Title: A physicist's adventures in virology

Speakers: Catherine Beauchemin

Collection: Perimeter Public Lectures

Date: November 04, 2020 - 7:00 PM

URL: http://pirsa.org/20110068

Abstract: In her live Perimeter Public Lecture webcast on November 4, 2020, physicist Catherine Beauchemin used contemporary examples from COVID-19 and influenza to explain eroding public trust in health research â€“ and why a dose of physics may be just the prescription we need. Beauchemin is a Professor of Physics at Ryerson University and a Deputy Program Director in the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program in Japan.

Disclosure

In the past, I have received consultant fees and research funds from the pharmaceutical companies: F. Hoffmann-La Roche, AstraZeneca, and Adamas Pharmaceuticals.

Currently, my salary and research funding are from public (government) sources only.

The Scientific Method

Some of the key ingredients involve:

- The hypothesis of a rational universe: there exist laws of nature
- Skepticism (keeping an open mind)
- Falsifiable hypotheses and theories
- Honesty & transparency
- Ability to independently verify the facts for oneself

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- Honesty & transparency
- Ability to independently verify the facts for oneself (**or a trust in the above**)

Public Trust in Physicians — U.S. Medicine in International Perspective

Robert J. Blendon, Sc.D., John M. Benson, M.A., and Joachim O. Hero, M.P.H.

The U.S. health care reform process i
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Research
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opinion data

Social Survey Programme (ISSP), a deal or quite a lot of confidence

All things considered, Doctors in my country can be trusted (agree or strongly agree):

Switzerland	83% (1st)
Denmark	79% (2nd)
Australia	73% (10th)
Taiwan	72% (12th)
South Korea	62% (20th)
Japan	60% (23rd)
United States	58% (24th)
Russia	45% (28th)

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N ENGL J MED 371;17 NEJM.ORG OCTOBER 23, 2014

The New England Journal of Medicine

Negative public impressions about health research

- experts disagree
- experts keep changing their minds
- experts have an agenda (profit, politics, social engineering, etc.)

Experts disagree — hydroxychloroquine

[Fauci] *So that study is a flawed study and I think anyone who examines it carefully sees that it is not a randomized, placebo-controlled trial.*

[Luetkemeyer] *It's been peer-reviewed...*

[Fauci] *It doesn't matter, you can peer-review something that's a bad study.*

US House Oversight & Reform Select Subcommittee on Coronavirus Crisis, July 31, 2020

A problem with research ethics — paper retractions

Rank. Name	# retracted	Field
01. Y Fuji	183	**Medicine**
02. J Boldt	129	**Medicine**
03. Y Sato	96	**Medicine**
04. J Iwamoto	74	**Medicine**
05. D Stapel	58	Psychology
06. Y Saitoh	53	**Medicine**
07. A Nazari	52	Engineering
08. A Maxim	48	Engineering
09. CY Chen	43	Engineering
10. F Sarkar	41	**Medicine**
11. H Zhong	41	**Medicine**
12. S Kato	40	**Medicine**
13. S Shamshirband	38	Computer Science
14. J Hunton	37	Business
15. H-I Moon	35	**Medicine**

9/15 (60%) from Medicine!

From

Retraction Watch Leaderboard

ORIGINAL ARTICLE

MAYO CLINIC

A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices

Vinay Prasad, MD; Andrae Vandross, MD; Caitlin Toomey, MD; Michael Cheung, MD; Jason Rho, MD; Steven Quinn, MD; Satish Jacob Chacko, MD; Durga Borkar, MD; Victor Gall, MD; Senthil Selvaraj, MD; Nancy Ho, MD; and Adam Cifu, MD

Of the 363 articles testing standard of care, 146 (40.2%) reversed that practice, whereas 138 (38.0%) reaffirmed it.

therapy. This study was conducted from August 1, 2011, through October 31, 2012.

Results: We reviewed 2044 original articles, 1344 of which concerned a medical practice. Of these, 981 articles (73.0%) examined a new medical practice, whereas 363 (27.0%) tested an established practice. A total of 947 studies (70.5%) had positive findings, whereas 397 (29.5%) reached a negative conclusion. A total of 756 articles addressing a medical practice constituted replacement, 165 were back to the drawing board, 146 were medical reversals, 138 were reaffirmations, and 139 were inconclusive. Of the 363 articles testing standard of care, 146 (40.2%) reversed that practice, whereas 138 (38.0%) reaffirmed it.

Conclusion: The reversal of established medical practice is common and occurs across all classes of medical practice. This investigation sheds light on low-value practices and patterns of medical research.

Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2013;88(8):790-798

ORIGINAL ARTICLE

MAYO CLINIC

A Decade of Reversal: An Analysis of 146

E.g. The practice of implanting Gentamicin-collagen sponge to prevent infection following colorectal surgery, used in millions of patients worldwide since 1985...

A single-centre, randomized trial found a 70% decrease in surgical site infection with this practice.

In a larger, multi-centre, phase 3 trial it resulted in significantly more infections, more visits to emergency departments, and more hospitalization for resulting infection.

A problem with basic (lab) health research

Review

Reproducibility in Science

Improving the Standard for Basic and Preclinical Research

C. Glenn Begley, John P.A. Ioannidis

Abstract: **Medical and scientific advances are predicated on new knowledge that is robust and reliable and that serves as a solid foundation on which further advances can be built. In biomedical research, we are in the midst of a revolution with the generation of new data and scientific publications at a previously unprecedented rate. However, unfortunately, there is compelling evidence that the majority of these discoveries will not stand the test of time. To a large extent, this reproducibility crisis in basic and preclinical research may be as a result of failure to adhere to good scientific practice and the desperation to publish or perish. This is a multifaceted, multistakeholder problem. No single party is solely responsible, and no single solution will suffice. Here we review the reproducibility problems in basic and preclinical biomedical research, highlight some of the complexities, and discuss potential solutions that may help improve research quality and reproducibility. (*Circ Res*. 2015;116:116-126. DOI: 10.1161/CIRCRESAHA.114.303819.)**

Key Words: funding ■ journals ■ research integrity ■ universities

Problem

As physicians and scientists, we want to make a contribution that alters the course of human health. We all want to make

remarkably well with estimates of 85% for the proportion of biomedical research that is wasted at-large.[4–9] This irreproducibility is not unique to preclinical studies. It is seen across the

A problem with basic (lab) health research

Review

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Table 1. Examples of Some Reported Reproducibility Concerns in Preclinical Studies (Modified - cut)

Author	Field	Reported Concerns
Ioannidis et al (2009)[22]	Microarray data	16/18 studies unable to be reproduced in principle from raw data
Sena et al (2010)[24]	Stroke animal studies	Overt publication bias: only 2% of the studies were negative
Prinz (2011)[1]	General biology	75% to 80% of 67 studies were not reproduced
Begley & Ellis (2012)[2]	Oncology	90% of 53 studies were not reproduced
Elliott et al (2006)[31]	Commercial antibodies	Commercial antibodies detect wrong antigens
Prassas et al (2013)[32]	Commercial ELISA	ELISA Kit identified wrong antigen

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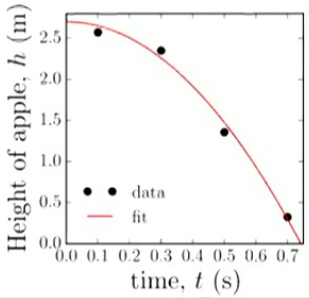
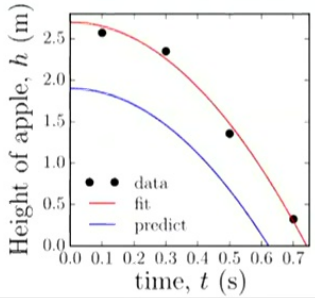
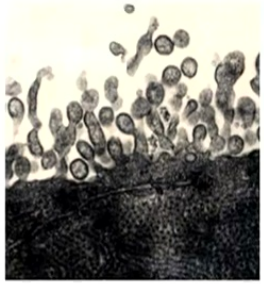
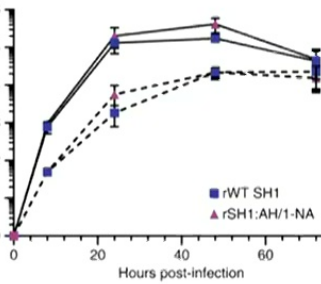
Negative public impressions about health research

- experts disagree
- experts keep changing their minds
- experts have an agenda (profit, politics, social engineering, etc.)

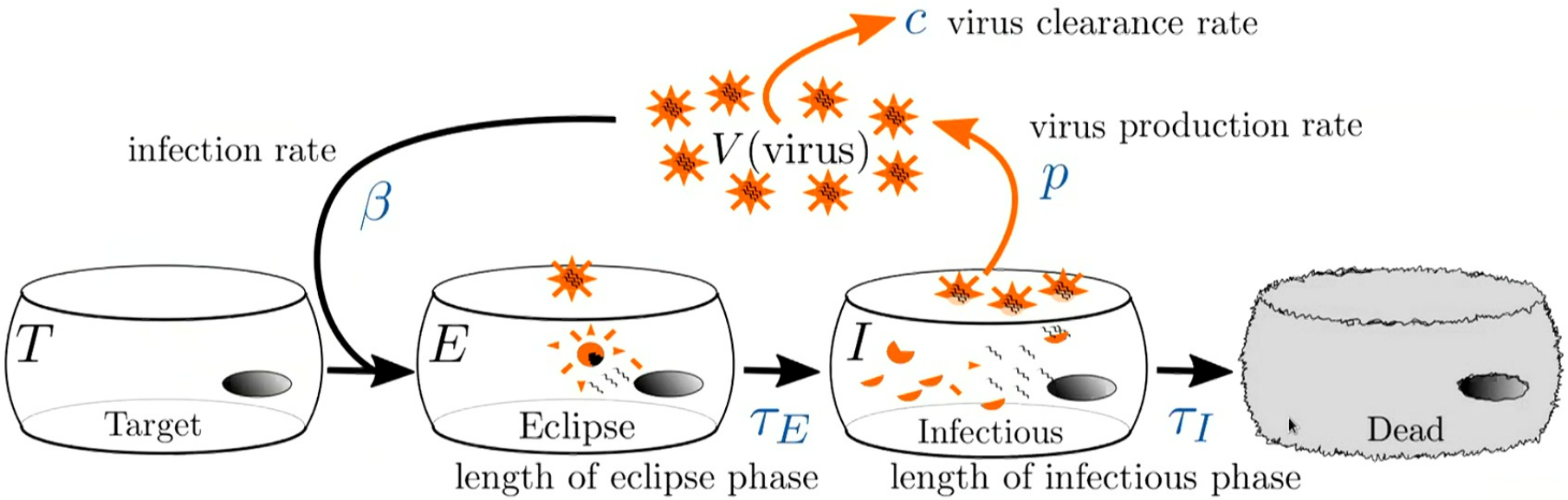
some of the reasons ...

- disregarding data in favour of opinion
- an aversion to basic, exploratory research
- aim to prove rather than disprove hypothesis (**a math issue!**)
- routinely major flaws in study design or analysis (**a math issue!**)

Physics vs Virology: the difference is Math

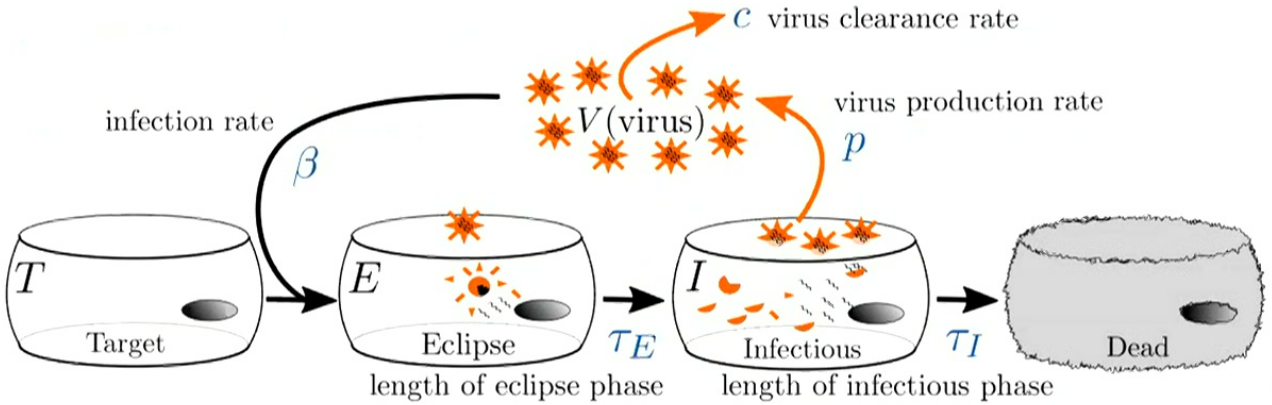
	observe	analyze	explain	predict
Physics			$F = ma$ $a = g$ $v_f = v_i - gt$ $h_f = h_i - \frac{1}{2}gt^2$	
Virology			When cells are infected with influenza, approx. 10^6 pfu/mL virions are produced.	Additional funding is required in order to determine what happens when a cell is infected with $2\times$ more virus...

Virophysics: the kinetics of a virus infection

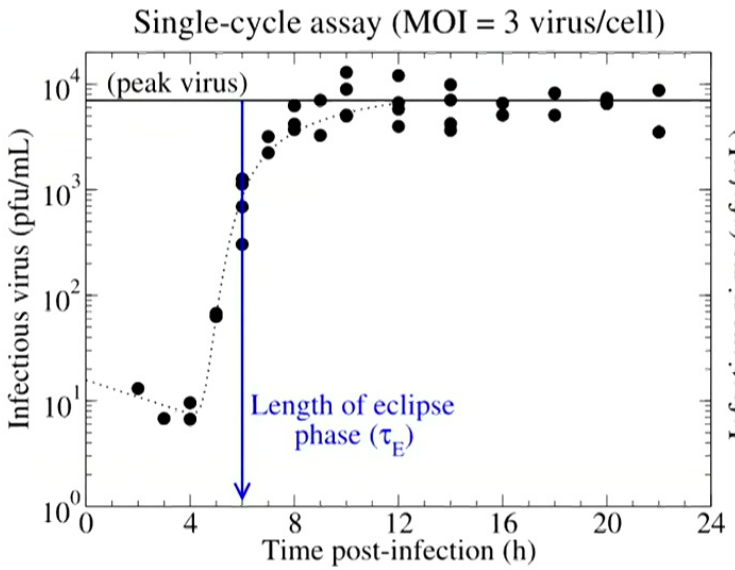


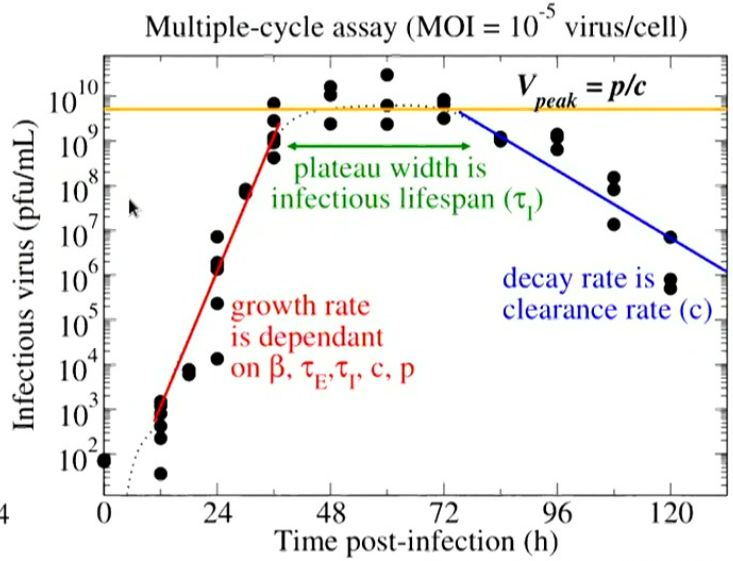
©BP Holder (modified)

Virophysics: calibrating the model from experiments

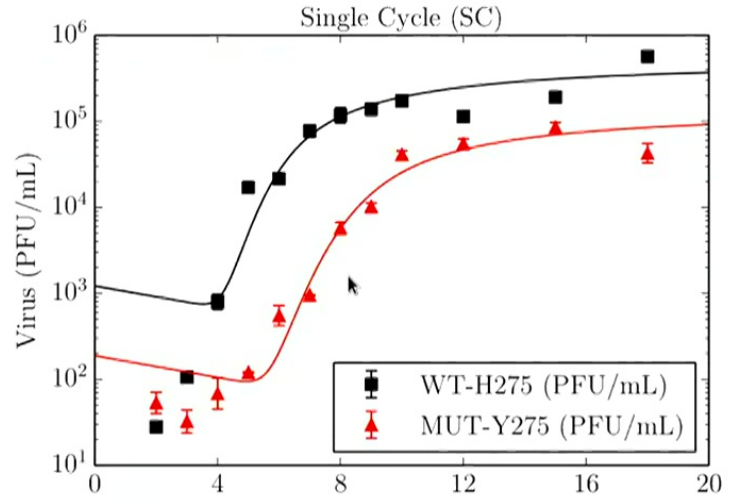


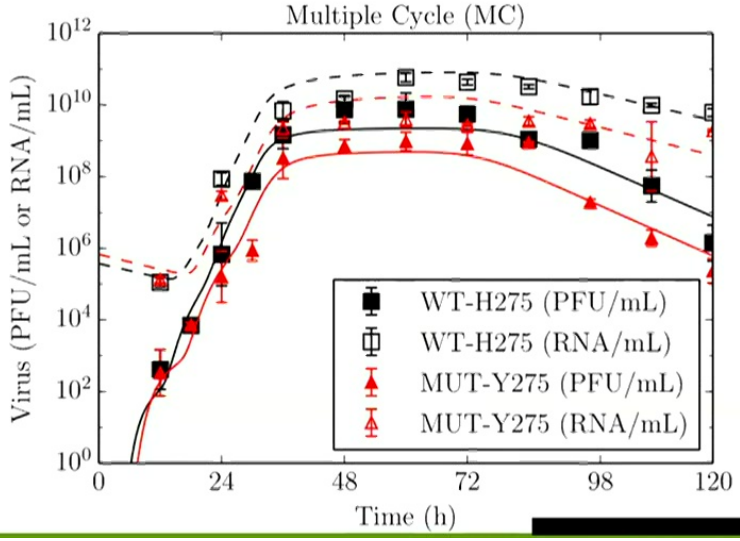
©BP Holder (modified)

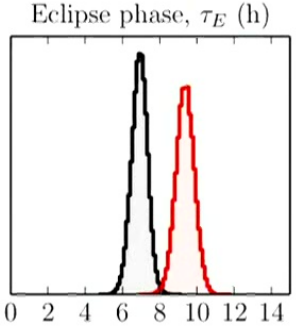


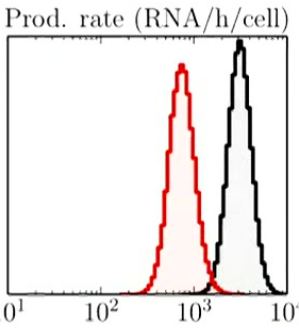


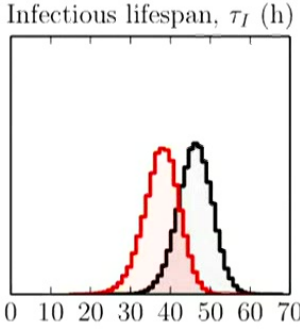
Differences between wild-type & mutant strain

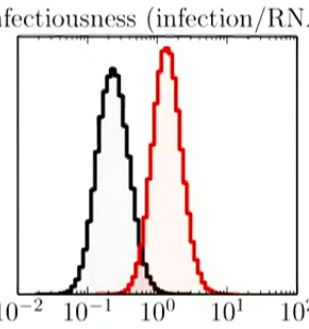


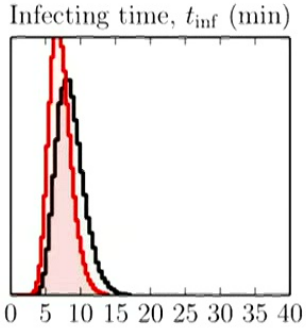


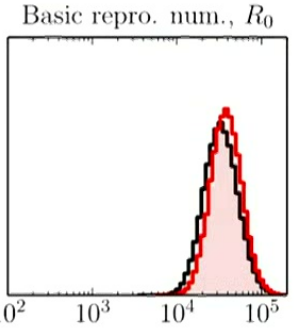










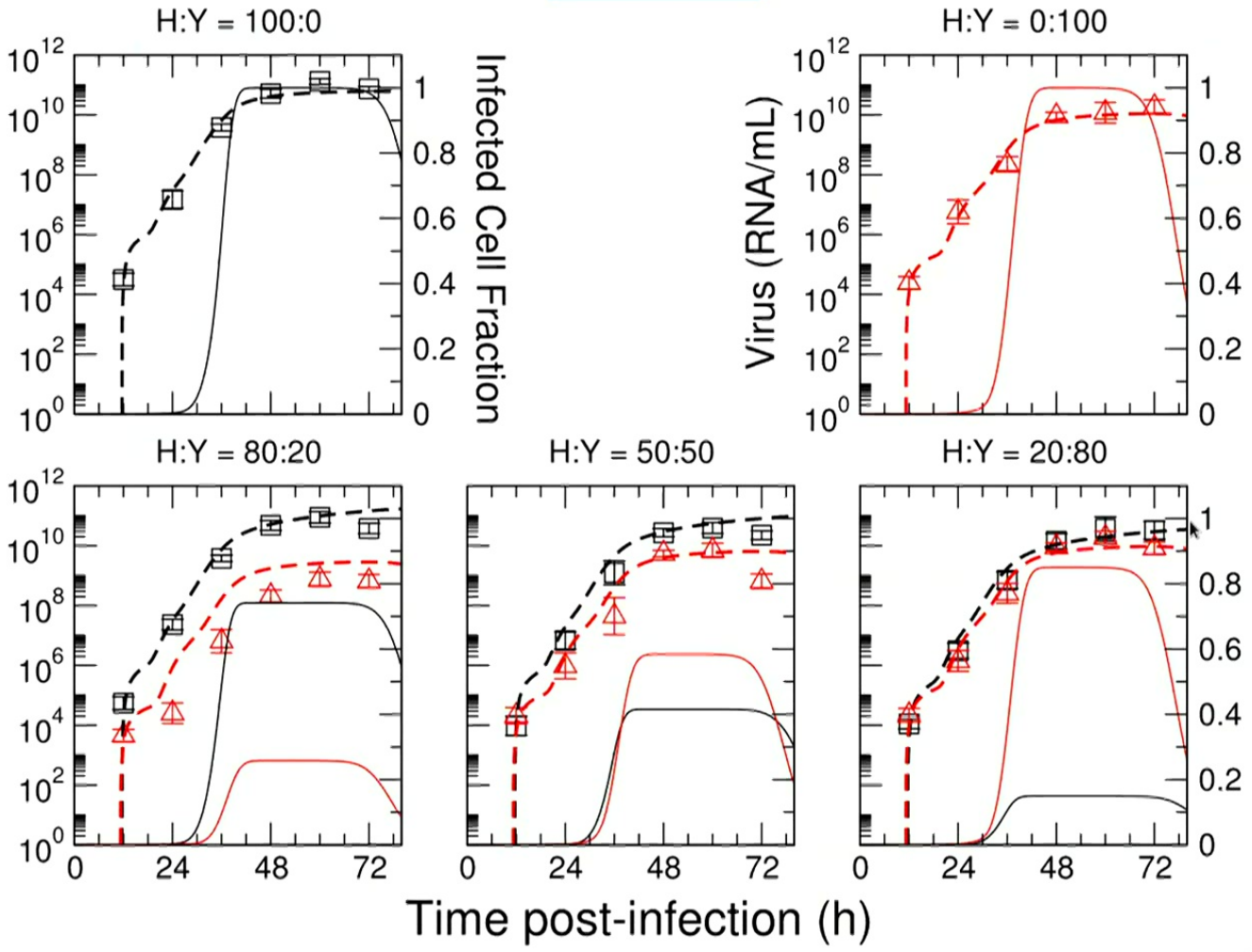


Adapted from

Pinilla et al.
J. Virol.
86(19), 2012

Paradis et al.
PLOS ONE
10(5), 2015

The model correctly predicts experimental outcomes. Yay!



Adapted from

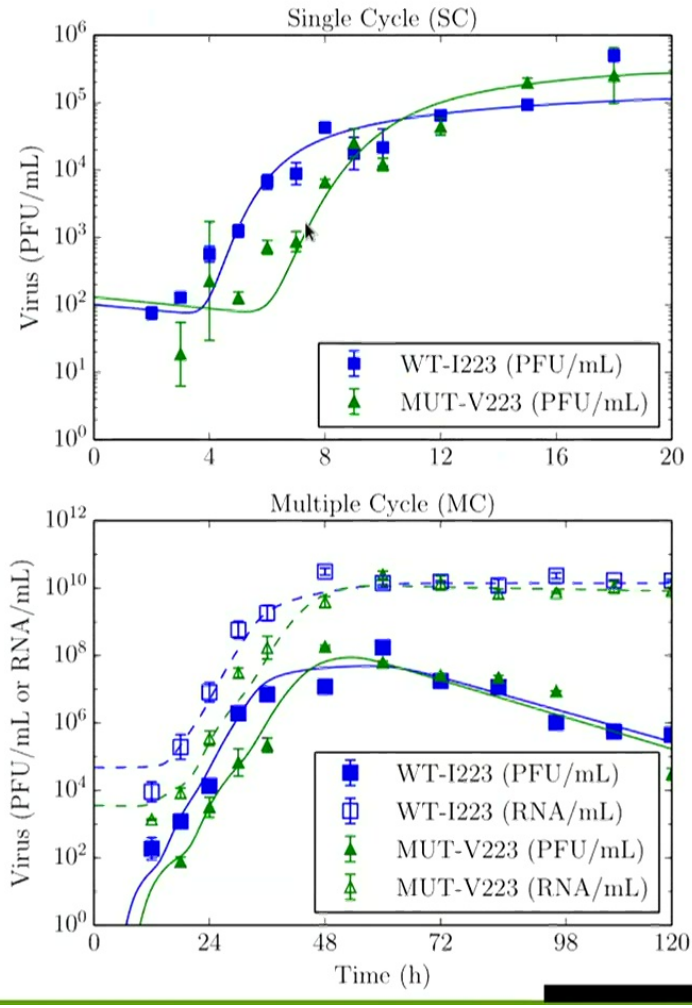
Paradis et al.
PLOS ONE
10(5), 2015

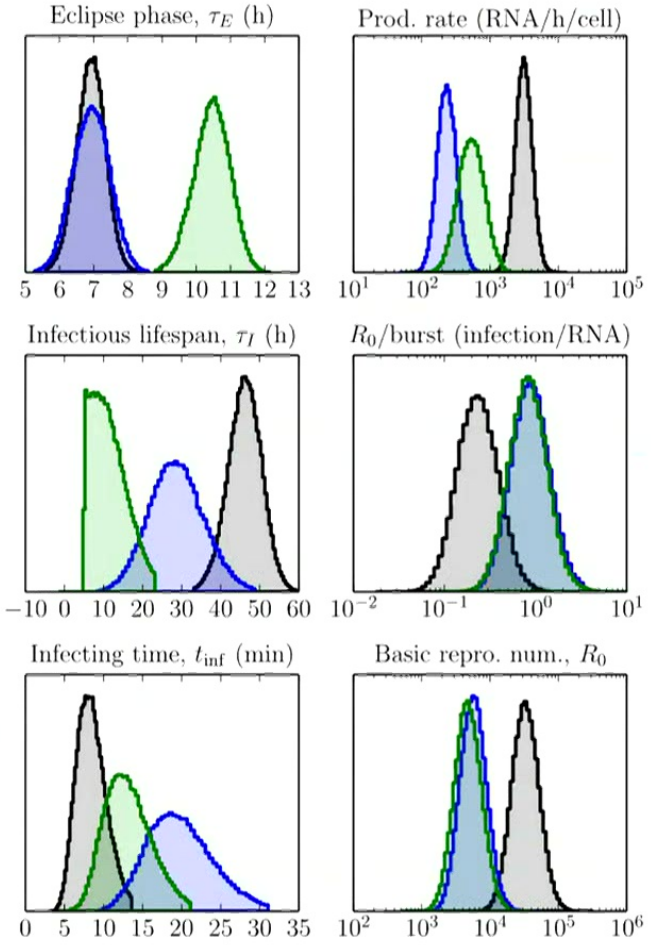
← These are not fits!!

Let's do it again in a new experiment
with the same WT but a new MUT...

Oups! :(

Same WT strain but measured parameters are different!





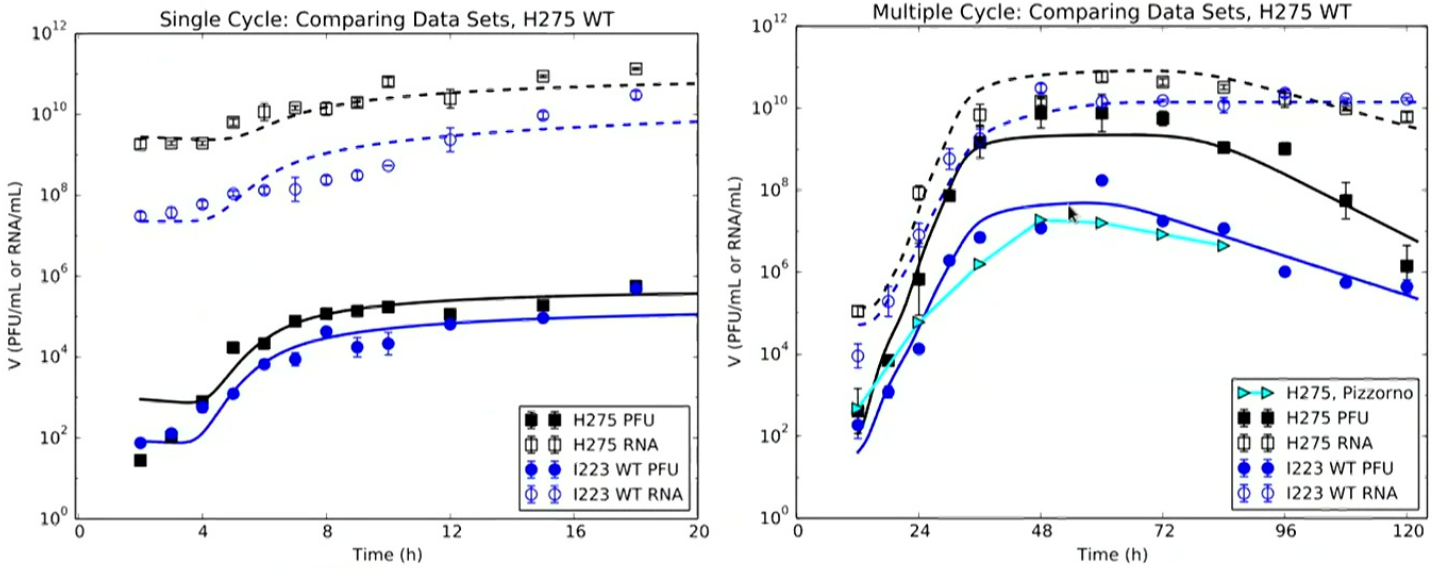
some WT parameters differ more between the **OLD** and **NEW** experiments ...

... than the **WT** differs from the **mutant** in either experiment

Adapted from

Paradis et al.
PLOS ONE
10(5), 2015

Problems come from experiment, not analysis



Adapted from

Paradis et al.
PLOS ONE
10(5), 2015

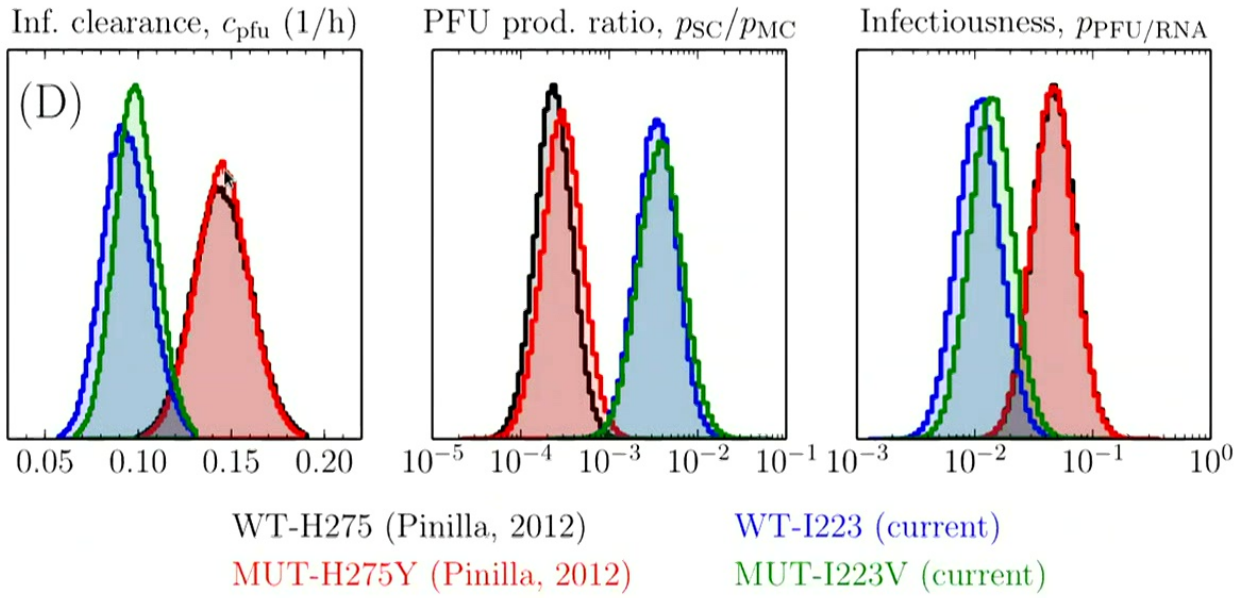
Between **OLD** → **NEW** experiments, we find:

Lower virus production rate (p) → lower peak virus in MC.

Shorter infectious lifespan (τ_I) → shorter virus plateau width in MC.

If the properties of a strain are experiment-specific, aren't experiments just producing random answers?

Parameters consistent within one experiment



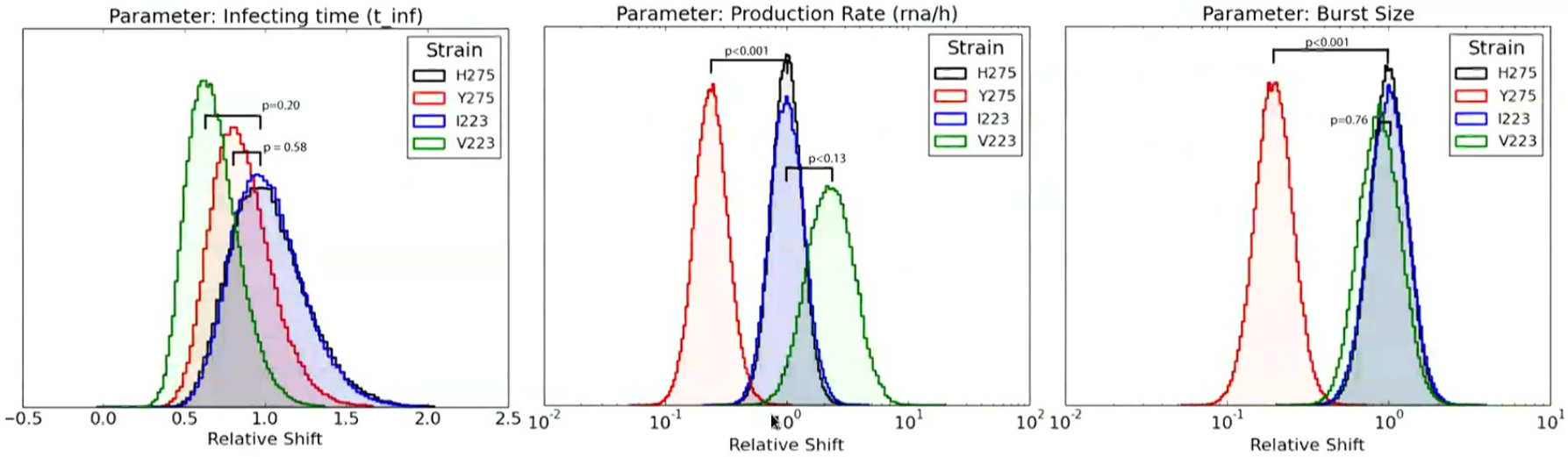
Paradis et al.
PLOS ONE
10(5), 2015

- Some parameters vary between experiments (WT in old $\neq$ new)
- But are consistent within a given experiment [(old WT = MUT), (new,WT = MUT)].

Maybe relative ($A = 3\times$standard strain) not **absolute** ($A = 5$) properties preserved between experiments.

Where does that leave us?

- Predictions work well within one experiment but...
- Inter-experimental variability often greater than changes studied. We must:
  - Express parameters (strain properties) **relative to a reference strain**; and/or
  - Isolate main cause(s) of variability and **account for it**.
- Either way, we'll need math models to do this.



Butting against a flawed institutional culture...

Quotes from a reviewer (who recommended our paper be rejected):

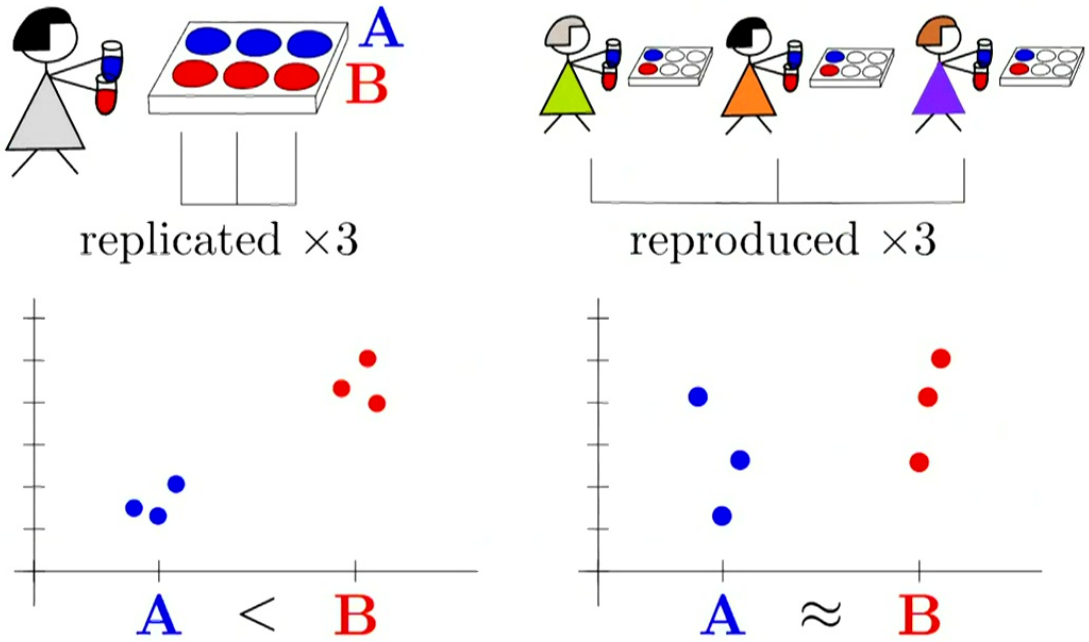
> *Further, a significant portion of the manuscript examines the issue of inter-experimental variability. I find this to be a major limitation of this work since this type of variability should not exist if proper techniques are used.* In general, variability of this nature in biological systems makes it difficult to believe the results.
>
> *There should be little to no inter-experimental variation, if proper techniques are used. Were two different people performing these experiments? [...] It is unlikely that the variation is true or biologically interesting.*

Wait... WHAT?!

variability in biology = bad/not trustworthy $\rightarrow$ reject paper.

proper technique = same person/day/equipment $\rightarrow$ redefining variability = redefine results significance.

Why are health results not reproducible?



Expressing a process in mathematical terms

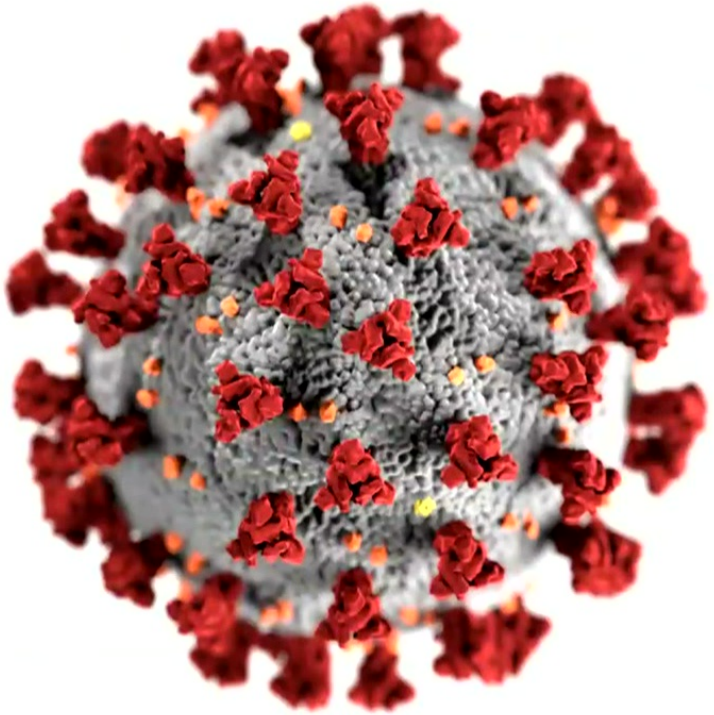
- requires sufficiently detailed understanding to express mathematically.
- helps identify knowledge gaps.
- replaces words with numbers and allows you to
  - detect systematic errors with experiment or data;
  - distinguish between noise and new phenomena;
  - predict beyond conducted experiments.

Take home messages

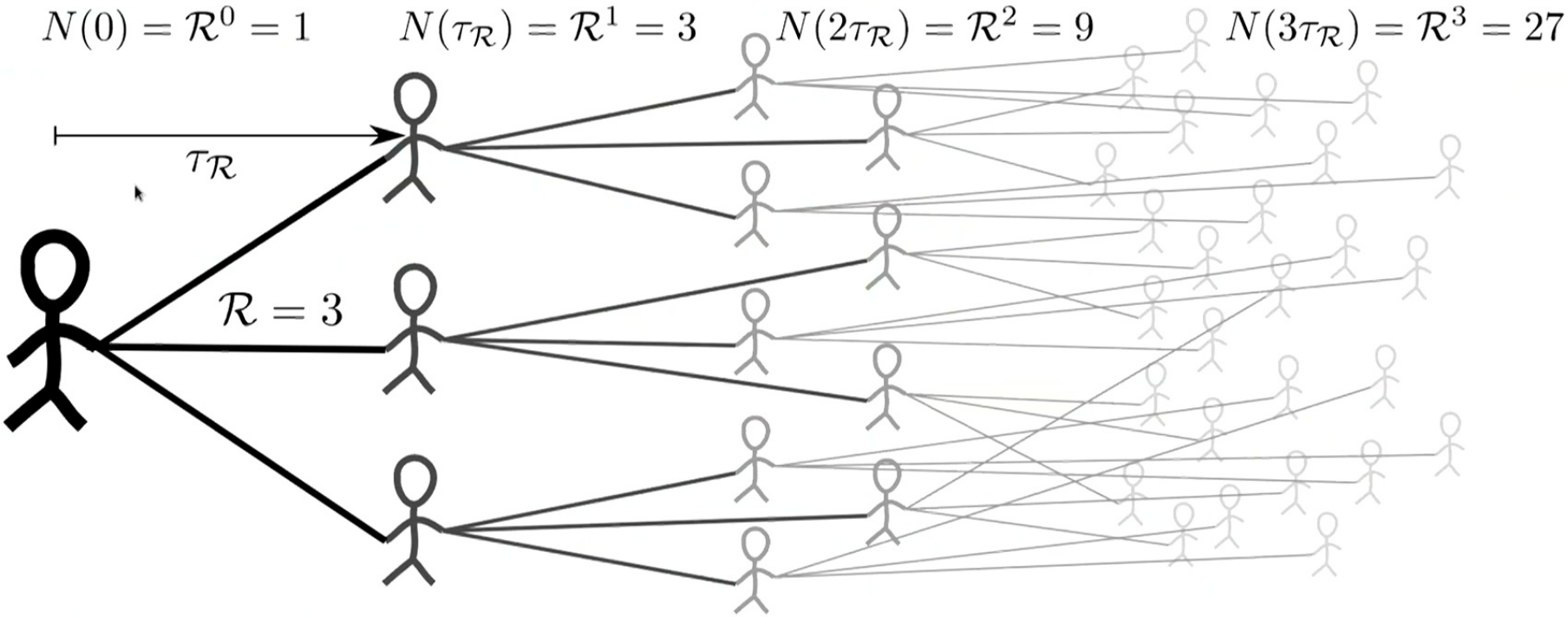
- being skeptical is healthy
- being absolutist (always/never/infallible) is not
- health science has some house-cleaning to do
- physics/math is an essential part of the solution

COVID-19

A quick intro to the epidemic



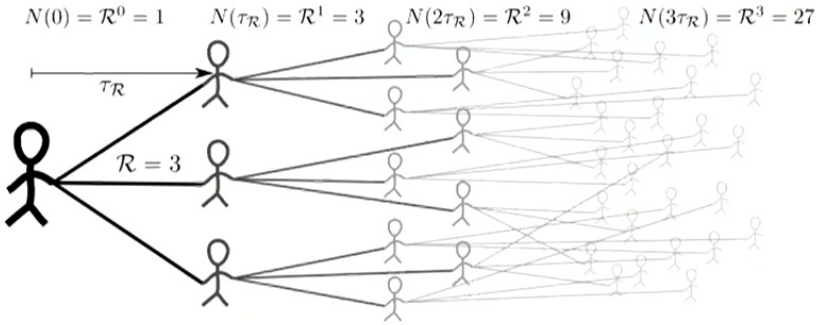
Starting with the basics

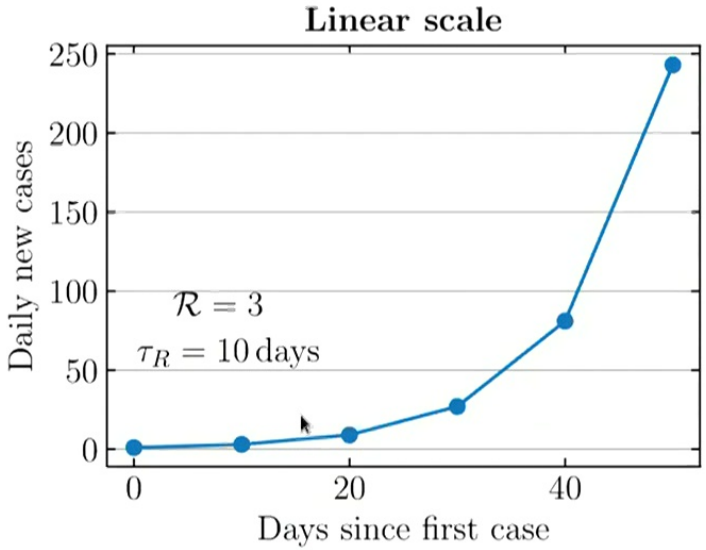


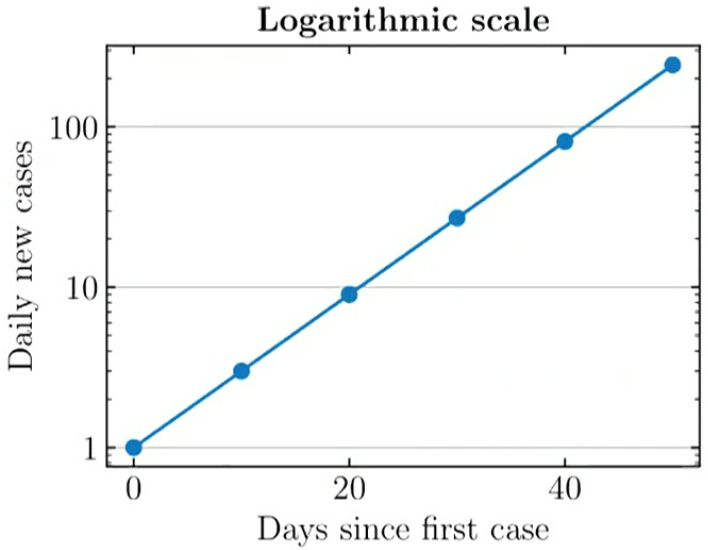
$\mathcal{R}$ the **reproductive number**, how many are infected by one infected person over their entire infectious period.

$\tau_\mathcal{R}$ the **serial interval**, the time from infection to infectious plus about half the average duration of the infectious period.

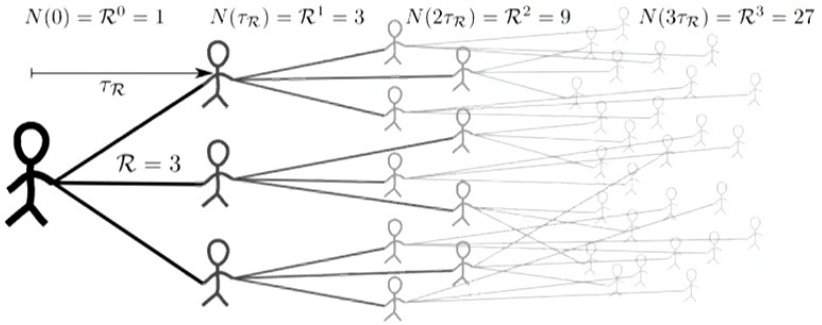
The case for using a logarithmic scale

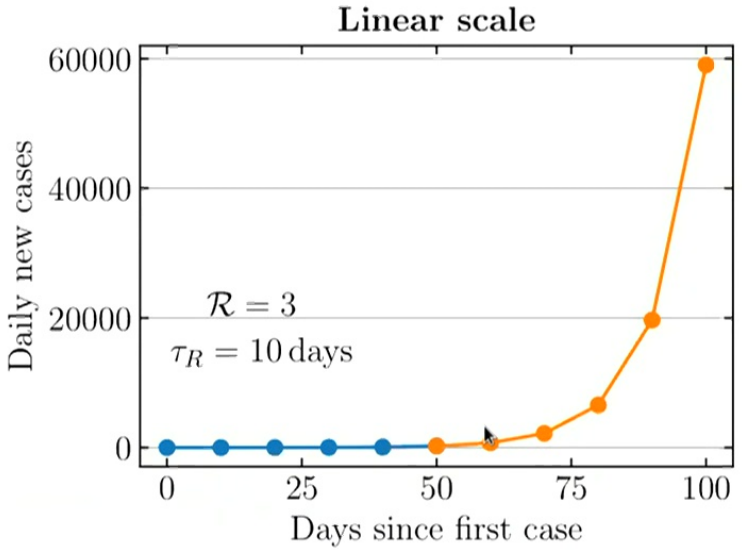


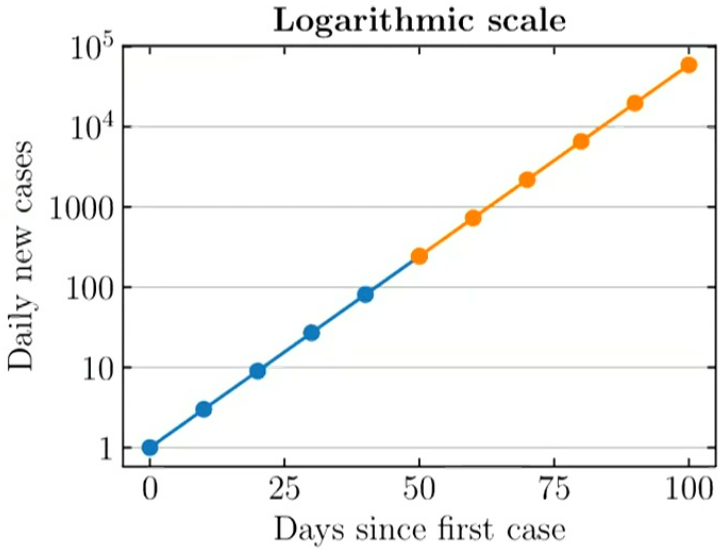




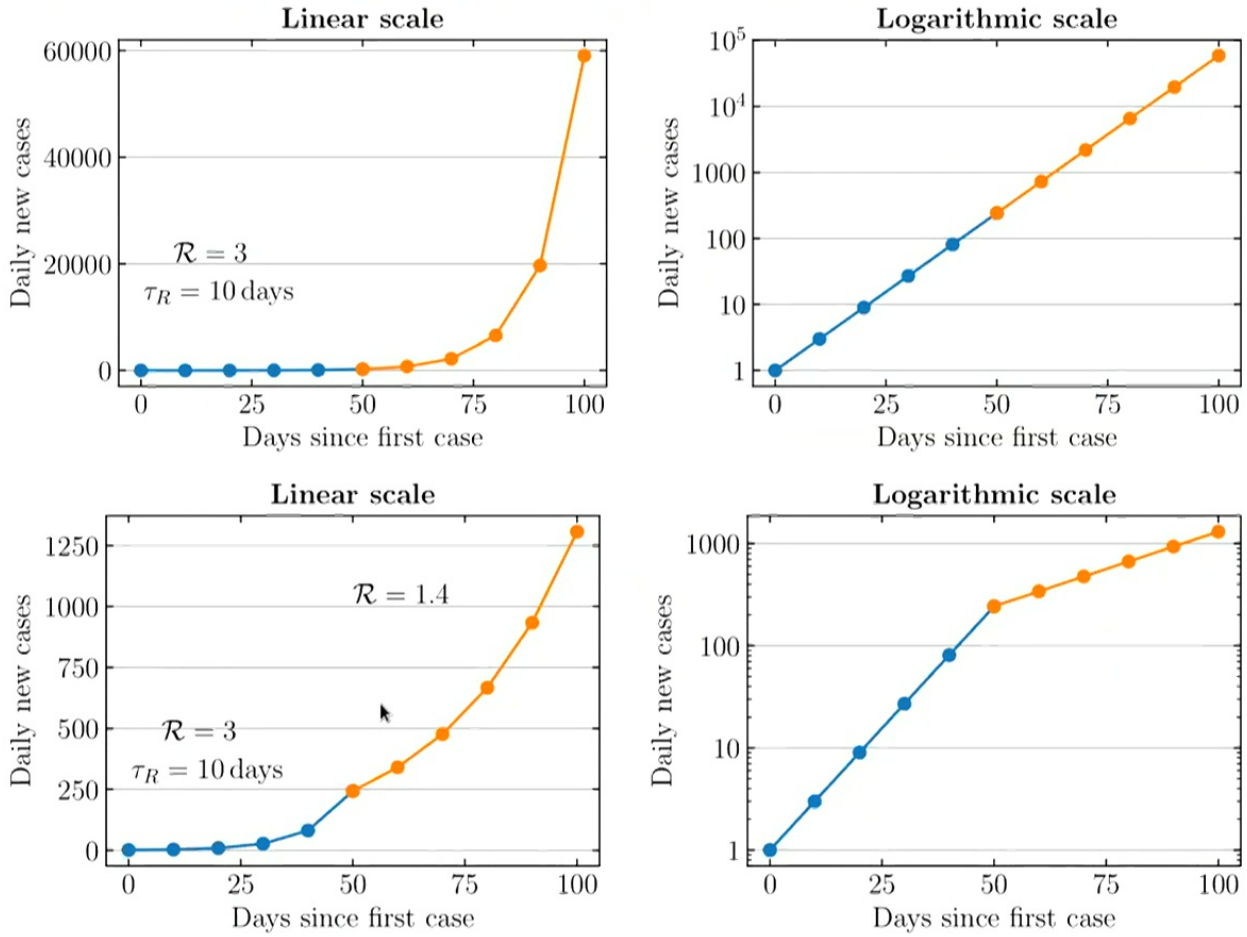
The case for using a logarithmic scale





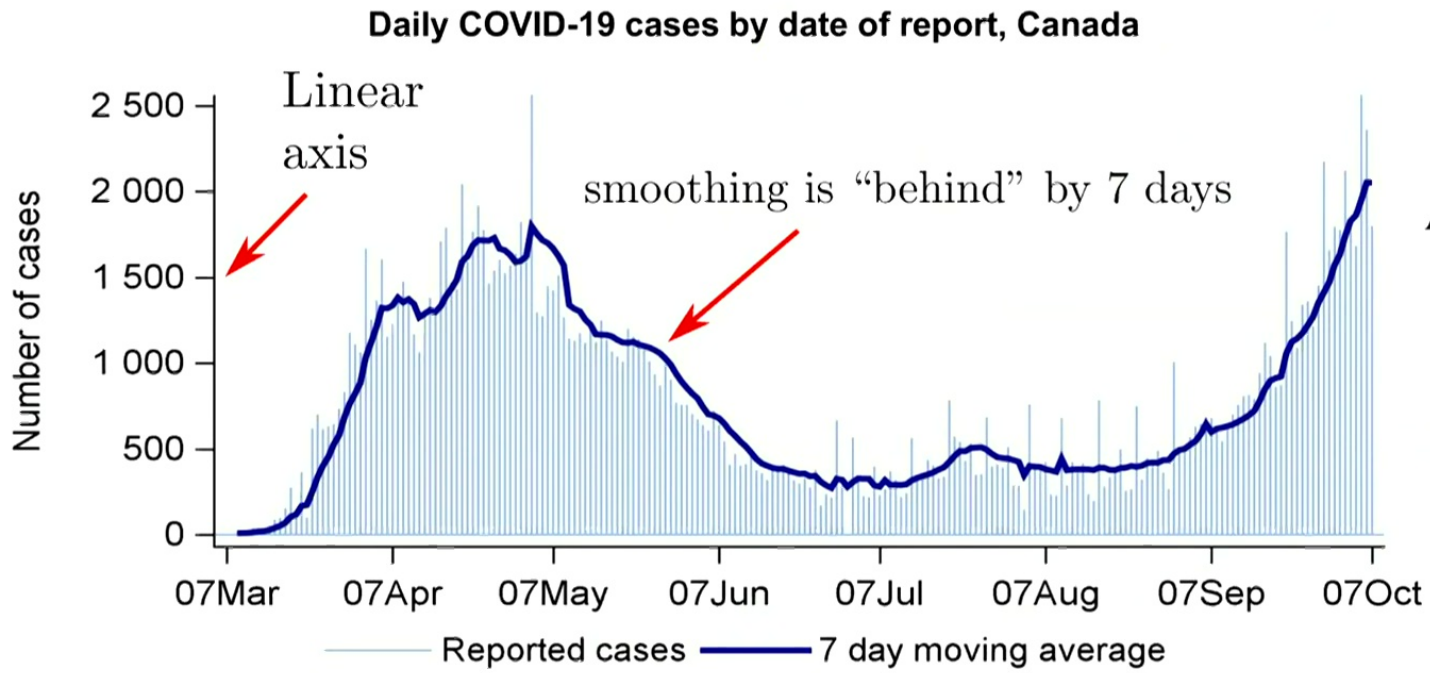


Changes in $\mathcal{R}$ more clearly seen in log-scale



Oh! Canada

Epidemic growth continues to accelerate nationally



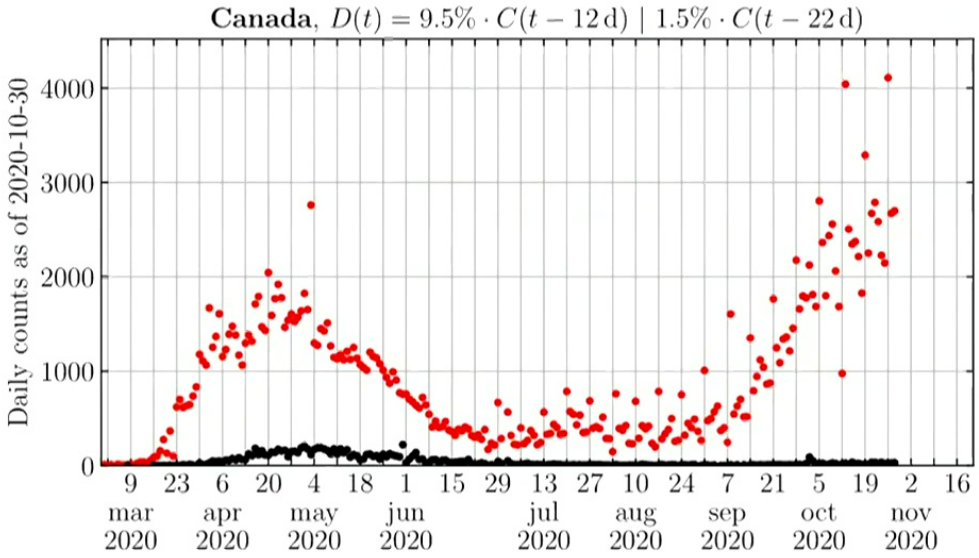
Modified from

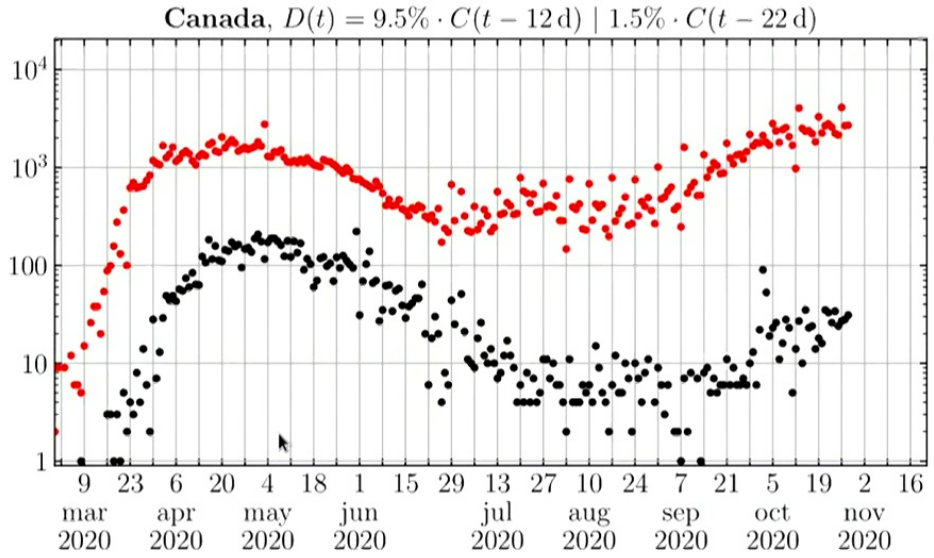
Public Health Agency of Canada Epidemiology & Modelling October 9, 2020

Data as of October 7, 2020

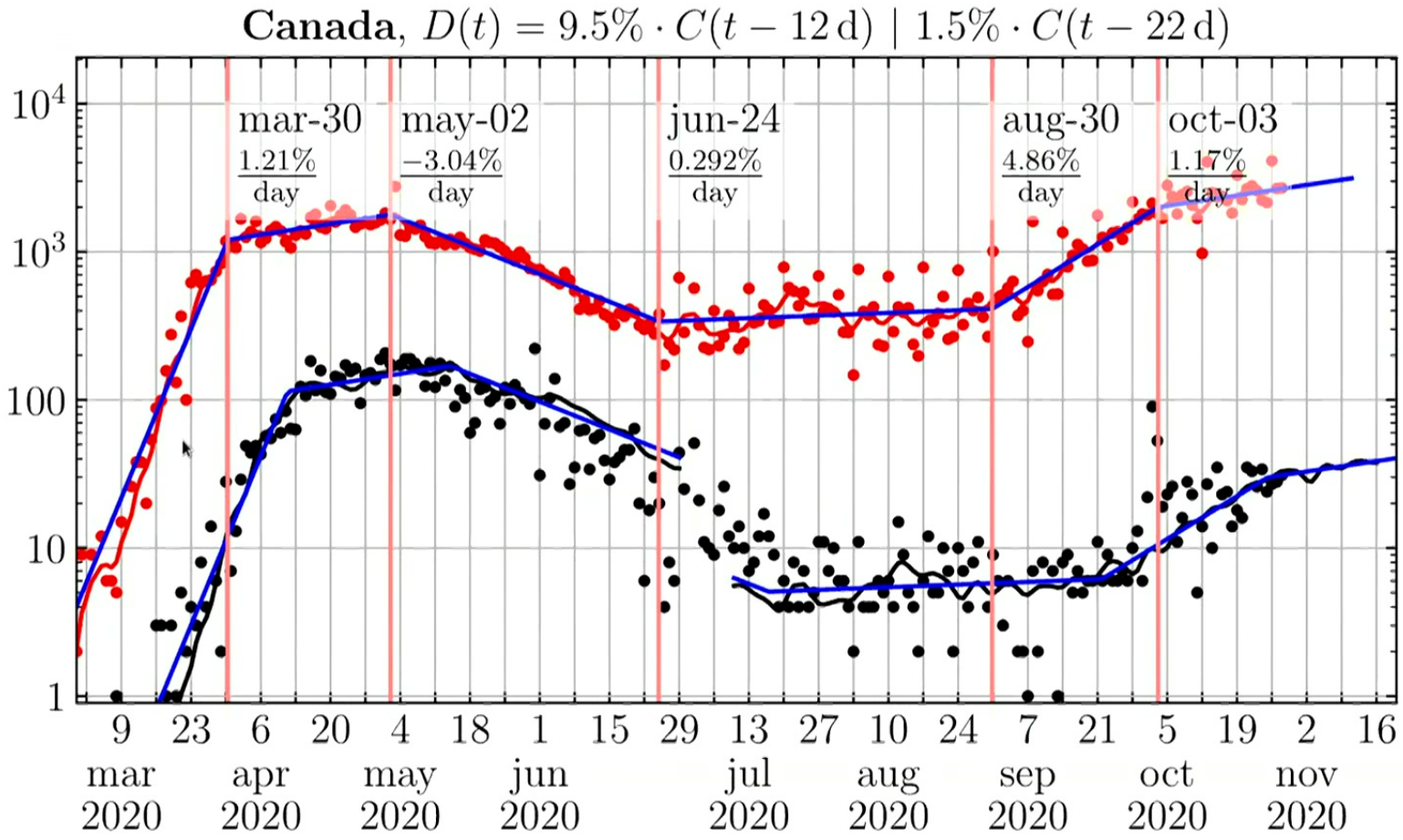
PUBLIC HEALTH AGENCY OF CANADA >

The case for using the logarithmic scale — real data



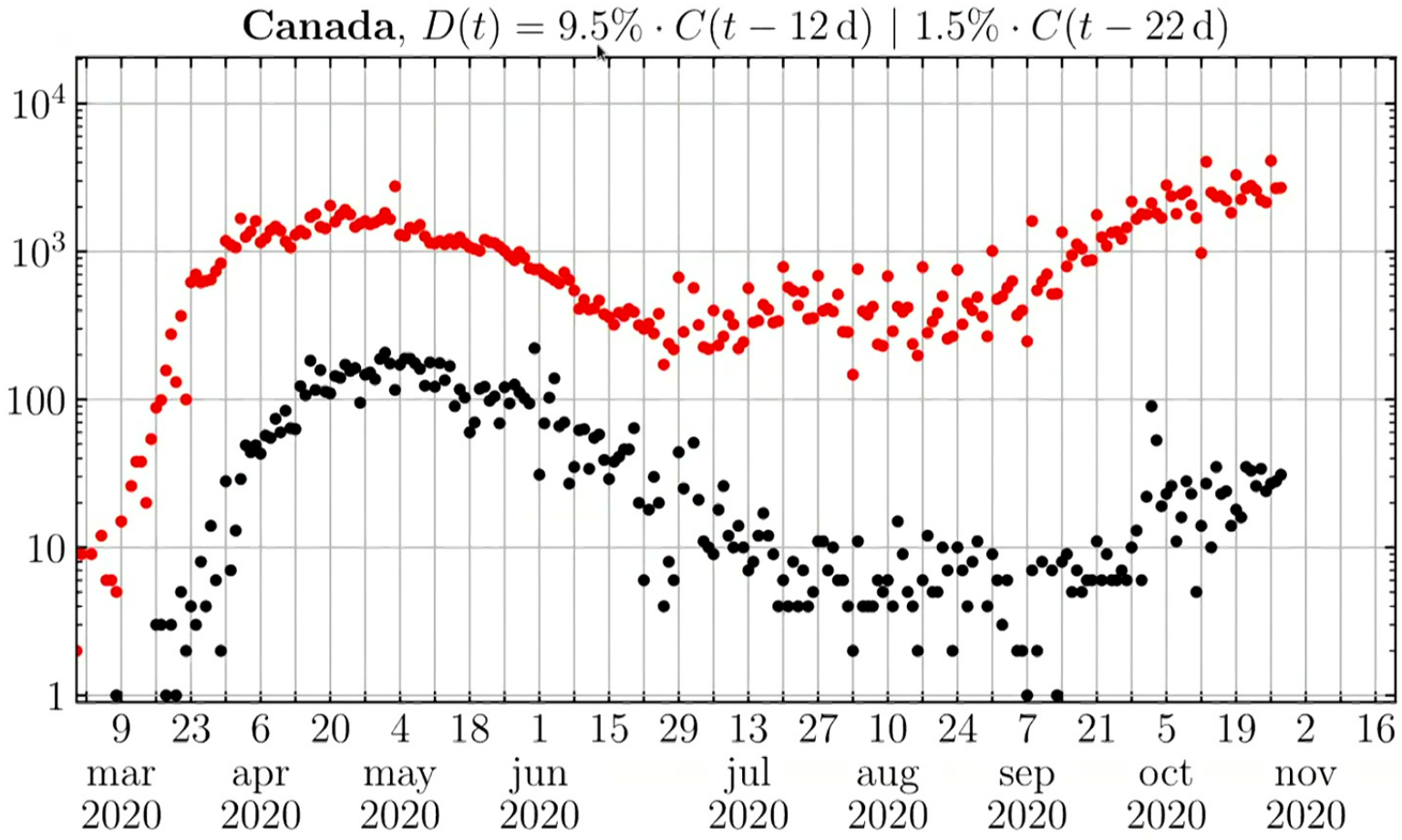


Identifying breakpoints for a set of exponential segments



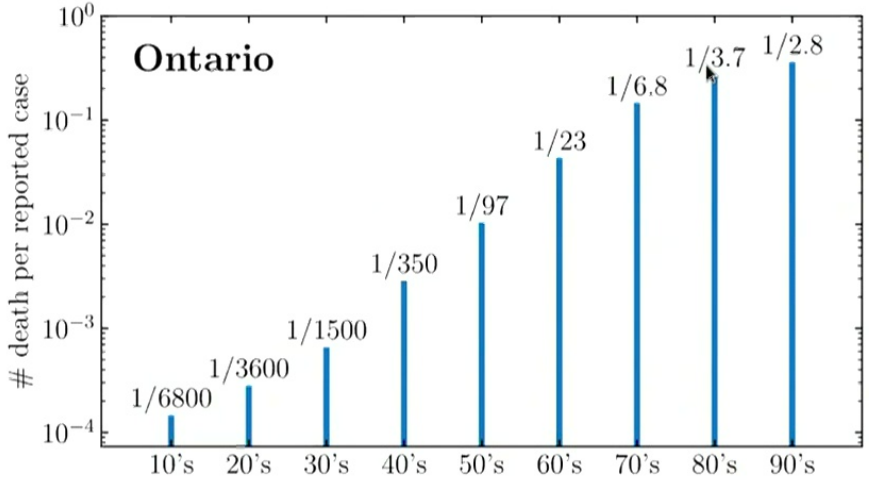
Beauchemin & Cannon COVID-19 #s updated daily

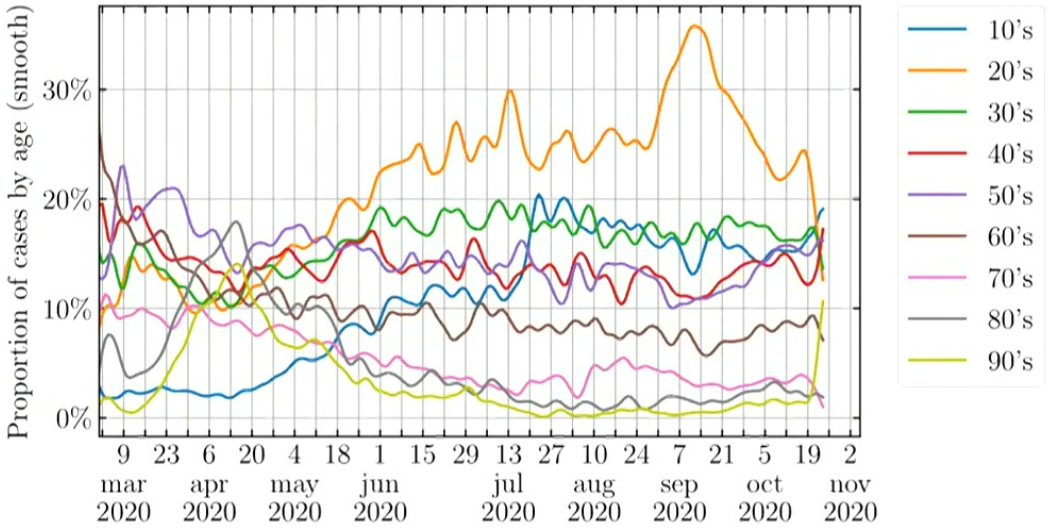
Identifying breakpoints for a set of exponential segments



Beauchemin & Cannon COVID-19 #s updated daily

The reason behind the reduction in death per case





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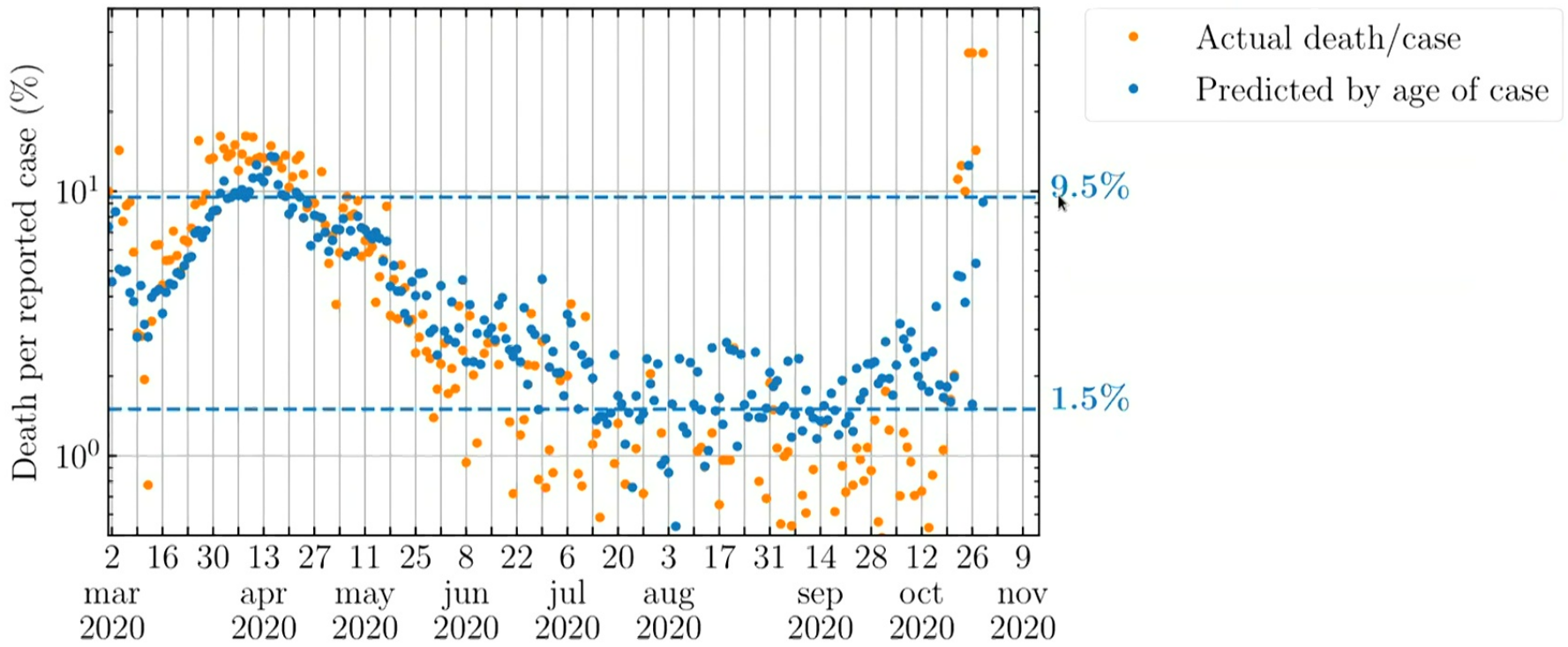

Take home message...

- Bad "science" in health research gives science a bad reputation!
- You should be skeptical of medical/health research, but even more so of random websites!
- **Math description is required to tackle the issues**, i.e. address/study reproducibility/variability; quantify info burried in data.
- Solid medical results exist, e.g. many vaccines (mumps, rubella, etc.) and antibiotics can save your life, limb re-attachment and cast for broken bones are awesome!
- Messaging in health research must improve. Drs should communicate degree of uncertainty in treatment with patient and involve them in decision-making.

The END.

Virophysics: A physicist's adventures in virology
Catherine Beauchemin (**cbeau@ryerson.ca**)
[URL: **https://phymbie.physics.ryerson.ca/~cbeau**]