FIGHTING THE COVID-19 PANDEMIC WITH CHEMICAL ENGINEERING INTUITION (AND ANALYSIS)

Matthew J Webber, Mark J McCready

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UNIVERSITY OF NOTRE DAME
Department of Chemical & Biomolecular Engineering
mjm@nd.edu
mwebber@nd.edu
chemeprof.com
www.WebberLab.com
@WebberLab

"FIRST LECTURE"

- "Professor"
  - Create, Curate, Transmit, Knowledge
- Classroom etiquette
- Next 4 years:
  - Great time, you get to define who you will become!

"CHEMICAL ENGINEERING"

- In many talks over the years I have referred to Chemical Engineering as the: "Ultimate Liberal Science Degree"
  - Fundamental subjects: Chemistry, Physics, Mathematics (more recently) Biology
  - Engineering topics: problem formulation, quantitative solution, design in light of uncertainty
  - Directly able to describe and give some quantification of:
    - Physiological processes, environmental phenomena (e.g., contaminants in the environment), consequences and limits of societal energy use

PROCESS DESIGN 2021

Production of Para-xylene via Crystallization from Mixed Xylenes
Analysis of Valacyclovir Production
Direct Air Capture of Carbon Dioxide
H2 Productions-Blue (H2 production using steam reforming process and capturing the CO2)
"Gray" hydrogen production
Zevalin Production
Production of the Monoclonal Antibody Alemtuzumab
Cell-based Influenza Vaccine
Multi-stage separation of bio-naptha reformate
Production of Remicade (infliximab)

Trastuzumab Production
Insulin: Exploring the Industrial Production and High Cost of Treatment for Diabetes
Manufacturing Artificial Blood Using Hemoglobin-based Products
Green Hydrogen Production from Offshore Wind Farm
Design of a Natural Gas Plant Carbon Capture and Sequestration System with Armine Absorbents
Herceptin Production
Carbon Dioxide Capture with an Activated Carbon Adsorbent
An Analysis of Continuous Production of the Monoclonal Antibody Trastuzumab
Membrane based carbon dioxide capture from a natural gas power plant

TOPICS TODAY

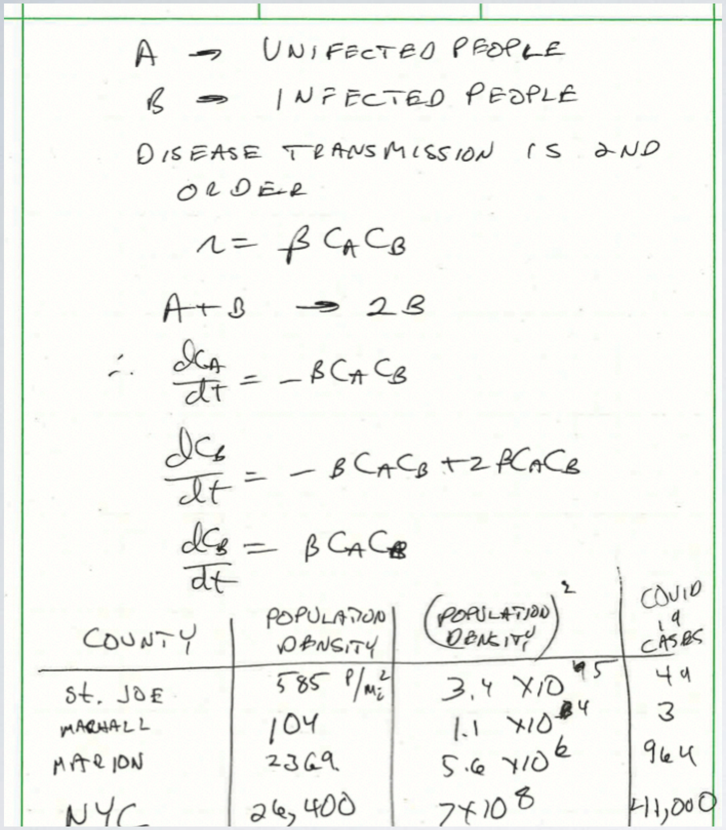
- Use of chemical engineering analysis to examine the spread of the virus and how we enabled "reopening" of various activities by staying below a minimum threat level
  - A finite "dose" of virus is needed to cause illness
    - We could adjust spacing and exposure time to allow safe execution of many different activities
- Description of the key details of the Pfizer Vaccine manufacturing process

"COVID 19"

- It became apparent within the first few weeks of the pandemic, that <u>no single field of expertise</u> had the knowledge and quantitative tools to deal effectively with the spread of the virus or the resulting disease
  - Chemical Engineering could certainly make a contribution!
- As appropriate we begin including examples in our classes and using our expertise to help the University <u>quickly</u> put research into hibernation and then later helped develop a plan for safe reopening and resumption of many activities.

INITIAL SPREAD OF THE VIRUS

- CBE 20255 "Introduction to Chemical Engineering" (Sophomore year)
  - Key topic: "Conservation of mass" (a.k.a. *chemical species*, or *particles in room*, includes chemical reactions)
- Observation: The rate of a chemical reaction depends on the "concentration" (e.g., moles/volume) of the chemicals.
- Speculation: Spread of the virus, which requires infected person ("B") interacting with a susceptible person ("A") would, by analogy, spread as the population density to the second power.



A → UNIFECTED PEOPLE
B → INFECTED PEOPLE

DISEASE TRANSMISSION IS 2ND ORDER

$r = \beta C_A C_B$

$A + B \rightarrow 2B$

$\therefore \frac{dC_A}{dt} = -\beta C_A C_B$

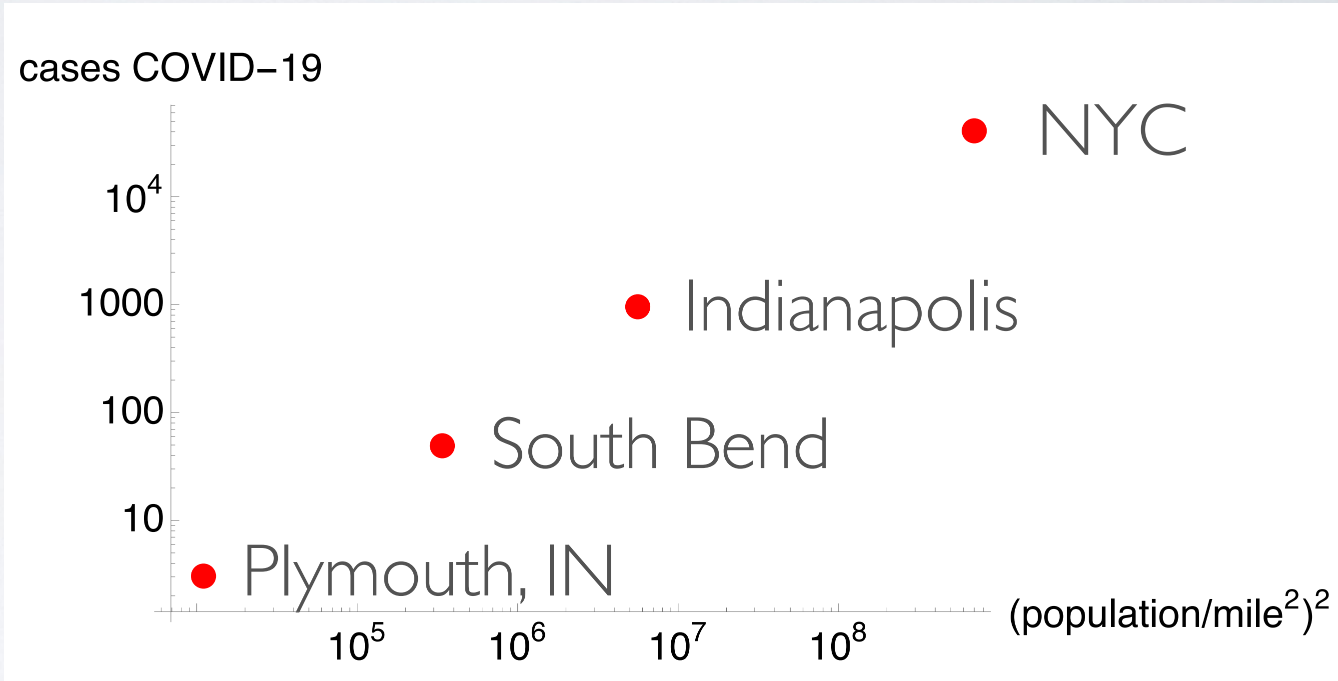
$\frac{dC_B}{dt} = -\beta C_A C_B + 2\beta C_A C_B$

$\frac{dC_B}{dt} = \beta C_A C_B$

COUNTY	POPULATION DENSITY	$(\text{POPULATION DENSITY})^2$	COVID 19 CASES
St. JOE	585 P/mi²	3.4×10^5	44
MARHALL	104	1.1×10^4	3
MARION	2369	5.6×10^6	964
NYC	26,400	7×10^8	41,000

CBE 20255: 4/7/20

Disease spread modeled as a "2nd order" chemical reaction:
Instead of A + B -> D
The disease is:
A + B-> 2B



This differs from the standard "SEIR" model since I use "concentration" (population density), not "number" of people

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mjm@nd.edu
mwebber@nd.edu
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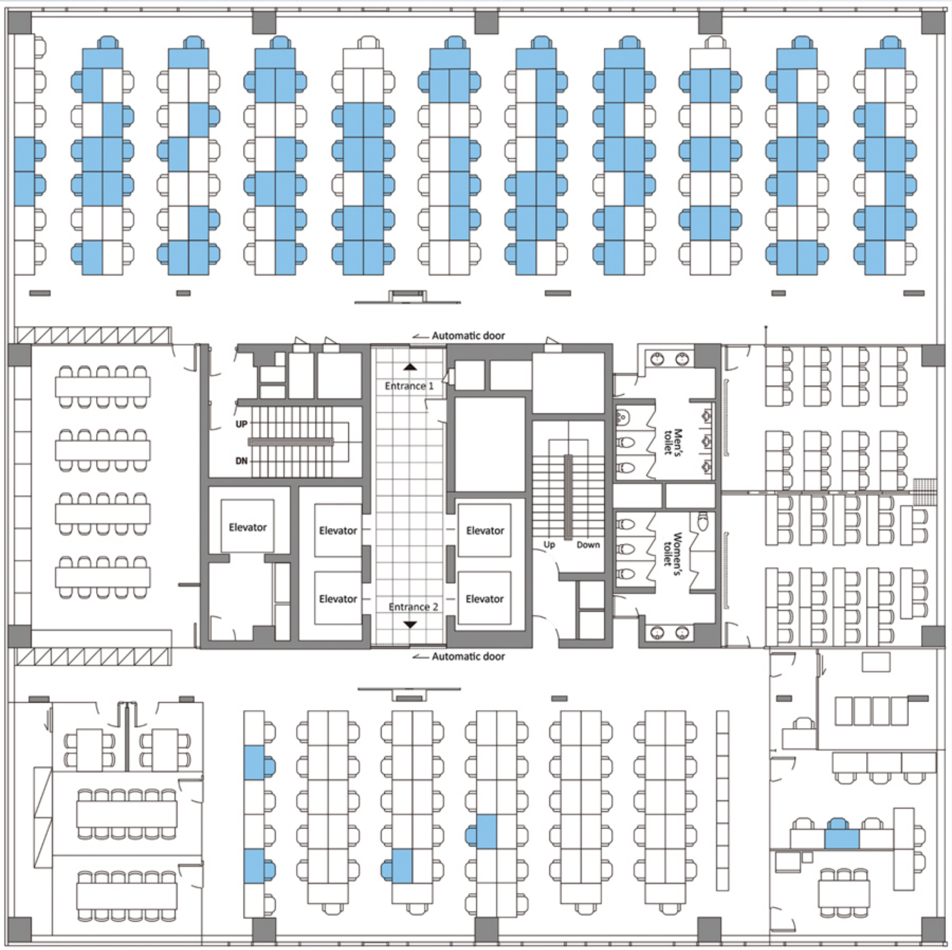
HOW DOES SPREAD OCCUR ??

- Initially there was much talk about
  - Surfaces
  - Large droplets
- Evidence of Aerosol transmission was available by the end of March.
  - Another topic of CBE 20255: *Concentration of particles in the air*

QUANTIFYING AEROSOL TRANSMISSION

By late March 2020, the following data were available. Blue seats were people who were infected during a 2 day period



CBE 20255
Spring 2020
Final Exam
5/7/20

1. Potential for aerosol spread of SARS CoV 2 virus.

Relevant "mass balance"

$$V\frac{dC_A}{dt} = q_{Af}C_{Af} - qC_A + S - D$$

$$C_A = \frac{S}{q}$$

The concentration of virus carrying particles is proportional to the number emitted/time divided by the flow rate of fresh air into the room

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mwebber@nd.edu
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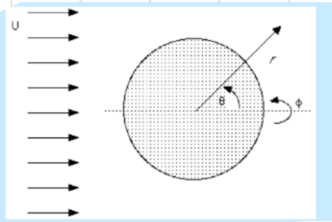
PARTICLE EMISSION

- Depending on:
  - Breathing, Speaking, Shouting, Singing
  - You emit a "distribution of sizes" of liquid particles that could carry the virus.
  - We can analyze this situation!

SETTLING OF A SPHERICAL PARTICLE IN A GRAVITATIONAL FIELD

- CBE 30355 (Transport Phenomena I),
- 30357 (Biological Transport Phenomena)

CBE 30357:LECTURE 10/31/19



$$\left\{ \begin{array}{l} \vec{\nabla}\cdot\vec{v} = 0 \\ \vec{\nabla} p = \mu \nabla^2 \vec{v} \end{array} \right\}$$

USE SPHERICAL COORDINATES
- CONTINUITY EQ.
- r-DIRECTION N.S. EQ } Re→0
- θ-DIRECTION N.S. EQ

SEQUENTIALLY CONSIDER 3 PDE'S USING AN ASSUMED FORM OF SOLUTION

$v_r \sim f(r)\cos\theta$ } FROM
$v_\theta \sim g(r)\sin\theta$ } B.C.'S

Navier-Stokes Equations

TABLE 3.4

(*Continued*)

Spherical coordinates

r direction

$$\rho\left[\frac{\partial v_r}{\partial t} + v_r\frac{\partial v_r}{\partial r} + \frac{v_\theta}{r}\frac{\partial v_r}{\partial \theta} + \frac{v_\phi}{r\sin\theta}\frac{\partial v_r}{\partial \phi} - \frac{v_\theta^2 + v_\phi^2}{r}\right] = -\frac{\partial p}{\partial r} + \rho g_r$$
$$+\mu\left[\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v_r}{\partial r}\right)\right) + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial v_r}{\partial\theta}\right) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 v_r}{\partial\phi^2} - 2\frac{v_r}{r^2} - \frac{2}{r^2}\frac{\partial v_\theta}{\partial\theta} - \frac{2}{r^2}v_\theta\cot\theta - \frac{2}{r^2\sin^2\theta}\frac{\partial v_\phi}{\partial\phi}\right] \quad (3.3.28a)$$

TYPO ∂r

θ direction

$$\rho\left(\frac{\partial v_\theta}{\partial t} + v_r\frac{\partial v_\theta}{\partial r} + \frac{v_\theta}{r}\frac{\partial v_\theta}{\partial\theta} + \frac{v_\phi}{r\sin\theta}\frac{\partial v_\theta}{\partial\phi} + \frac{v_\theta v_r}{r} - \frac{v_\phi^2\cot\theta}{r}\right) = -\frac{1}{r}\frac{\partial p}{\partial\theta} + \mu\left[\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v_\theta}{\partial r}\right)\right.$$
$$\left. + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial v_\theta}{\partial\theta}\right) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 v_\theta}{\partial\phi^2} + \frac{2}{r^2}\frac{\partial v_r}{\partial\theta} - \frac{v_\theta}{r^2\sin^2\theta} - \frac{2\cos\theta}{r^2\sin^2\theta}\frac{\partial v_\phi}{\partial\phi}\right] + \rho g_\theta \quad (3.3.28b)$$

ϕ direction

$$\rho\left(\frac{\partial v_\phi}{\partial t} + v_r\frac{\partial v_\phi}{\partial r} + \frac{v_\theta}{r}\frac{\partial v_\phi}{\partial\theta} + \frac{v_\phi}{r\sin\theta}\frac{\partial v_\phi}{\partial\phi} + \frac{v_\phi v_r}{r} + \frac{v_\theta v_\phi}{r}\cot\theta\right) = -\frac{1}{r\sin\theta}\frac{\partial p}{\partial\phi} + \mu\left[\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v_\phi}{\partial r}\right)\right.$$
$$\left. + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial v_\phi}{\partial\theta}\right) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 v_\phi}{\partial\phi^2} + \frac{2}{r^2\sin\theta}\frac{\partial v_r}{\partial\phi} - \frac{v_\phi}{r^2\sin^2\theta} + \frac{2\cos\theta}{r^2\sin^2\theta}\frac{\partial v_\theta}{\partial\phi}\right] + \rho g_\phi \quad (3.3.28c)$$

$= 0$

WE GET: SETTLING VELOCITY

Force balance on settling particle

$\Sigma F =$ GRAVITY + BUOYANCY + DRAG

$\Sigma F = \rho g V - \rho_f g V - 6\pi\mu U R$

$= \rho g \frac{4}{3}\pi R^3 - \rho_f g \frac{4}{3}\pi R^3 - 6\pi\mu U R$

$6\pi\mu U R = \frac{4}{3}(\rho - \rho_f) g \pi R^3$

$U = \frac{2}{9}\frac{(\rho-\rho_f) g R^2}{\mu}$

Stokes ' Law

PARTICLES EMITTED BY SPEAKING

- If the transmission is by aerosol particles that are present everywhere, even in a large room, how does distance matter?

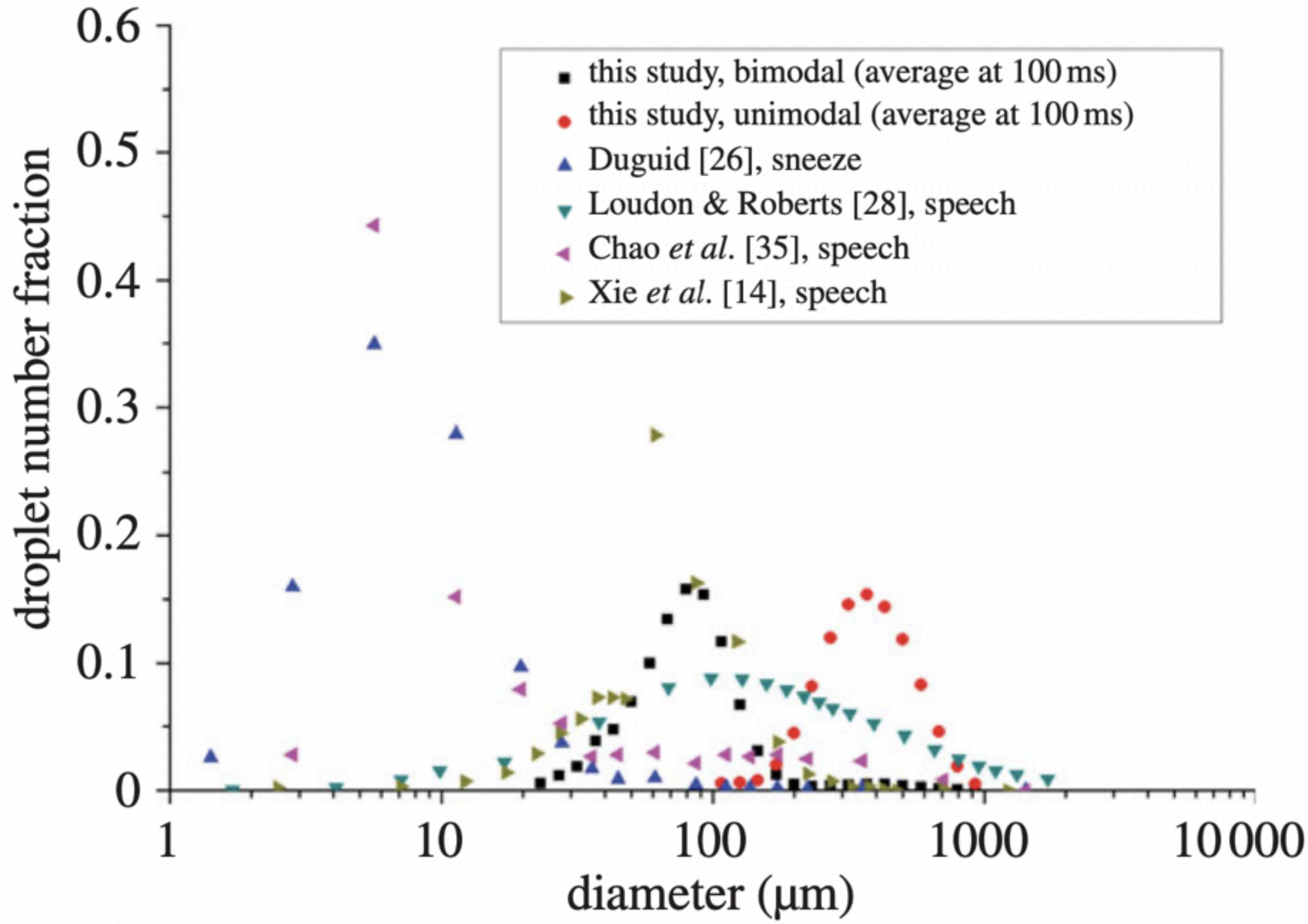
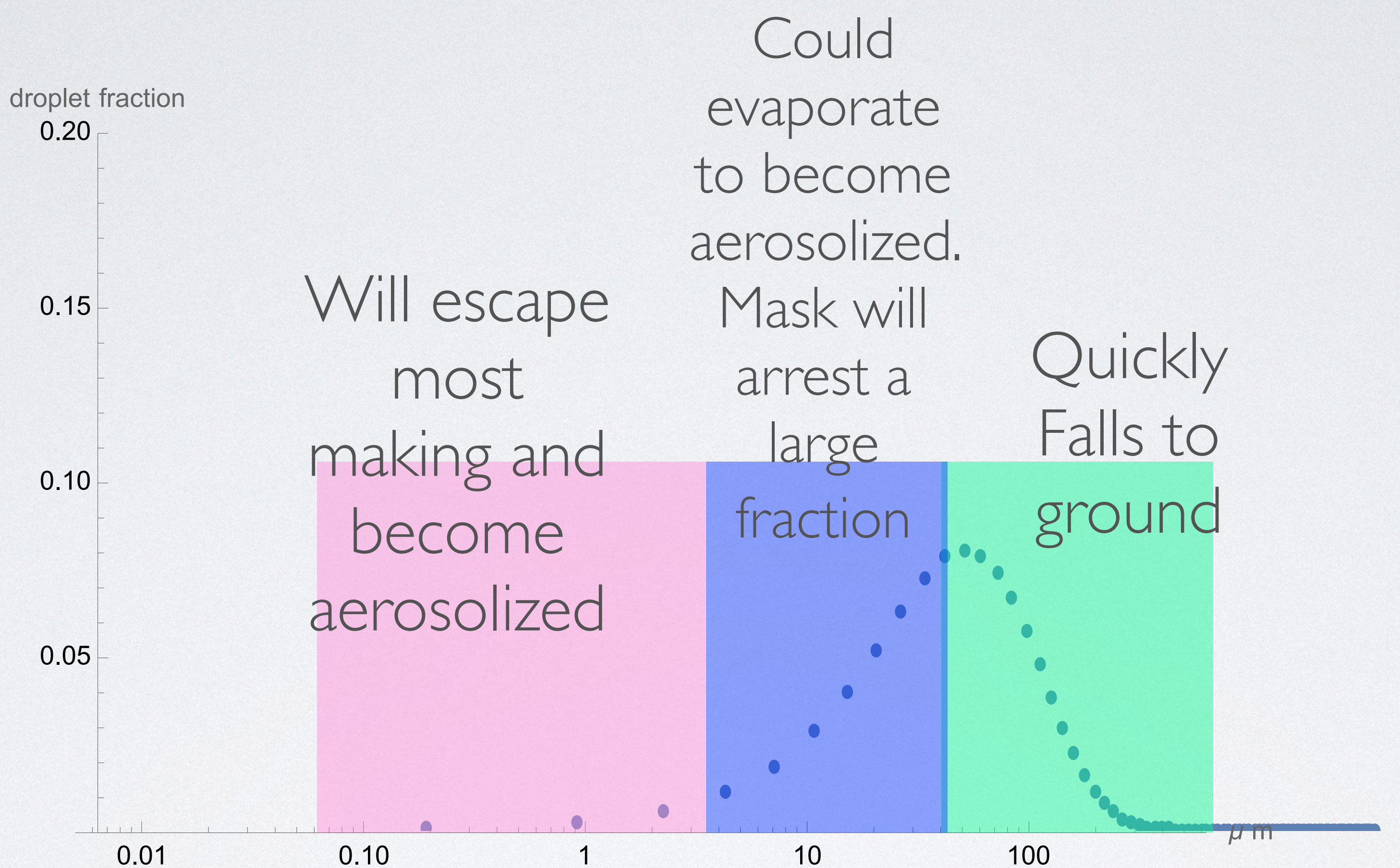


Figure 5. Comparison of the number size distribution of the droplets exhaled by sneeze and speech. (Online version in colour.)

Drop emissions from speaking

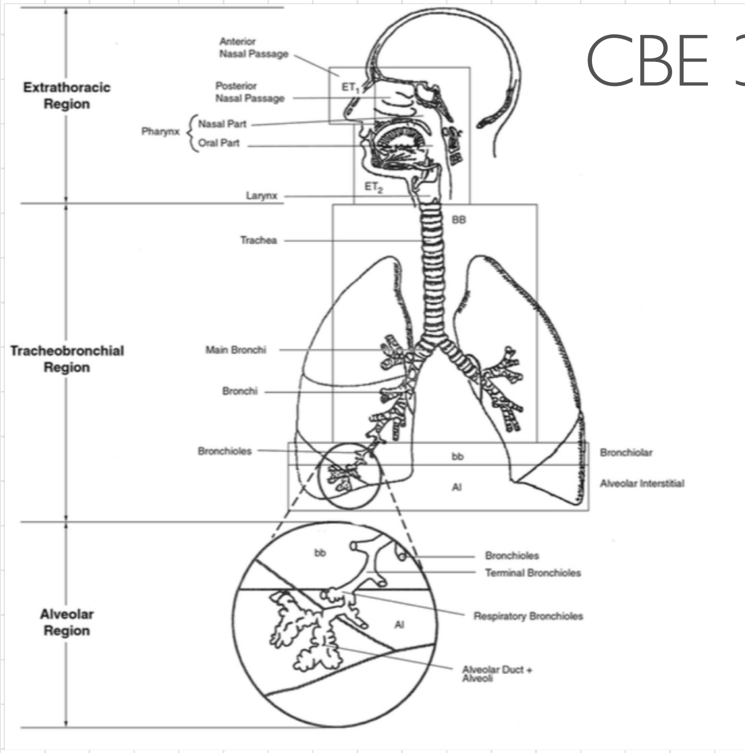


Note that this is idealized: All masks leak!

ANOTHER RELEVANT TOPIC

CBE 30357

PARTICLE CLEARING MECHANISMS



TORTUOUS PATH, PARTICLES STICK TO WALL: CLEARED BY CILIA.
LONG PATH: ONLY LAST ~5 BRANCHES ABSORB
OR, COULD BREATH BACK OUT.

2 T.C. Carvalho et al. / International Journal of Pharmaceutics 406 (2011) 1–10

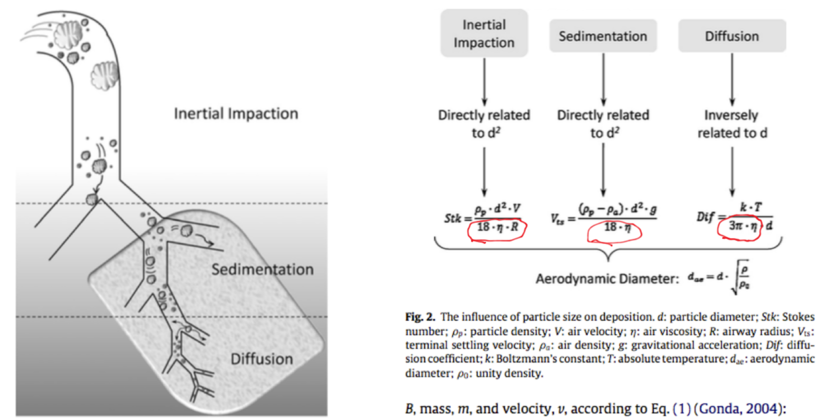


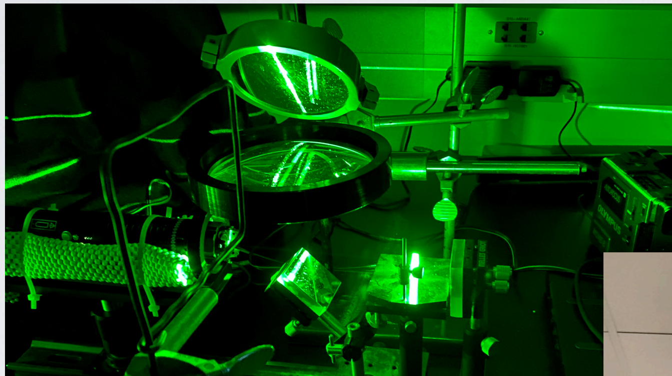
Fig. 2. The influence of particle size on deposition. d: particle diameter; Stk: Stokes number; ρ_p: particle density; V: air velocity; η: air viscosity; R: airway radius; V_{ts}: terminal settling velocity; ρ_a: air density; g: gravitational acceleration; Dif: diffusion coefficient; k: Boltzmann's constant; T: absolute temperature; d_{ae}: aerodynamic diameter; ρ_0: unity density.

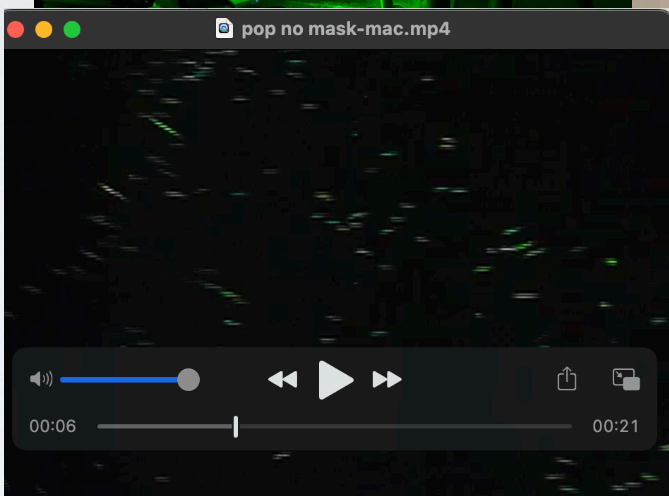
B, mass, m, and velocity, v, according to Eq. (1) (Gonda, 2004):

WHERE DO EQUATIONS COME FROM?

SOLUTION TO NAVIER-STOKES EQUATIONS FOR FLOW PAST A SPHERE: $Re \to 0$

MASKS—CLASSROOM, FOOTBALL (WITH PROFESSOR LEIGHTON)

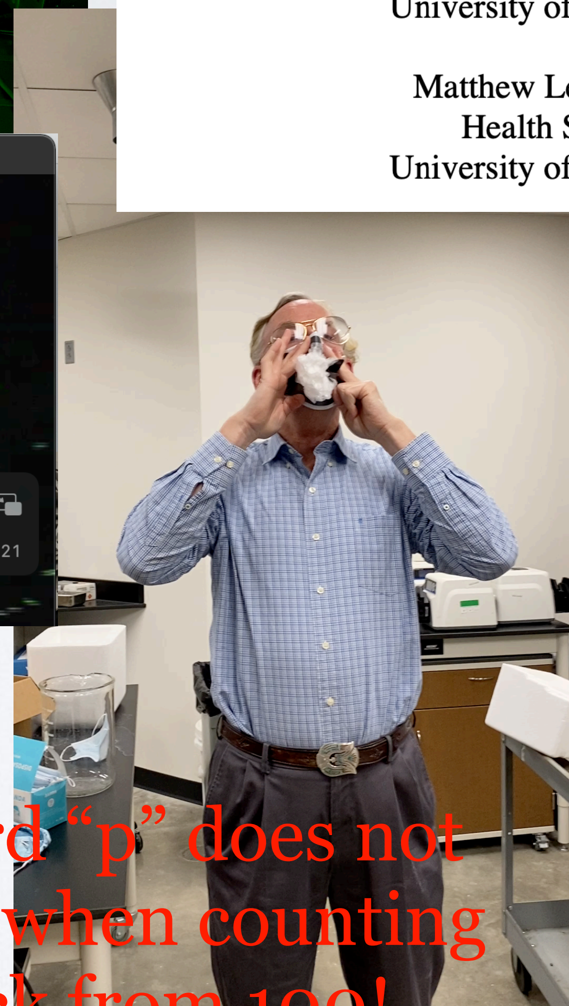


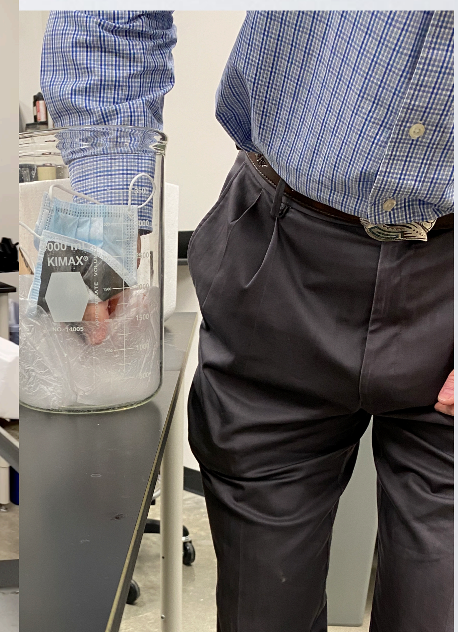


Strategies for Aerosol Mitigation in a Football Competition

David T. Leighton, Jr.
Mark J. McCready
Department of Chemical and Biomolecular Engineering
University of Notre Dame

Matthew Leiszler, MD
Health Services
University of Notre Dame

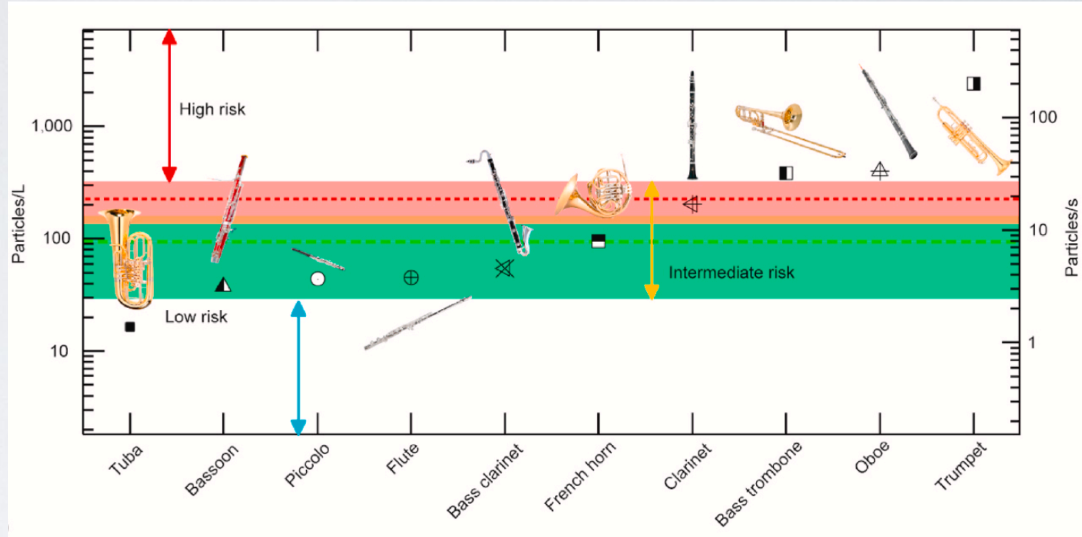




A hard "p" does not occur when counting back from 100!

MUSICAL REHEARSAL AND PERFORMANCE

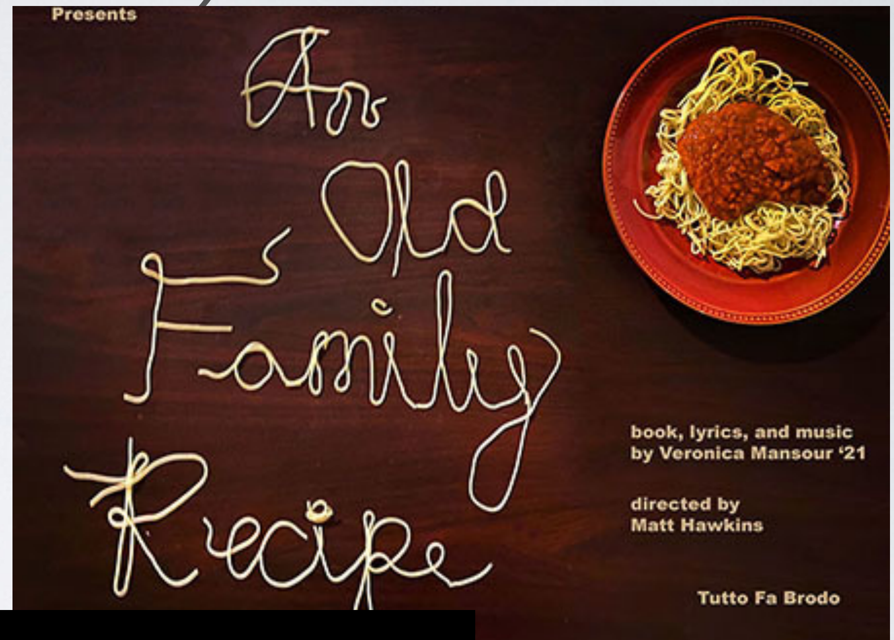
- Fog tests:



Different instruments needed different spacing

THE (ORIGINAL) MUSICAL

- The musical production was written by a graduating senior who had been working on it for 3 years.
- They staged scenes to hide "fans" — e.g. when the cast is sitting around a table.
- Needed to edit out the fan noise"
- They had one problem I could not help them with:
    - A kiss!



Chemical Engineering in Support of Vaccine R&D

The development and scalable manufacturing of many COVID vaccines, and especially mRNA vaccines, was a Herculean effort the ***likes of which was unprecedented in the biotechnology sector***

These vaccines did not just appear out of nowhere, but were a result of decades of research by many scientists and (importantly) ***Chemical Engineers***

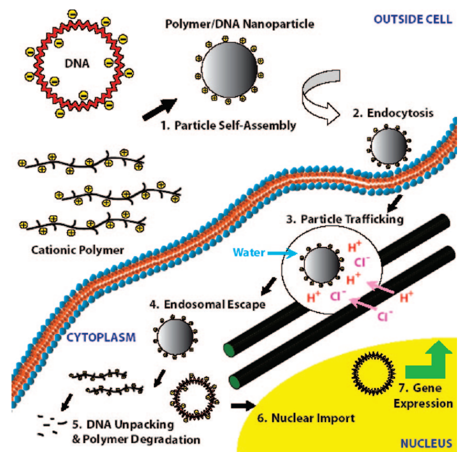
ACCOUNTS
of chemical research

A Combinatorial Polymer Library Approach Yields Insight into Nonviral Gene Delivery

JORDAN J. GREEN,[†] ROBERT LANGER,[†,‡] AND DANIEL G. ANDERSON[‡,*]

[†]Department of Chemical Engineering, [‡]The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

RECEIVED ON OCTOBER 25, 2007

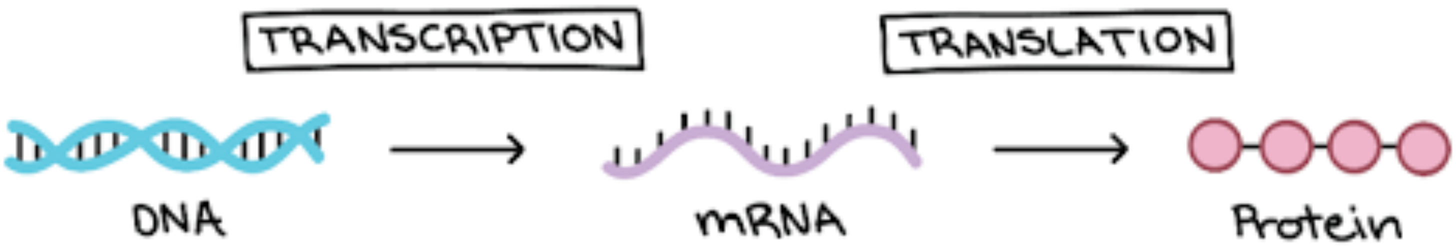


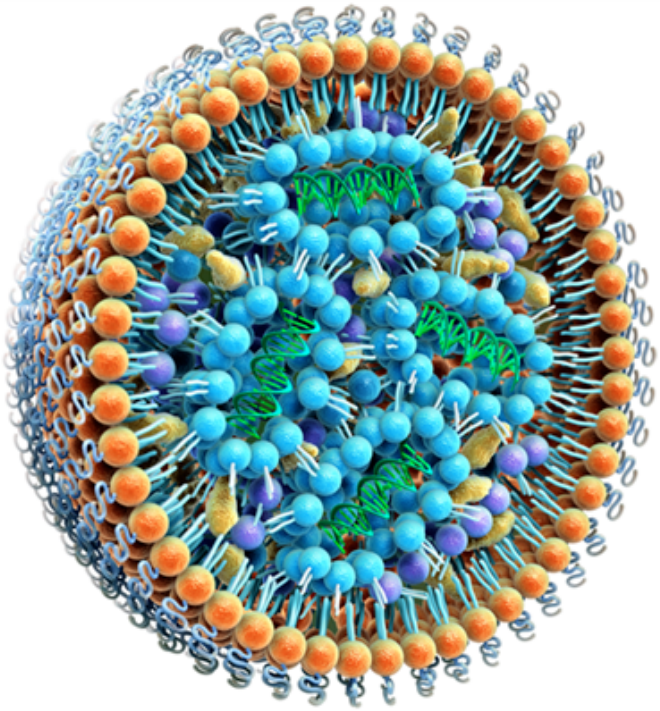
This dedicated research enabled modular platforms for rapid implementation

EXAMPLE: Moderna had a fully formulated vaccine before the first American had died of COVID (February 6, 2020)

What is Actually in the Vaccine?

*The **"Central Dogma"** of biology:*





The 5 components of LNP vaccines:

1. mRNA (codes the protein antigen — Spike)

2. Ionizable lipid (proprietary)

3. "Helper" lipid (makes a particle)

4. Cholesterol (stabilizes the particle)

5. PEG-Lipid (keeps particles from clumping)

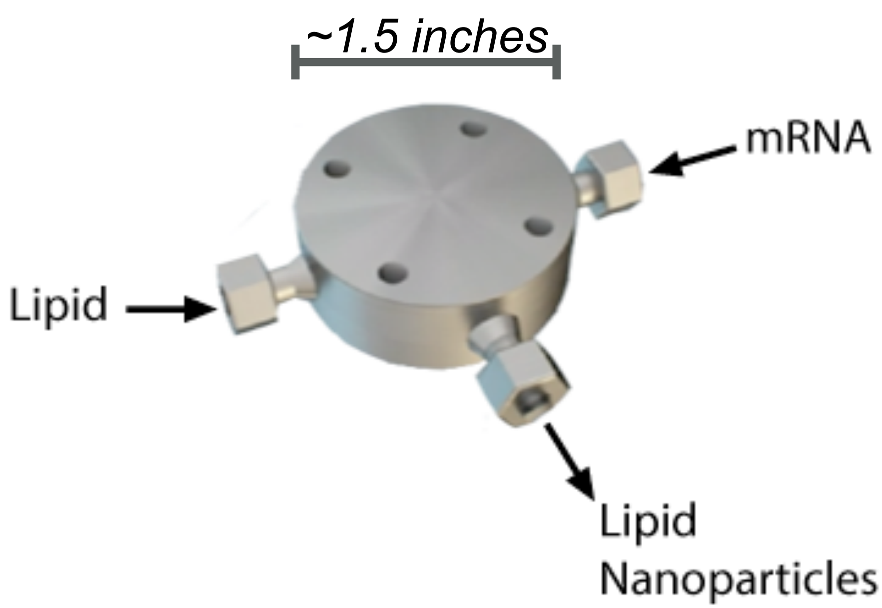
*See the recent TED talk by **Prof. Kathryn Whitehead** (Carnegie Melon)*

TED Ideas worth spreading

How is the Vaccine Made?

Massively parallel small-batch production

Jet Impingement Mixer:



Scale: Pfizer now manufacturing 100M doses per month!

University of Notre Dame
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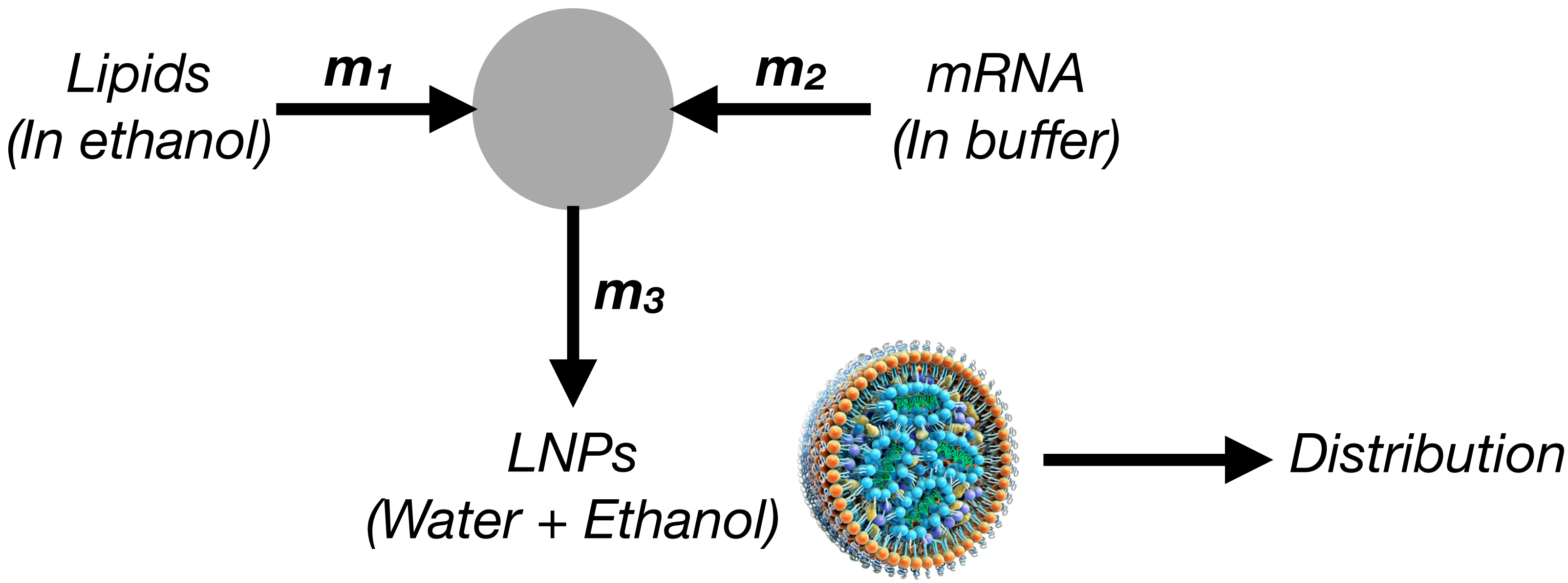
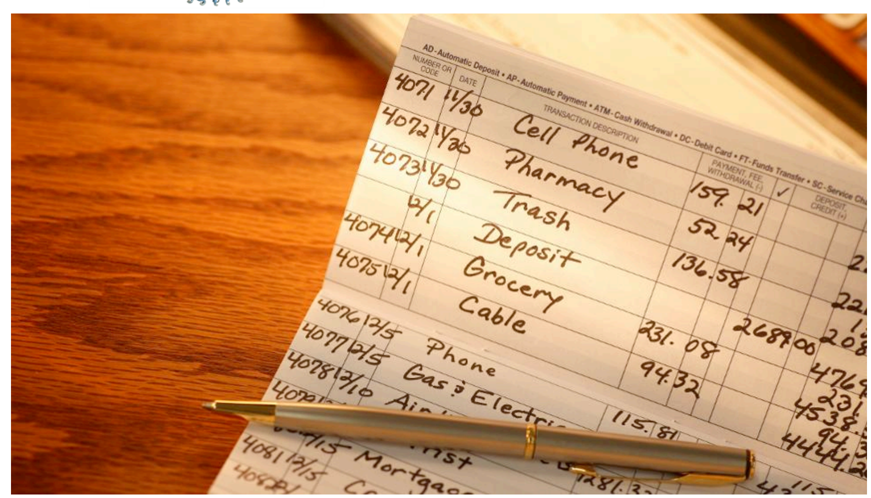
Chemical Engineering Tools to Enable Vaccine Production

Introduction to Chemical Engineering (Sophomore Level)





Mass is never created or destroyed!

$$m_1 + m_2 = m_3$$

$$x_{E,1} * m_1 = x_{E,3} * m_3$$

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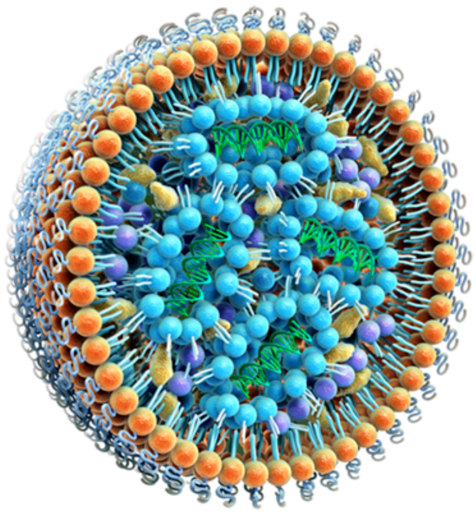
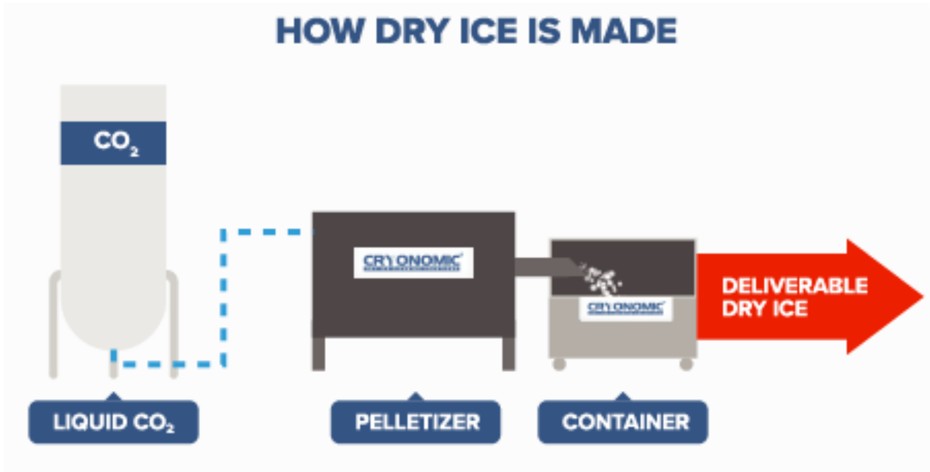
Chemical Engineering Tools to Enable Vaccine Production

Thermodynamics (Sophomore Level)



Free Energy of LNP Self-Assembly



Dry Ice Production

Pfizer built their own dry ice production facility because existing suppliers couldn't match the need

Chemical Engineering Tools to Enable Vaccine Production

Phase Equilibrium and Separations (Junior Level)

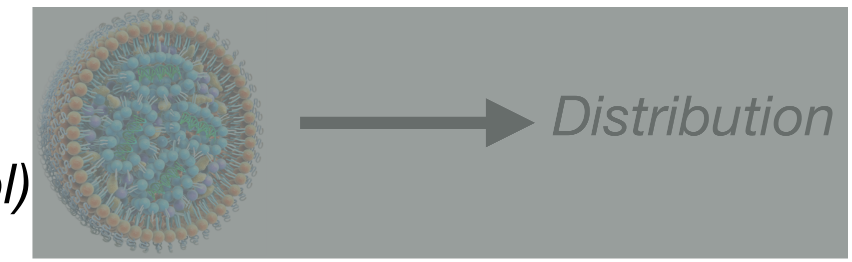
Fundamental equation for phase equilibria

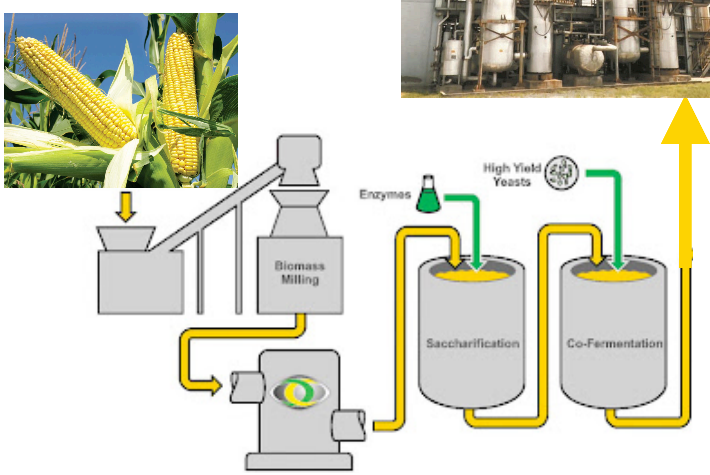
$f_i^{I} = f_i^{II}$

Lipids
(In ethanol)

mRNA
(In buffer)

LNPs
(Water + Ethanol)





Vacuum Evaporator

(Or Solvent Exchange?)
(or Membranes?)

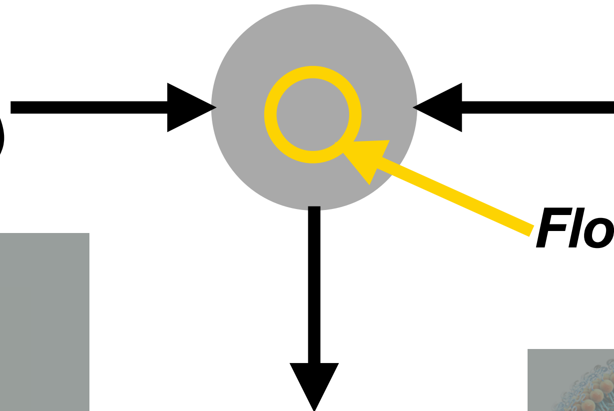
Ethanol Production

Product Isolation

Chemical Engineering Tools to Enable Vaccine Production

Transport Phenomena (Junior Level)

Lipids
(In ethanol)

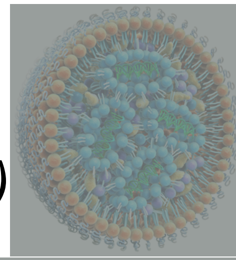


mRNA
(In buffer)

Flow rates/pressured needed for reliable mixing?

LNPs
(Water + Ethanol)

Ethanol Production



Distribution

Vacuum Evaporator

(Or Solvent Exchange?)
(or Membranes?)

Product Isolation

Chemical Engineering Tools to Enable Vaccine Production

Chemical Reaction Engineering (Senior Level)

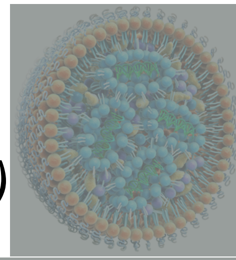
Scalable synthesis of raw materials

Lipids
(In ethanol)

mRNA
(In buffer)

LNPs
(Water + Ethanol)

Ethanol Production



Distribution

Vacuum Evaporator

(Or Solvent Exchange?)
(or Membranes?)

Product Isolation

University of Notre Dame
Department of Chemical & Biomolecular Engineering

UNIVERSITY OF NOTRE DAME

mwebber@nd.edu ***www.WebberLab.com*** ***@WebberLab***

Chemical Engineering Tools to Enable Vaccine Production

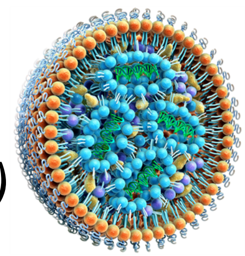
Process Design (Senior Level Capstone)

How to do this rapidly, at scale, while being economical?

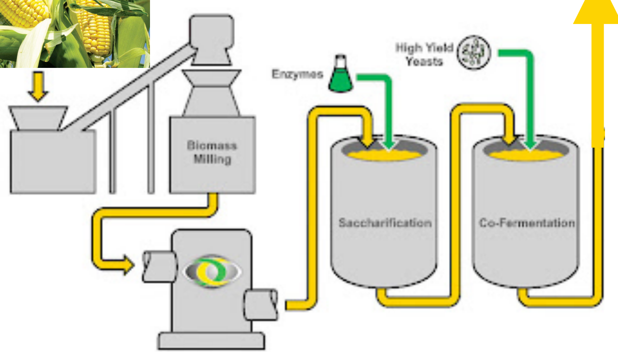
Lipids
(In ethanol)

mRNA
(In buffer)

LNPs
(Water + Ethanol)



Distribution



Vacuum Evaporator

(Or Solvent Exchange?)
(or Membranes?)

Ethanol Production

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Vaccine Production Outcomes

4.7 Billion doses administered globally in ~9 months

- *A combination of mRNA, adenoviral, inactivated whole virus, etc.*
- *Regardless of platform, all had production issues that only chemical engineers could solve!*

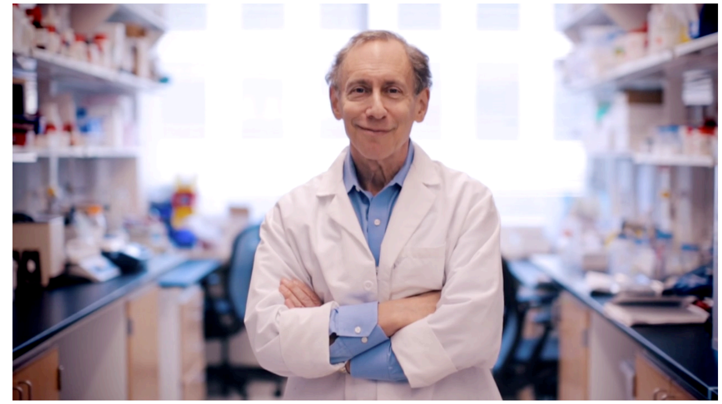
A variety of other supply chain/logistics components presented problems that were solved by chemical engineering intuition

- *Continuous cold-chain distribution*
- *Manufacturing of needles, glass vials, consumables*

Key Chemical Engineering Contributors

Moderna Cofounder Prof. Robert Langer (MIT)

Most cited engineer in history
1000+ patents; 1500+ publications
~40 successful biotechnology start-ups



These Contributions Were Highly Remunerative

Forbes

EDITORS' PICK | Nov 12, 2020, 04:06pm EST | 23,661 views

MIT Scientist Bob Langer Becomes A Billionaire Thanks To Moderna Stock Rally

Where Do Our Graduates Work? (2020)

3M Cordova
abbvie
Accenture
Aerotek for Pfizer
Ahlstrom-Munksjö
Air Products and Chemicals
Airgas
Alcami Corp
Anheuser-Busch
Archer Daniels Midland
Armstrong Flooring
Armstrong World Industry
Barry-Wehmiller Design
Beghou Consulting
Booz Allen Hamilton
BP
Bresco Investimentos
Carrier
Catalent Pharma Solutions
Chevron

Citi
ClearView Healthcare
Design Group
Dow Chemical
E & J Gallo Winery
Edwards Lifesciences
Eli Lilly
Endress + Hauser
Epic Systems
Exelead Biopharma
ExxonMobil
SalesForce
FSI Architecture, PC
GE Power Nuclear
Gen. Dyn. Electric Boat
GlaxoSmithKline
Hecto Group
Honeywell
Huron
Ipsum Diagnostics LLC

JM Schmucker
Kite Pharma
Kymanox
Lockheed Martin
Lummus Technology
Merck
MilliporeSigma
NextEra Energy Resources
P&G
Paustenbach & Associates
Pfizer
Technip Energies
Proctor & Gamble
PwC
RBC Capital Markets
Realync
The Kraft Heinz Company
US Navy
Verista
Vista Equity Partners

W.R. Grace
Auburn University
Caltech
Carnegie Mellong University
ESTEEM Program UND
New York Medical College
Stanford University
Texas A&M, Med School
UC Irvine
UNC Pharmacoengineering
University of Chicago
University of Ill. Urb-Cham
University of Michigan
University of Texas Austin
University of Washington