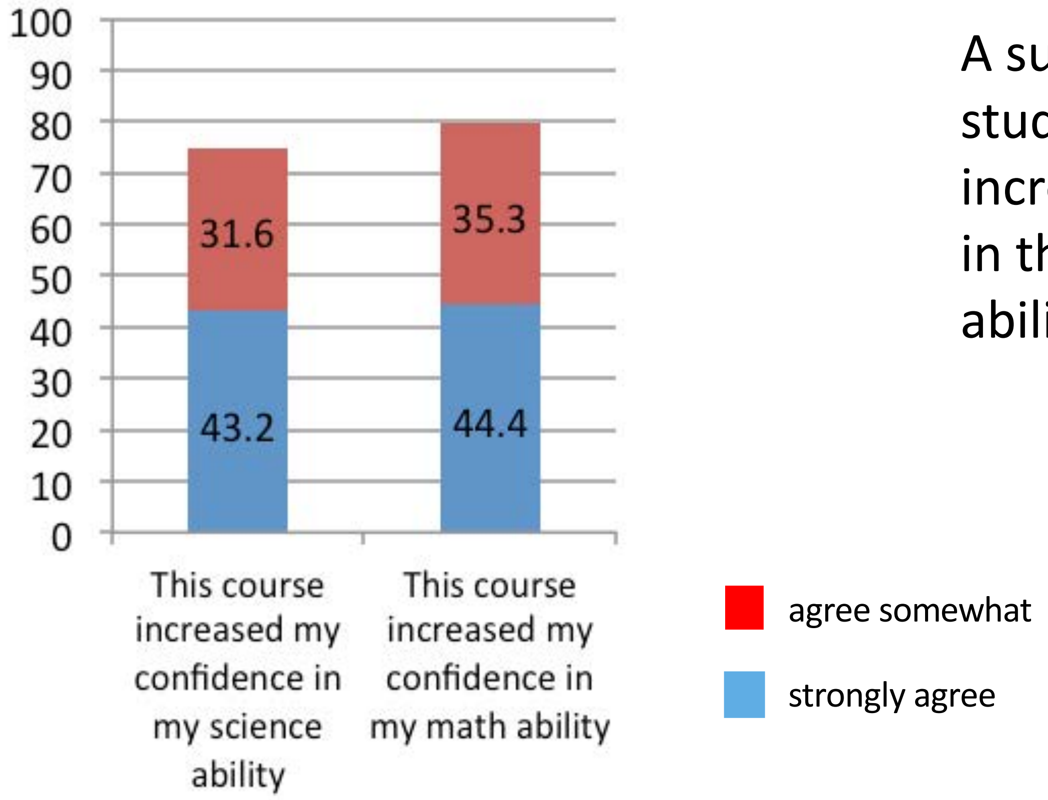


Higher interest in math after this course

- currently ~2000 students/year
- freshmen/sophomores
- 45% no previous calculus

O'Leary, E. S., H. W. Sayson, C. Shapiro, A. Garfinkel, W. J. Conley, M. Levis-Fitzgerald, M. K. Eagan and B. Van Valkenburgh (2021). "Reimagining the Introductory Math Curriculum for Life Sciences Students." CBE—Life Sciences Education

Student Perceptions of LS30



A supermajority of LS 30 students felt that LS30 increased their confidence in their math and science abilities.

O'Leary, E. S., H. W. Sayson, C. Shapiro, A. Garfinkel, W. J. Conley, M. Levis-Fitzgerald, M. K. Eagan and B. Van Valkenburgh (2021). "Reimagining the Introductory Math Curriculum for Life Sciences Students." CBE—Life Sciences Education

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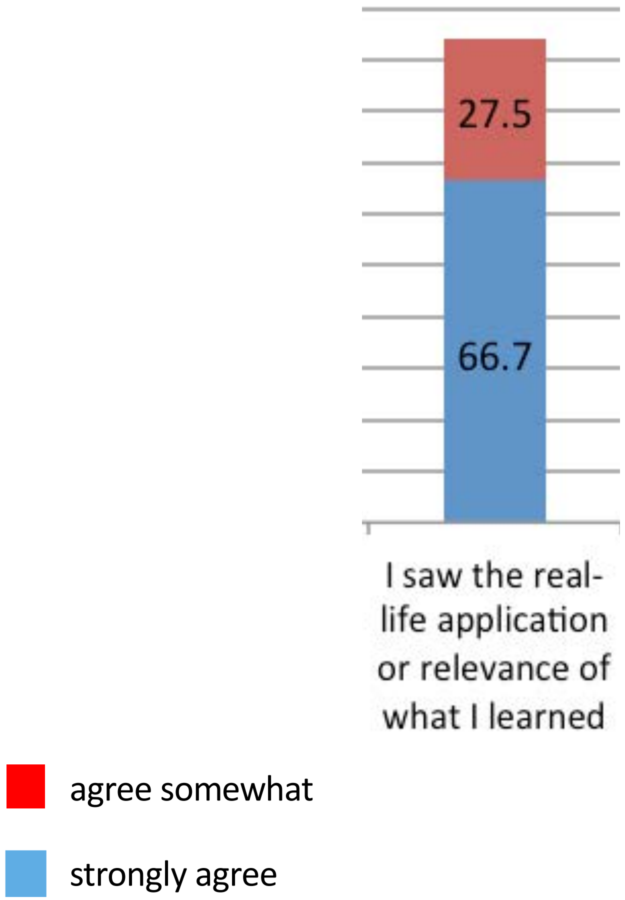
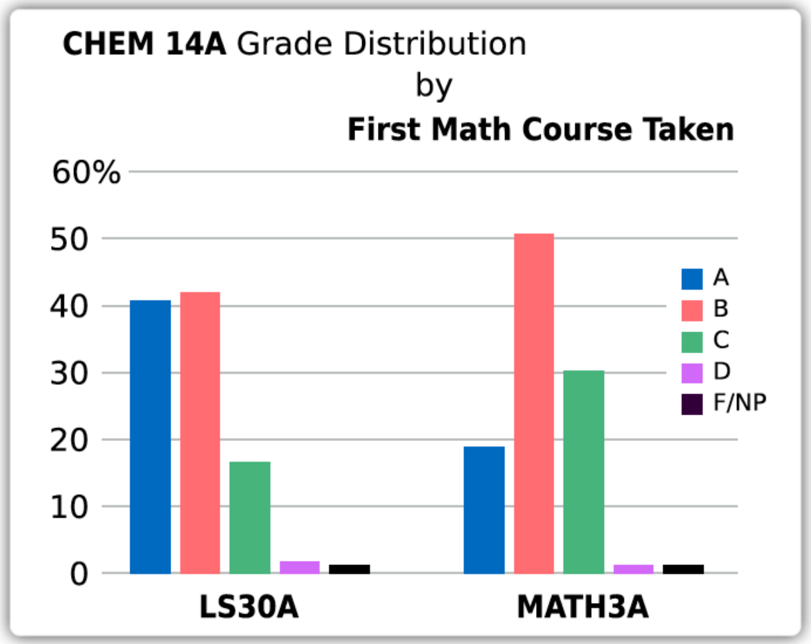
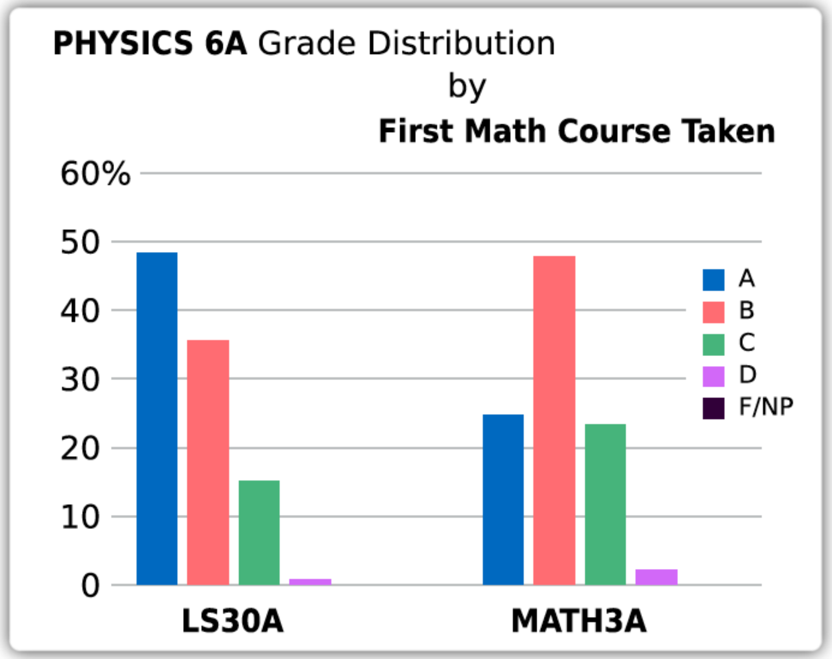
Student Perceptions of LS30



In addition, after completing LS30, 94% of the students saw the relevance of the course.

Whereas about 40% of the Math 3 students indicated what they learned was "useless" or "not applicable to other courses or majors."





LS30A = our course
Math 3A = calculus

Under-Represented Minorities

URM students who had completed the LS30 series earned a grade of A or A+ in Physics 6A at nearly twice the rate of their URM counterparts in the Math 3 sample (11.8% versus. 6.0%).

	Non-URM		URM	
	LS30 (N=129)	Math 3 (N=792)	LS30 (N=34)	Math 3 (N=266)
A or A+	35.7	16.2	11.8	6.0
A- or B+	31.0	28.5	23.6	17.7
B or B-	20.9	31.5	26.5	30.4
C+ or C	8.5	15.3	35.3	27.8
C- or D+	2.4	4.4		9.0
D or D-		2.2		6.1
F	1.6	2.4	2.9	4.2

URMMean

LS 30	**2.79**
Math 3	**2.51**

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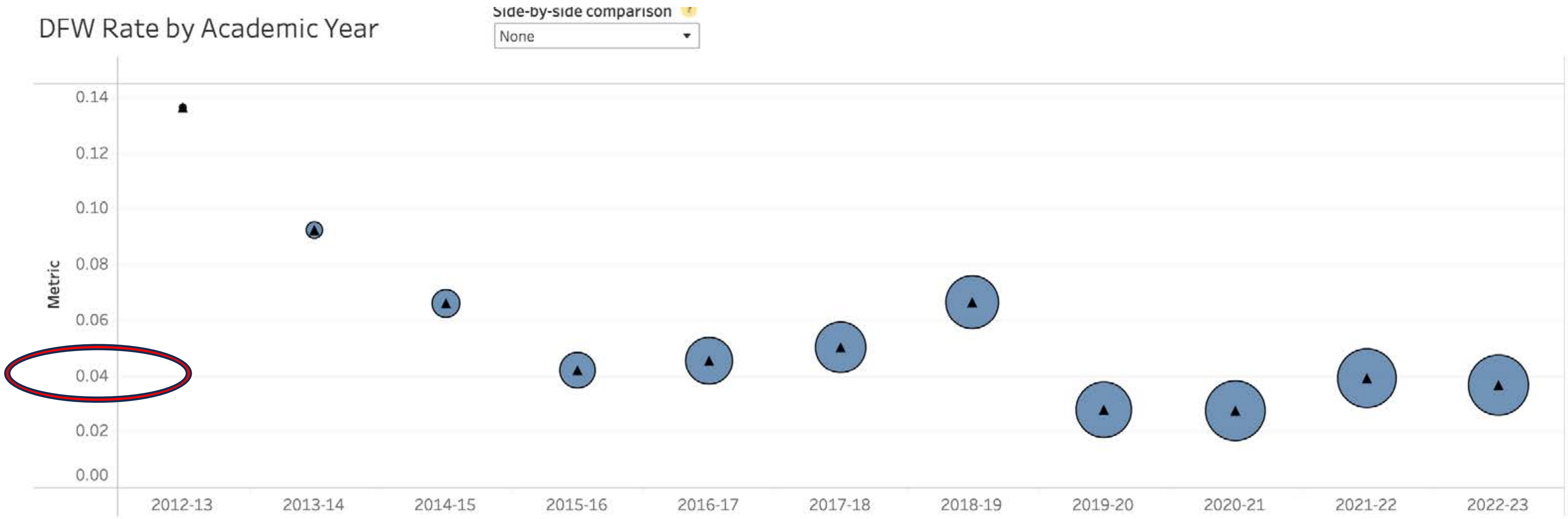

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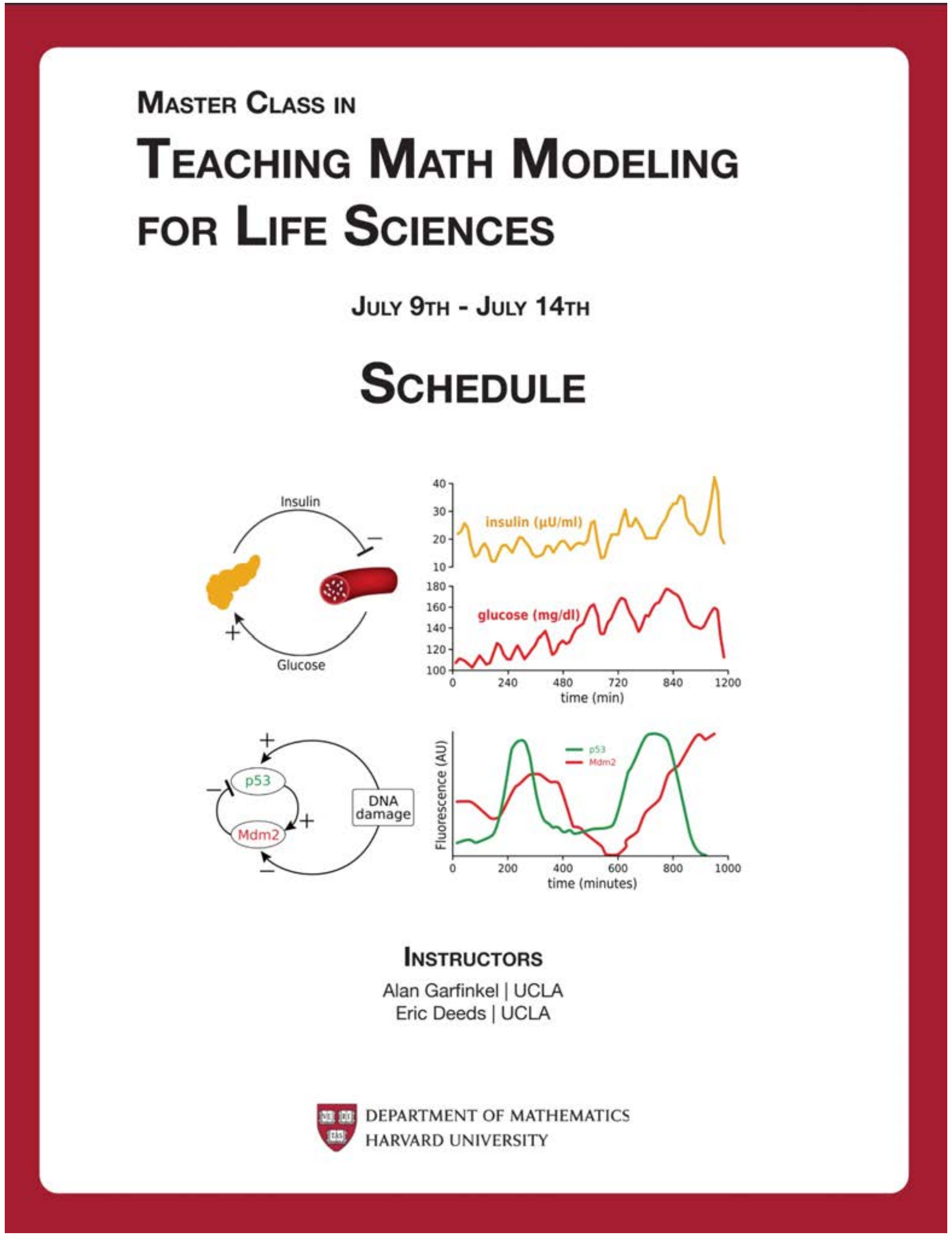

Organized by:
Brendan Kelly, Harvard
Jennifer Czocher, Texas State

~ 40 high school students
taught by 30 visiting faculty and Harvard Instructors

USA TODAY

New effort aims to revamp calculus to keep students in science, technology, engineering fields

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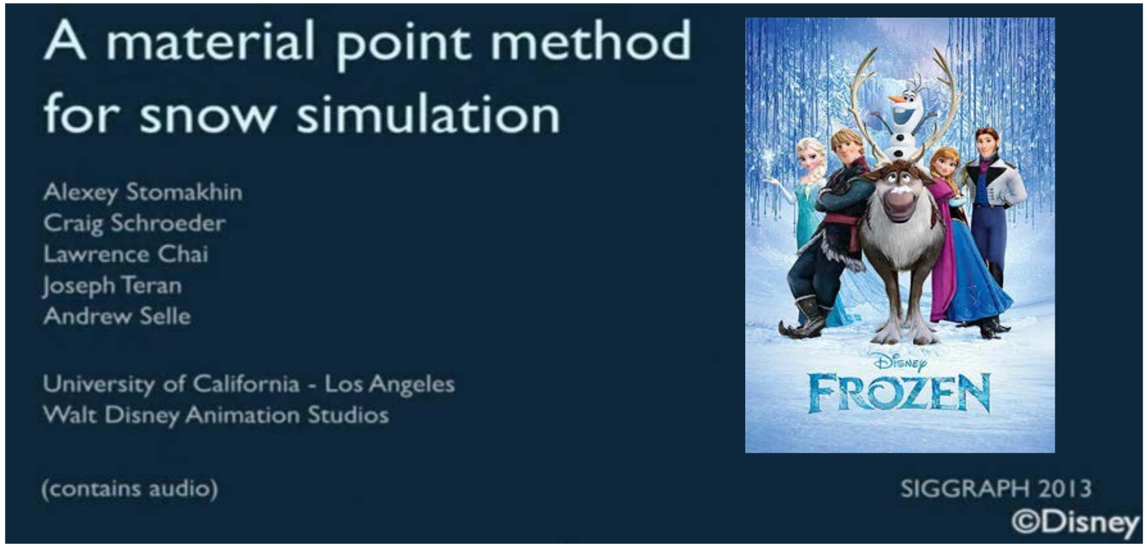

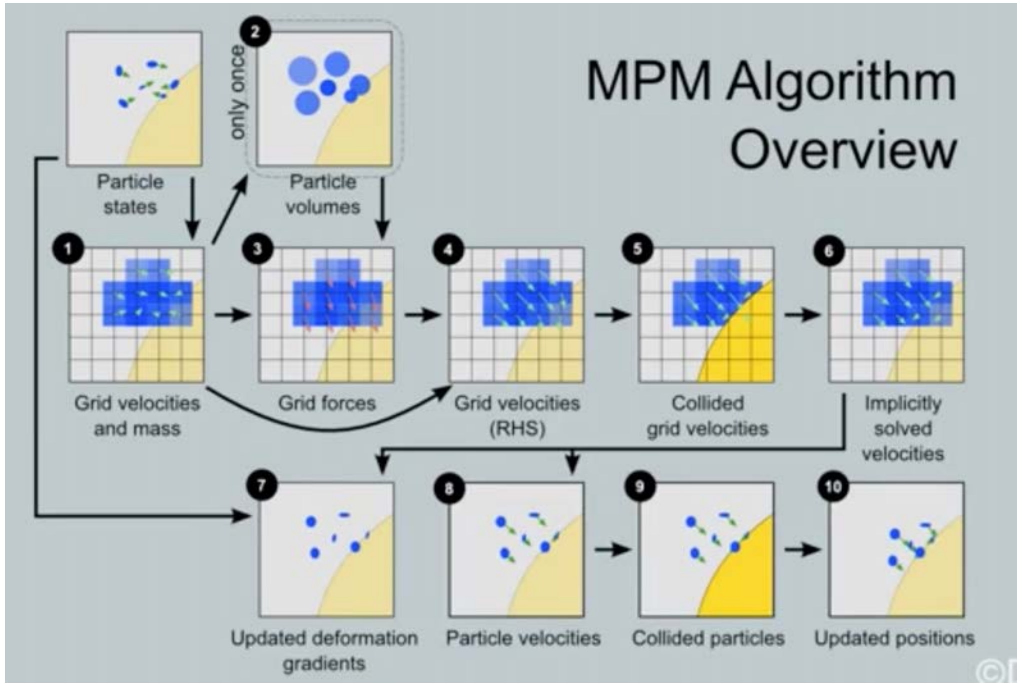

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Schools that are adopting an LS30-style course

UCLA
Cornell University
CSUDH California State University Dominguez Hills
Utah State University
Columbia University
UC Santa Cruz
SDSU San Diego State University
California State University San Marcos
College of the Holy Cross
University of Central Florida 1963
Curry College
California State University Long Beach
Harvard University
KU The University of Kansas
Cal State East Bay
UAB The University of Alabama at Birmingham
The University of Arizona
University of San Diego

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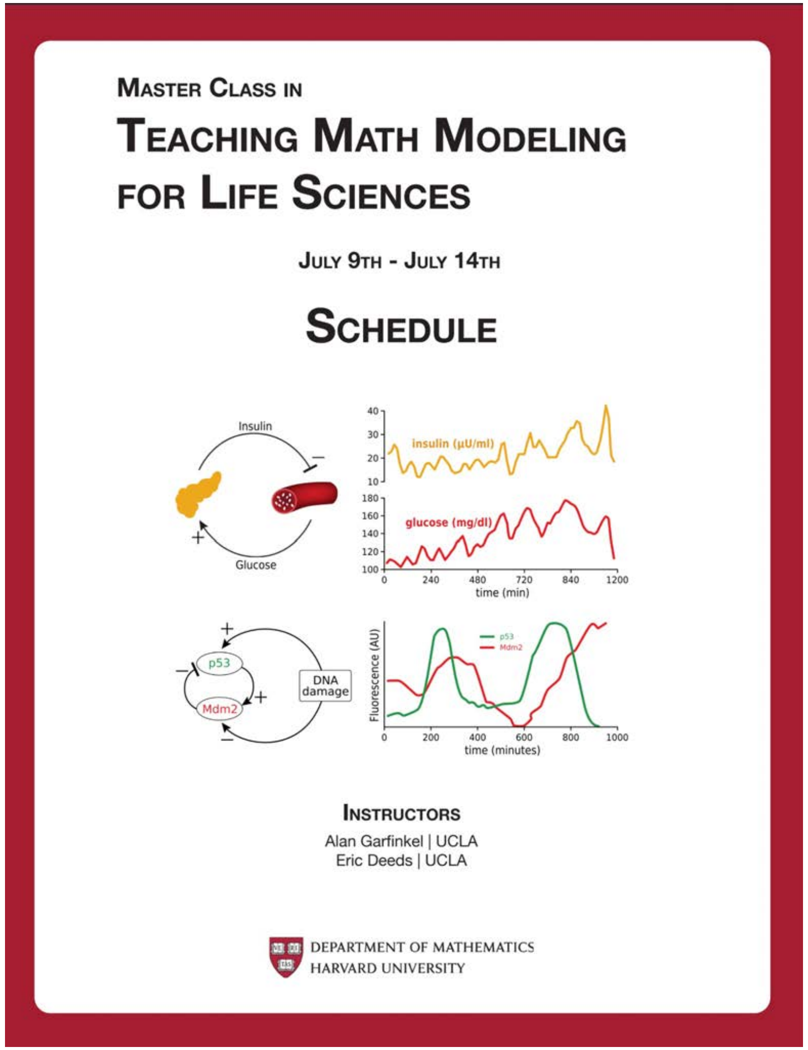

We are doing this again in the Summer of 2024.

please apply!

ps. we are seeking funding!

Essay

Mathematics Is Biology's Next Microscope, Only Better; Biology Is Mathematics' Next Physics, Only Better

Joel E. Cohen

In the coming century, biology will stimulate the creation of entirely new realms of mathematics. In this sense, biology is mathematics' next physics, only better.

PLoS Biology | www.plosbiology.org

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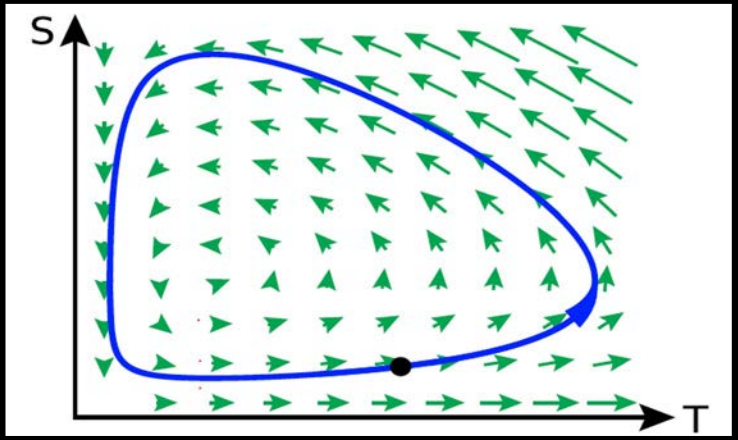
The End



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