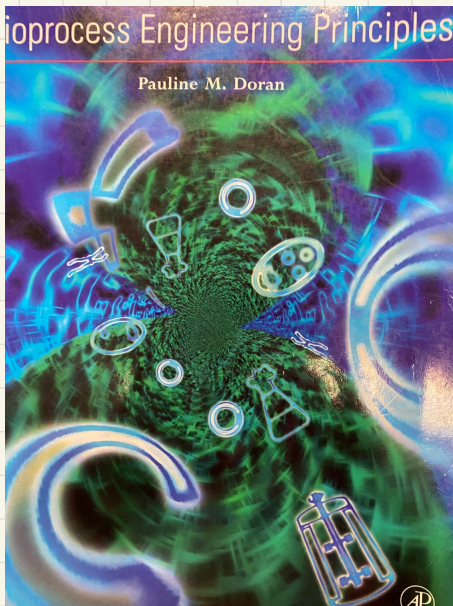


# SOME TOPICS WITHIN BIO REACTION ENGINEERING.



## KINETICS OF ENZYME- CATALYZED REACTIONS



ELEMENTARY STEPS

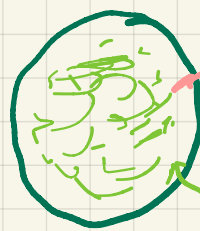
STEADY-STATE APPROXIMATION

FITTING OF DATA TO

NONLINEAR EXPRESSIONS...

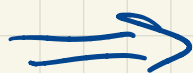


## IMMOBILIZED ENZYMES



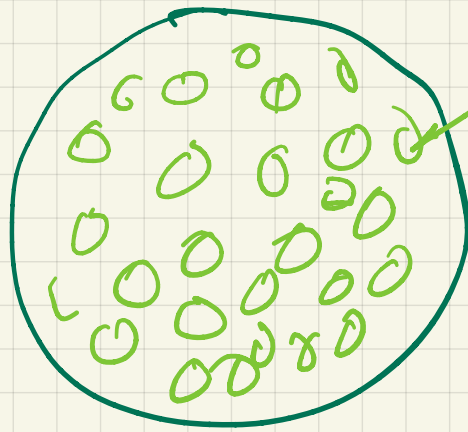
GEL MADE INTO  
BEAD

ENZYME DISPERSED  
INSIDE



## THIELE MODULUS

PROBABLY NOT 1ST ORDER  
KINETICS

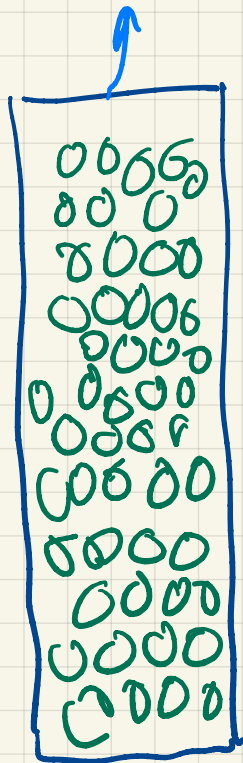


BACTERIA  
IMMOBILIZED  
IN A BEAD

THE BACTERIA  
WOULD BE USED FOR  
A SPECIFIC  
FUNCTION

= REMOVE NITRATES  
FROM GROUND  
WATER

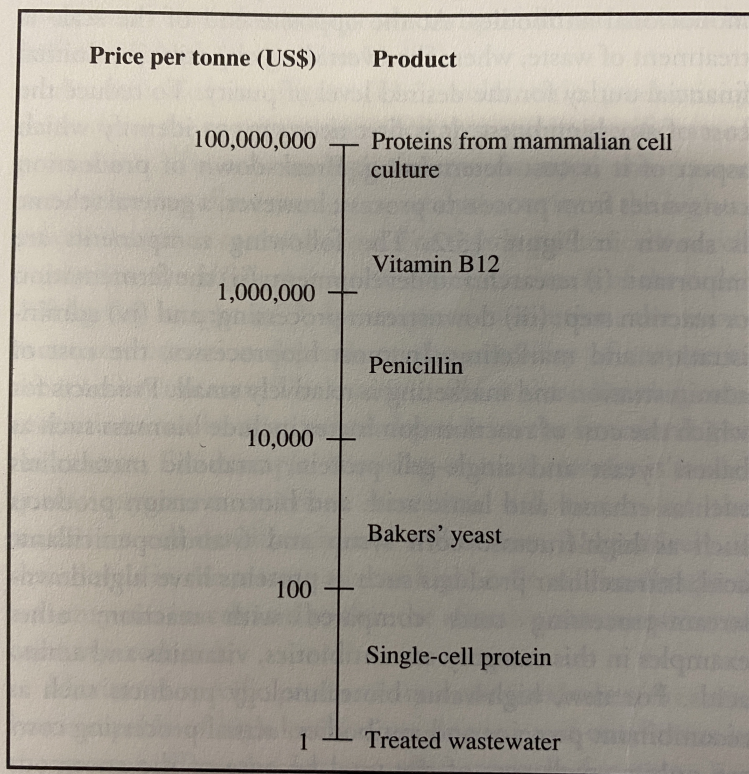
PACKED  
BED  
OF  
SUCH  
BEADS



BIO REACTORS ALMOST  
ALWAYS HAVE A  
GAS  $\rightarrow$  LIQUID  
TRANSFER PROCESS

$\uparrow$  WATER +  $O_2$

(From P.N. Royce, 1993, A discussion of recent developments in fermentation monitoring and control from a practical perspective. *Crit. Rev. Biotechnol.* 13, 117-149.)

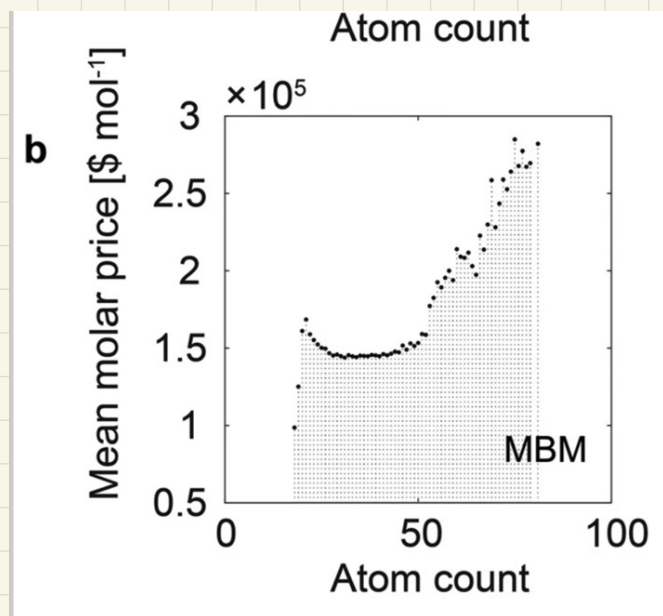


HOW MUCH "TROUBLE"  
YOU ARE WILLING  
TO GO THROUGH TO  
MAKE SOMETHING  
DEPENDS ON  
VALUE OF  
PRODUCT !!

FOR "CHEMICALS"  
RANGE IS NOT  
LARGE

STANDARD CHEMICALS  
↓ PHARMACEUTICALS  
FROM CHEMICAL  
PROCESSING

$\$ \sim M.W.$   
↑  
MOLE



## SCIENTIFIC REPORTS

OPEN Molecular descriptor data explain market prices of a large commercial chemical compound library

Received: 06 April 2016  
Accepted: 25 May 2016  
Published: 23 June 2016

Jaroslaw Polanski<sup>1</sup>, Urszula Kucia<sup>1</sup>, Roksana Duszewicz<sup>2</sup>, Agata Kurczyk<sup>2</sup>,  
Tomasz Magdziarz<sup>2</sup> & Johann Gasteiger<sup>\*</sup>

The relationship between the structure and a property of a chemical compound is an essential concept in chemistry guiding, for example, drug design. Actually, however, we need economic considerations to fully understand the fate of drugs on the market. We are performing here for the first time the exploration of quantitative structure-economy relationships (QSER) for a large dataset of a commercial

Figure 13.2 Contributions to total production cost in bioprocessing.

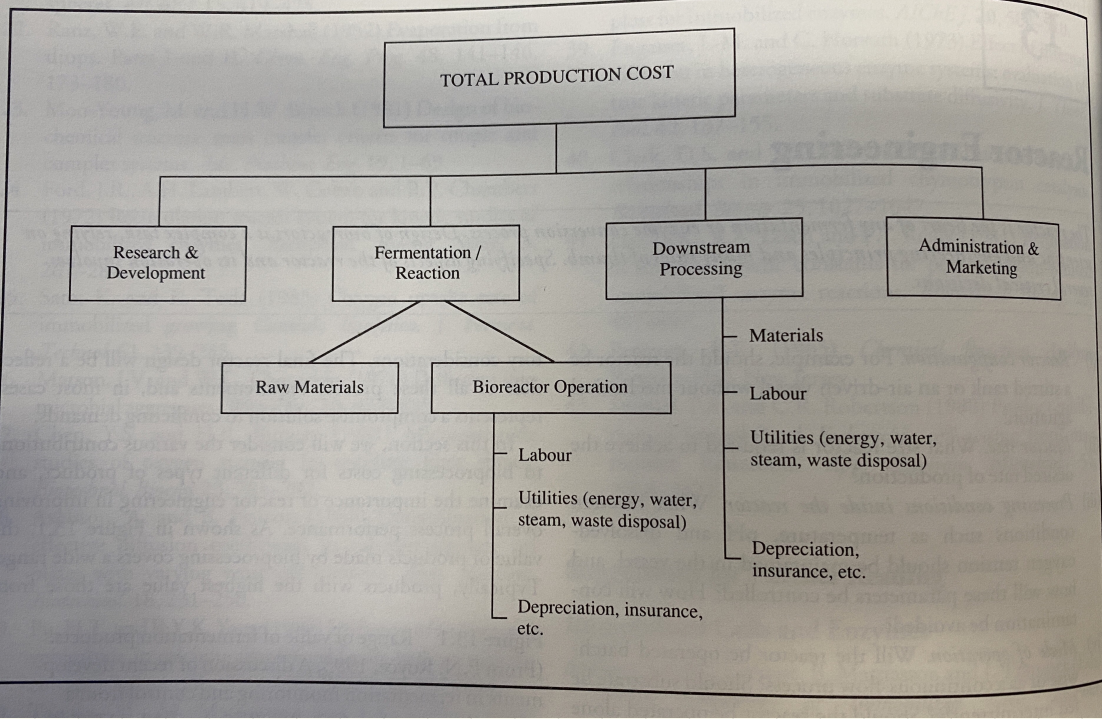
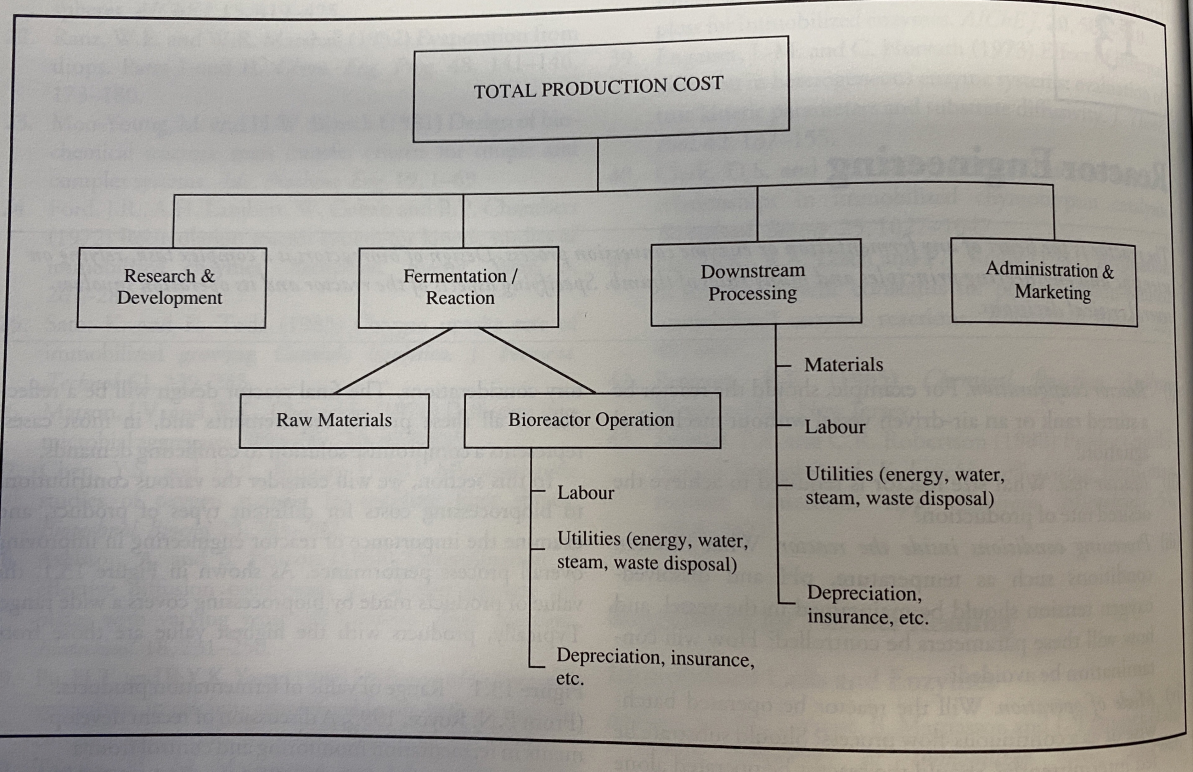


Figure 13.2 Contributions to total production cost in bioprocessing.



# BIOREACTORS FOR CHEMICAL PRODUCTION

→ FERMENTER

*Zymomonas mobilis*

GLUCOSE → ETHANOL

- COMMONLY BATCH

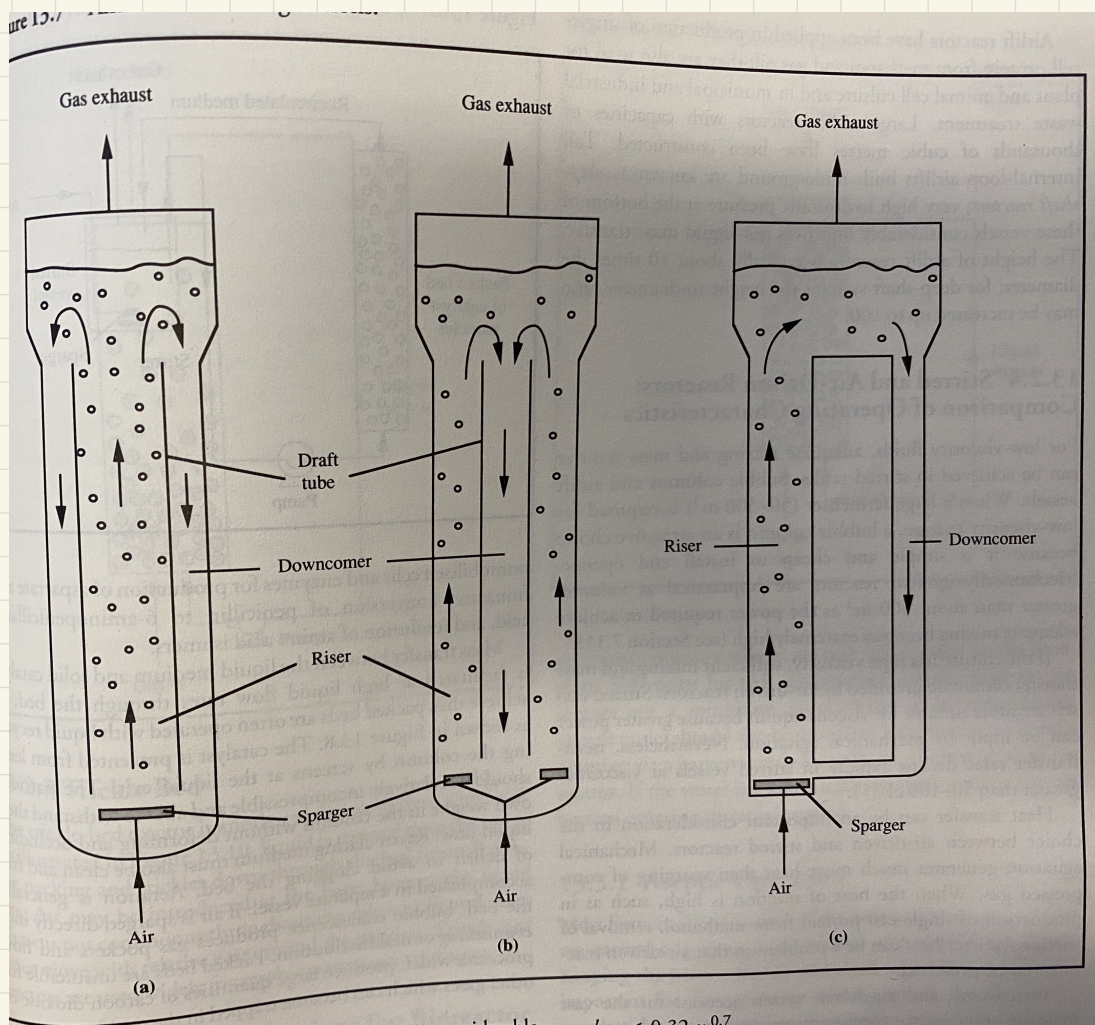
BUT IF CSTR → "CHEMOSTAT"

- HAVE TO KEEP CELLS ALIVE TO PRODUCE PRODUCT

→ CELL MASS WON'T BE CONSTANT

→ AS MENTIONED ABOVE!

WILL HAVE GAS ABSORPTION PROBABLY AIR



RECALL  $\dot{W}_S = q \Delta P$

$q \rightarrow$  VERY LARGE

$\Delta P \rightarrow$  SIGNIFICANT FOR A

BIG REACTOR

BOBBLE SIZE  $\downarrow$  AS  $\Delta P \uparrow$

FOR INJECTOR.

COULD USE A CSTR  
WITH IMMOBILIZED ENZYME  
(SPHERICAL BEADS)

- ENZYME REMAINS IN REACTOR
- GROWING CELLS, HAVE TO WORRY ABOUT "WASHOUT"

A COMPLETELY DIFFERENT  
TOPIC IS PHYSIOLOGICAL  
OR PHARMACOLOGICAL  
MODELING.



# Elements of Chemical Reaction Engineering

Fourth Edition

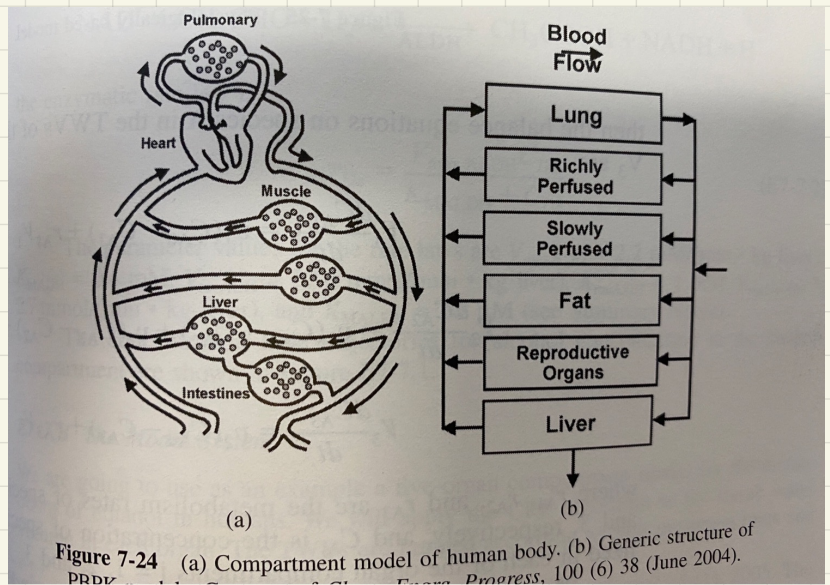


Figure 7-24 (a) Compartment model of human body. (b) Generic structure of blood flow through various tissue types. *PRDY... Progress, 100 (6) 38 (June 2004).*

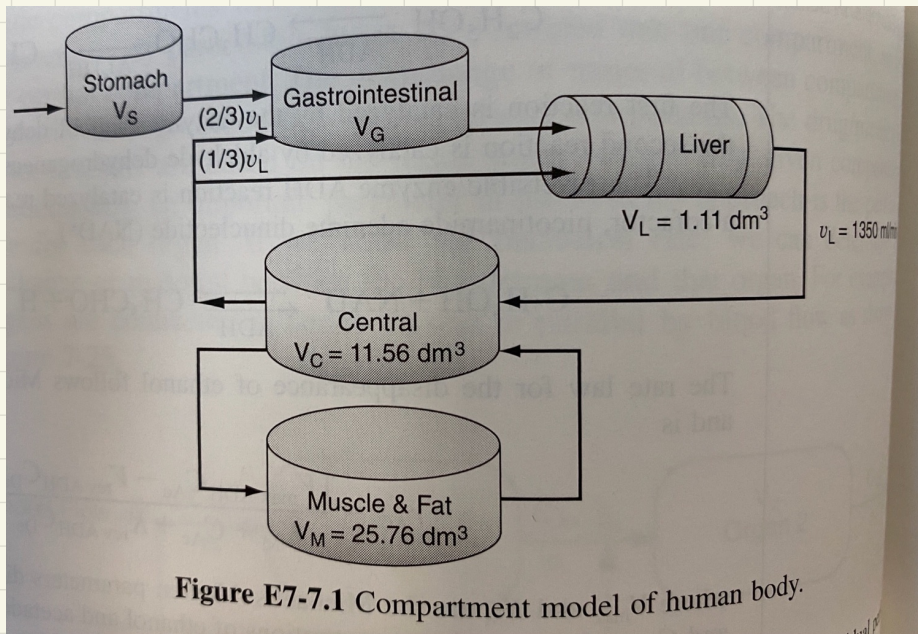


Figure E7-7.1 Compartment model of human body.

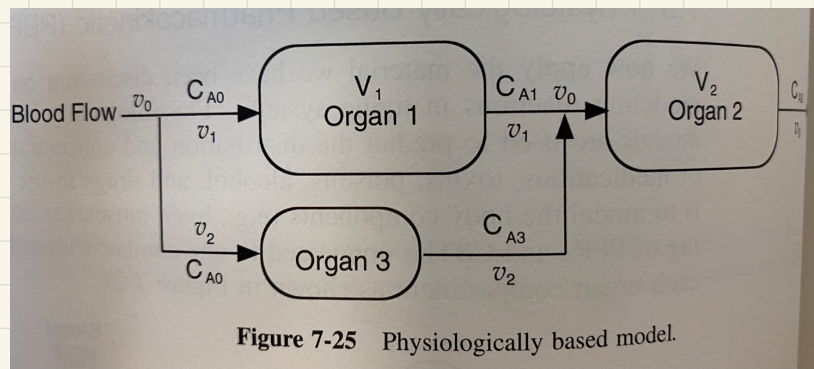


Figure 7-25 Physiologically based model.

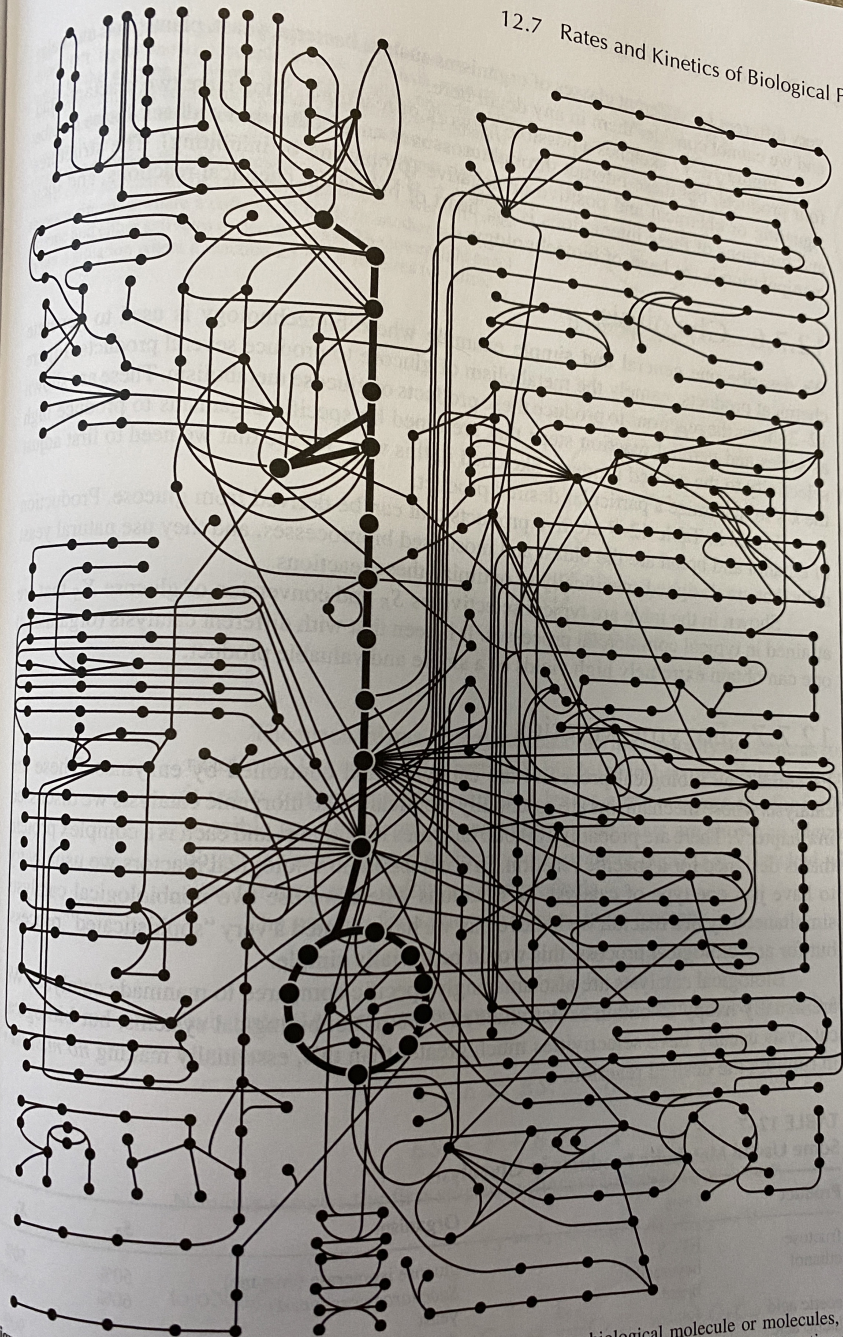
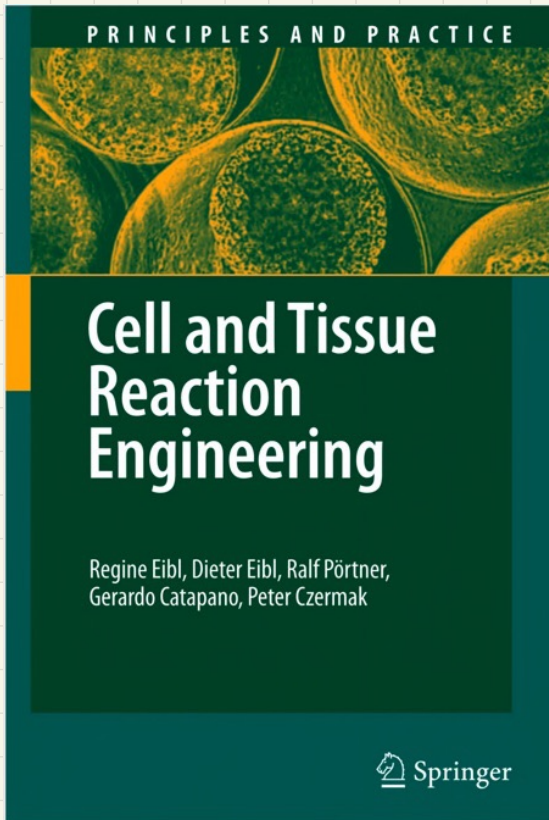


Figure 12-18 Generic metabolic pathway diagram. Each dot represents a biological molecule or molecules, and each line connecting them represents a reaction. This is a highly simplified pathway diagram, which approximates the general reaction pathways in all eukaryotic systems. The heavy line and circle are the glycolysis pathway of glucose to  $\text{CO}_2$  which supplies the "engine" for all reactions.

# USE OF MAMMALIAN CELLS TO PRODUCE "BIOLOGICAL" MOLECULES



## CURRENT PRODUCTS

- VIRAL VACCINES
- MONOCLONAL  
ANTIBODIES
- INTERFERONS
- RECOMBINANT  
THERAPEUTIC  
PROTEINS

## STILL EMERGING

### TISSUE ENGINEERING

FOR REPLACEMENT  
OR THERAPEUTIC  
TESTING

### GENE THERAPY

"MESSAGE" IS THAT WHILE  
THERE ARE BENEFITS TO  
KNOWING (SOME) MOLECULAR  
-CELLULAR BIOLOGY,  
KEY DIFFICULTIES IN  
PROCESSES CAN BE OVERCOME  
WITH THE STANDARD TOOLS  
THAT ALL OF US  
CHEMICAL ENGINEERS  
POSSESS. !!

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# VIRAL VACCINES :

HUMAN [ POLIO, HEPATITIS B, MEASLES  
MUMPS,

VETERINARY [ RUBELLA, RABIES,  
FOOT + MOUTH DISEASE

PRODUCTS ARE PRODUCED  
IN "BIOREACTORS"

2 L  $\longrightarrow$  20,000 L

SPECIFIC MANUFACTURING  
DIFFICULTIES!

$\rightarrow$  GETTING APPROPRIATE  
CELLS TO START PROCESS

— SLOW GROWTH RATES

12-24 h DOUBLING  
TIMES

— LOW PRODUCTIVITY OF  
PRODUCTS

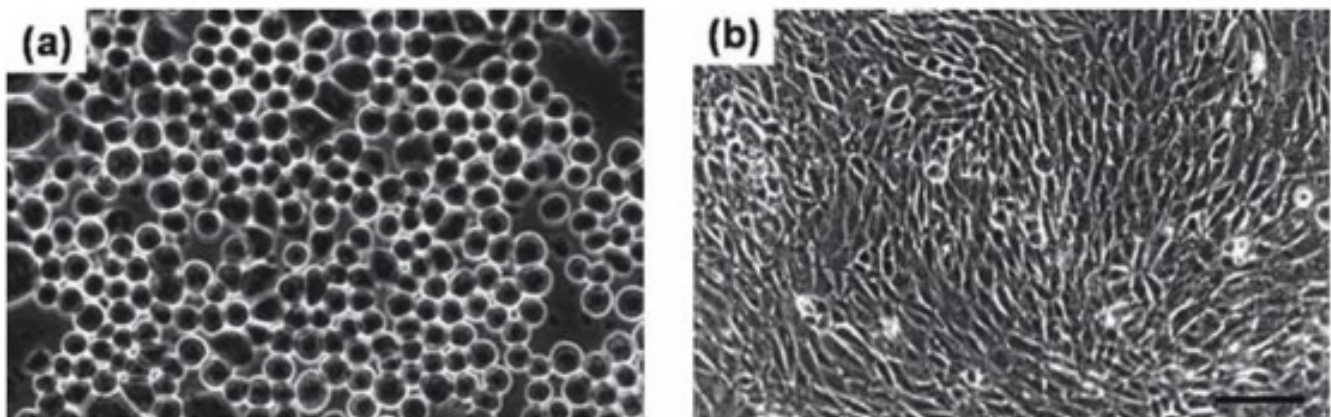
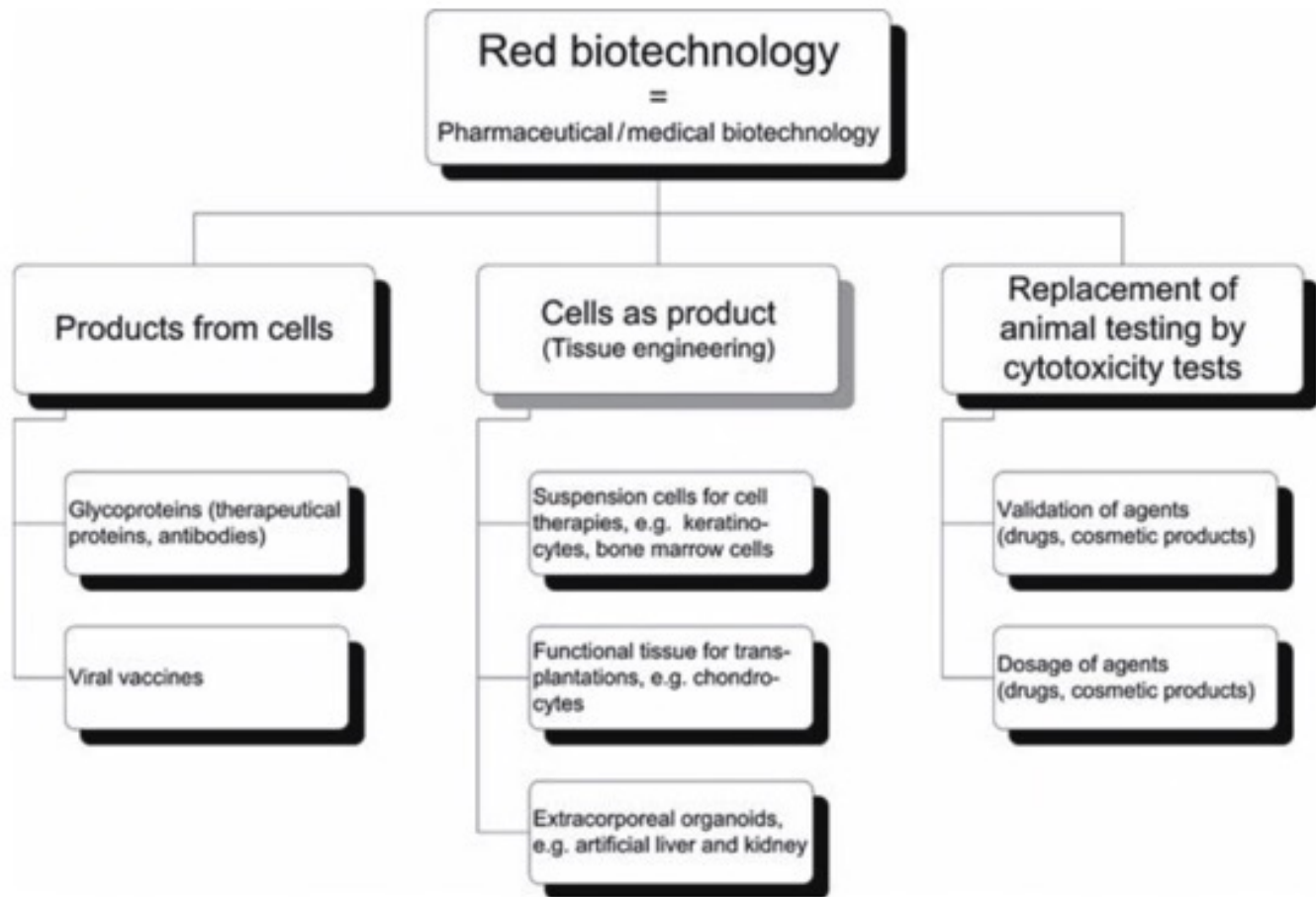
WIF KNOW A  
LOT ABOUT  
THIS!!!  
!!!

— SENSITIVITY TO SHEAR  
STRESS BECAUSE OF THE  
LACK OF A CELL WALL

— COMPLEX GROWTH MEDIUM

— SOME KINDS NEED TO  
GROW ON A SOLID<sup>\*</sup> SURFACE

\*!!!  
!!!



**Fig. 1.2** Morphology of (a) suspensible and (b) adherent mammalian cells (bar approx. 30 $\mu$ m)



**Table 2.1** Culture characteristics (suspension) of microbial, plant cell and mammalian cell culture ( $t_d$ : doubling time, vvm: volume of gas per volume of liquid and minute)

Characteristic	Microbial culture	Plant cell culture	Mammalian cell culture
Size	2–10 $\mu\text{m}$	10–100 $\mu\text{m}$	10–30 $\mu\text{m}$
Individual cells	Often	Often aggregates	Sometimes adherent
Inoculation density	Low	High (10%)	High (5–10%)
Growth rates	Rapid ( $t_d = 1\text{--}2\text{ h}$ )	Slow ( $t_d = 2\text{--}7\text{ d}$ )	Slow ( $t_d = 20\text{--}50\text{ h}$ )
Shear sensitivity	Low	Moderate	High
Stability	Stable	Unstable	Unstable
Product accumulation	Intra-/extracellular	Mostly intracellular	Mostly extracellular
Culture medium	Often simple	Often complex	Complex
Temperature	26–36 $^{\circ}\text{C}$	25–27 $^{\circ}\text{C}$	29–37 $^{\circ}\text{C}$
Aeration	Often high (1–2 vvm)	Low (0.1–0.3 vvm)	Low (~ 0.1 vvm)
Foaming	Often high	sometimes foaming	Sometimes foaming
pH-value	3–8	5–6	7.0–7.4
Cell density	(Very) high	Low	Low–middle
Scale-up	Easy	Difficult	Difficult

## 2.2.2 Hybridoma Cells for Production of Monoclonal Antibodies

**Table 2.2** Comparison of “normal” and “transformed” cells

Normal	Transformed
Diploid (46 chromosomes for human cells)	Abnormal number of chromosomes
Non-malignant	Malignant (form tumour in mice)
Finite life-span (50+–10 subcultures max.)	Infinite life-span
Anchorage-dependent (except blood cells)	Non-anchorage-dependent (i.e. suspension culture possible)
Mortal; finite number of divisions	Immortal or continuous cell lines
Contact inhibition; monolayer culture	No contact inhibition; multilayer cultures
Dependent on external growth factor signals for proliferation	May not need an external source of growth factors
Longer retention of differentiated cellular function	Typically loss of differentiated cellular function
Display typical cell surface receptors	Cell surface receptor display may be altered

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Q&A | [Published: 21 October 2020](#)

## COVID-19 antibodies on trial

[Laura DeFrancesco](#) 

In October, US President Donald Trump received Regeneron Pharmaceuticals’ experimental monoclonal antibody (mAb) cocktail REGN-COV2 as part of his treatment for COVID-19. Buoyed by a positive response, both Regeneron and Eli Lilly have filed requests for Emergency Use Authorization from the US Food and Drug Administration, although Lilly had to pause clinical testing because the trial crossed a predetermined safety threshold. Lilly’s product, LY-CoV555, is a cocktail of two human IgG1 mAbs targeting different spike (S) glycoprotein epitopes. These and 11 other experimental mAb treatments targeting the SARS-CoV-2 S protein are



# Monoclonal antibodies could fill the COVID-19 treatment gap until vaccines arrive — but at a cost

Oct. 2, 2020 at 6:00 am | Updated Oct. 2, 2020 at 11:52 am



Seven out of the top 10 best-selling drugs globally are monoclonal antibodies — including Humira for rheumatoid arthritis and Crohn’s disease and Keytruda for melanoma and other types of cancer — and they’re all expensive.

The median cost for a year of treatment ranges from \$15,000 to more than \$140,000, according to the report by the International AIDS Vaccine Initiative and the British philanthropy Wellcome.

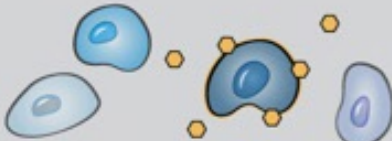
## A bridge to vaccines: Monoclonal antibodies could save lives and slow the spread of the coronavirus

### How to make monoclonal antibodies

1 Take blood from a person who recovered from COVID-19



2 Use “bait” molecules to fish out the B cells that produce antibodies for a key portion of the novel coronavirus spike protein and block infection



3 Decipher the DNA for those antibodies



4 Insert that DNA into cells that mass-produce the antibodies.



### Potential benefits:

- Prevention option before a vaccine is available
- Provide immediate protection or treatment for those exposed
- Benefits to people who cannot develop or maintain an adequate immune response after vaccination

### Monoclonal antibody limitations:

- Protection is short-lived
- The drugs are expensive

### HOW VACCINES AND MONOCLONAL ANTIBODIES WORK

Vaccines teach the body to recognize a foreign invader, through the creation of antibodies

Foreign invader (like a virus) enters body



SARS-CoV-2 virus that causes COVID-19

Activates immune system\*

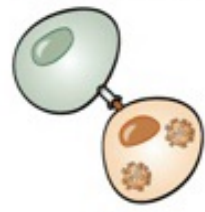
Viral genome

Monoclonal antibodies can be infused into patients

B cells begin to make antibodies (Y-shaped proteins)

T-helper cells activated

Cytotoxic T cells identify and destroy virus infected cells



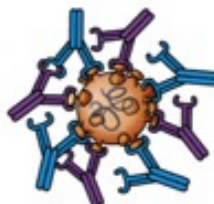
Virally infected cell

Activate helper B cells

Antibodies bind to foreign invaders

Neutralize and block invaders from entering and infecting other cells

Tags them for destruction



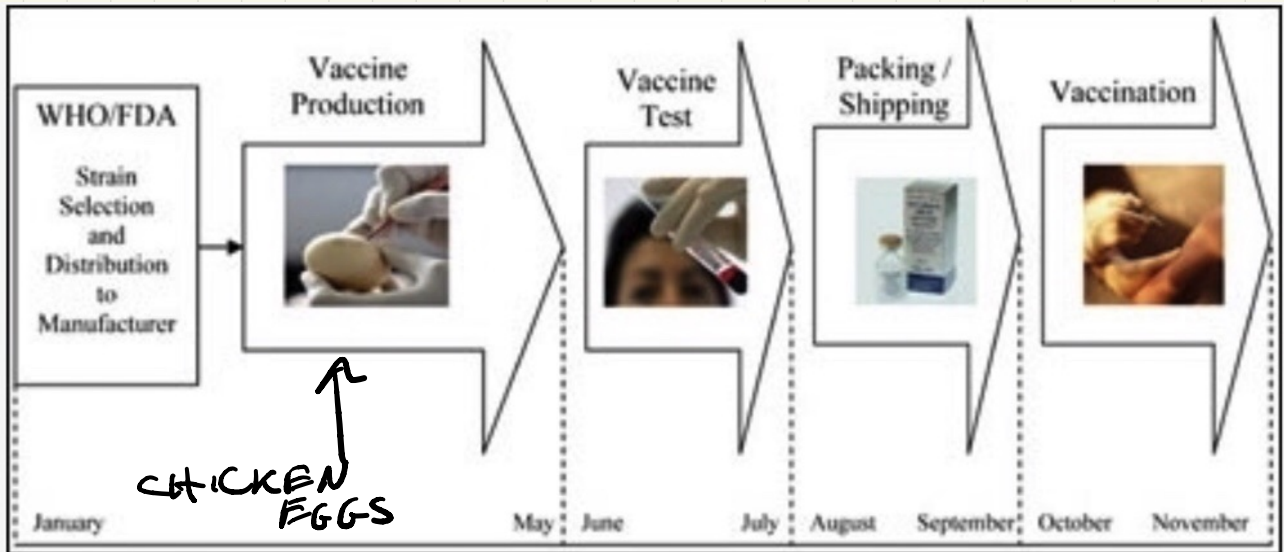
Macrophage cell

\*Simplified system with cells and viruses not to scale

Sources: Marion Pepper, University of Washington, COVID-19 Prevention Network

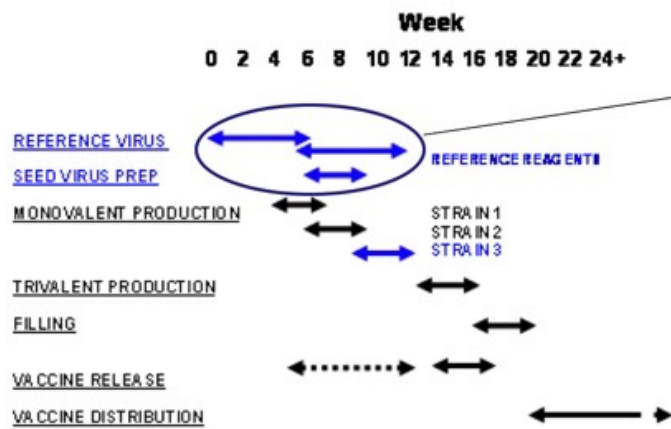
EMILY M. ENG / THE SEATTLE TIMES

# FLU "VACCINE" HAS LONG BEEN PRODUCED!



## Egg-based Manufacturing Current "Gold Standard"

### Time to First Trivalent Vaccine Lot after Strain Change



less critical when using "gene to vaccine" technologies

From a presentation by Norman Baylor, US FDA/CBER

# Examples of Influenza Vaccine products and manufacturing technologies



- **Products and Technologies requiring development of seed virus**
    - Egg-based manufacturing
      - Inactivated, split, purified subunit products
      - Live attenuated vaccines
    - Mammalian Cell-based manufacturing
      - Inactivated, split, purified subunit products
      - Live attenuated vaccines
  - **Products which are manufactured from “gene to vaccine”**
    - Baculovirus
      - insect cell culture, whole larvae manufacturing
      - subunit versus VLP
    - Prokaryotic manufacturing (*E. coli*)
    - Recombinant Adenoviral-vectored influenza vaccines
    - Plant-based manufacturing (subunit versus VLP)
    - Peptide epitope products (computational vaccinology)
- 