“ENGINEERING” FOR MEDICINE

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WHAT DO ENGINEERS DO?

- Or, you may have heard it stated that "engineers solve problems..."

- What engineers really do is:

- *Engineers understand how to use techniques of engineering analysis to design (i.e., synthesize) substances, devices and processes even though they have an imperfect understanding of important physical, chemical or biological issues. Furthermore engineers operate under constraints caused by a need to produce a product or service that is timely, competitive, reliable, and consistent with the philosophy and within the financial means of their company.*

- *We need to use all that we know to produce the best answer to a problem!!*

RISE OF OXYGEN (WHY WE BREATH AIR!)

Two classes of reactions that use glucose

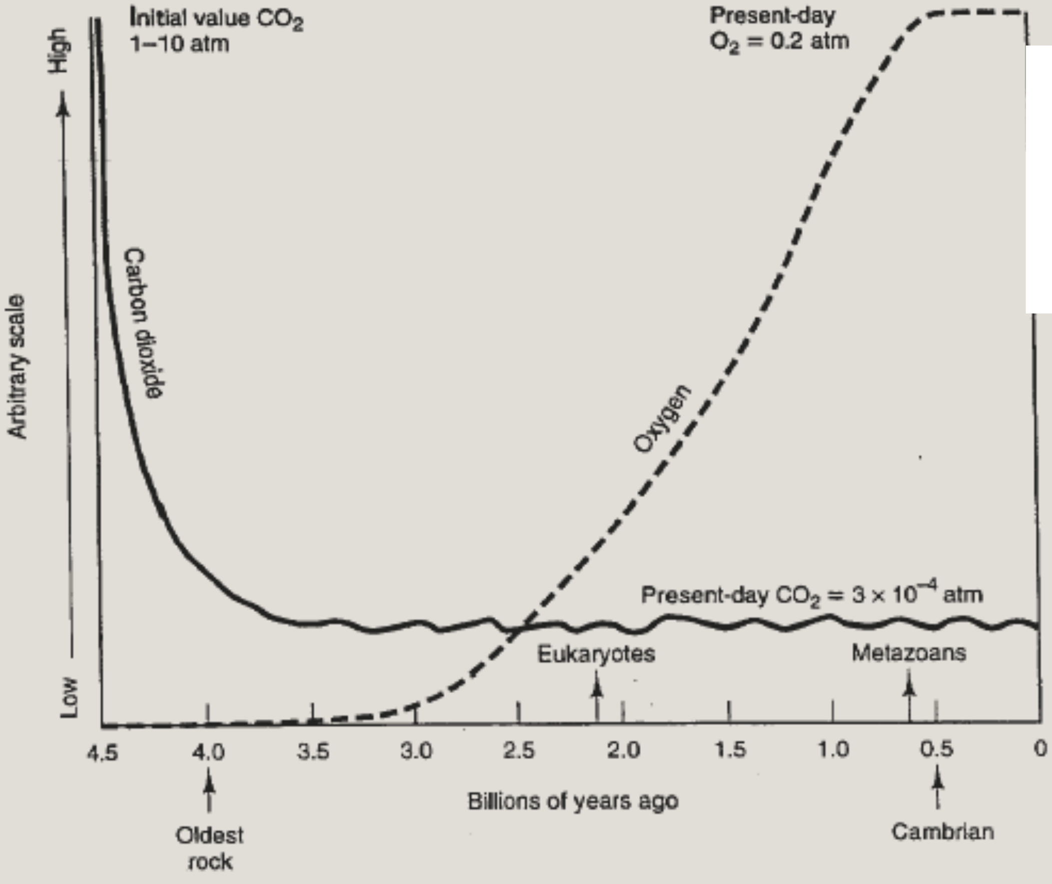


FIGURE 3–10 The history of oxygen and carbon dioxide in the atmosphere during Earth history.

$$C_6H_{12}O_6 \longrightarrow 3CO_2 + 3CH_4$$

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$$

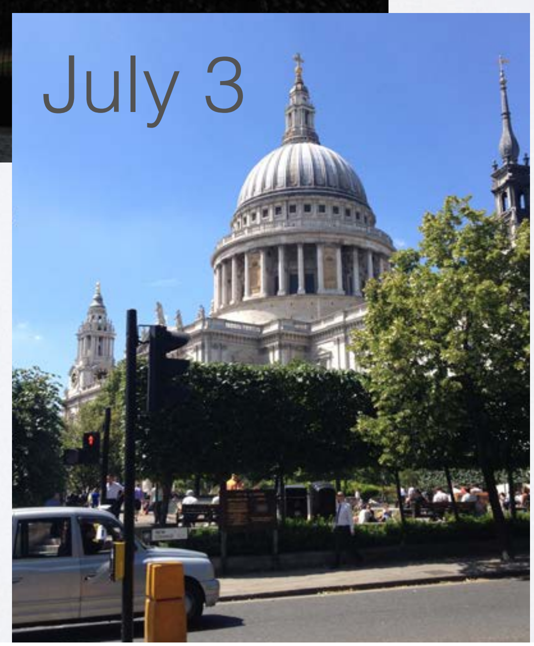
Aerobic digestion is **17** times more energetic than anaerobic digestion

Most of this oxygen comes from various kinds of plant growth

MAJOR ISSUES FOR HUMANITY

- Healthcare
- Energy
- The Environment
- The Economy
- Engineers are critically involved in all of these and will chart the future course
- "Society" may call these issues "problems", engineers see these as challenges to be met!
    - Major advances in all of these areas will require engineering!

LONDON, 2014: ...



CONTRIBUTIONS OF ENGINEERS TO MEDICINE

- New devices
- Better systems and allocation of resources
- New ways to get treatments to a specific location (targeting systems)
- New ways to regenerate tissue
- Increased understanding of diseases gained from engineering analysis

Some famous chemical engineers!

Bob Langer, MIT,
Brain cancer “patch”, skin replacement, tissue engineering for heart, liver

Adam Heller, U Texas
Artificial pancreas, technology will generalize to other diseases

Mark Davis, Caltech
Totally synthetic construct for gene delivery and molecular design of catalysts

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CANCER METASTATIS

- chemical engineers at Johns Hopkins University
- http://www.baltimoresun.com/health/bs-hs-cancer-trigger-20170625-story.html
- New understanding of the mechanism by which pieces of a tumor split off (cell density get too high) and how to stop this!

CONTRIBUTIONS OF ENGINEERS TO MEDICINE

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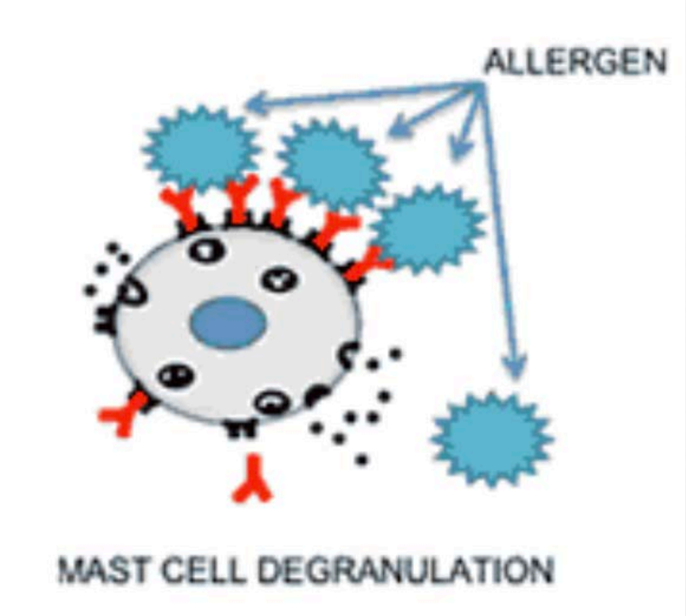
PRECISE TARGETING

- Professor Bilgicer has discovered the exact chemistry of immune response the leads to the peanut allergy and is developing a treatment that will prevent it.
- They design molecules that exactly bind in place of the allergen on the mast cells
- Only people with a peanut allergy have mast cells sensitive to these allergens
- https://www.youtube.com/watch?v=P5m9nsoWEb8



THINK MORE BROADLY ABOUT HUMAN HEALTH?

- What can engineers do?
- Two “extremes” to think about!

BOB LANGER

- A real quote:
- “When I finished graduate school (ScD from MIT) I went to work in a hospital. There I saw many sick people and I wanted to do anything I could to help them!”

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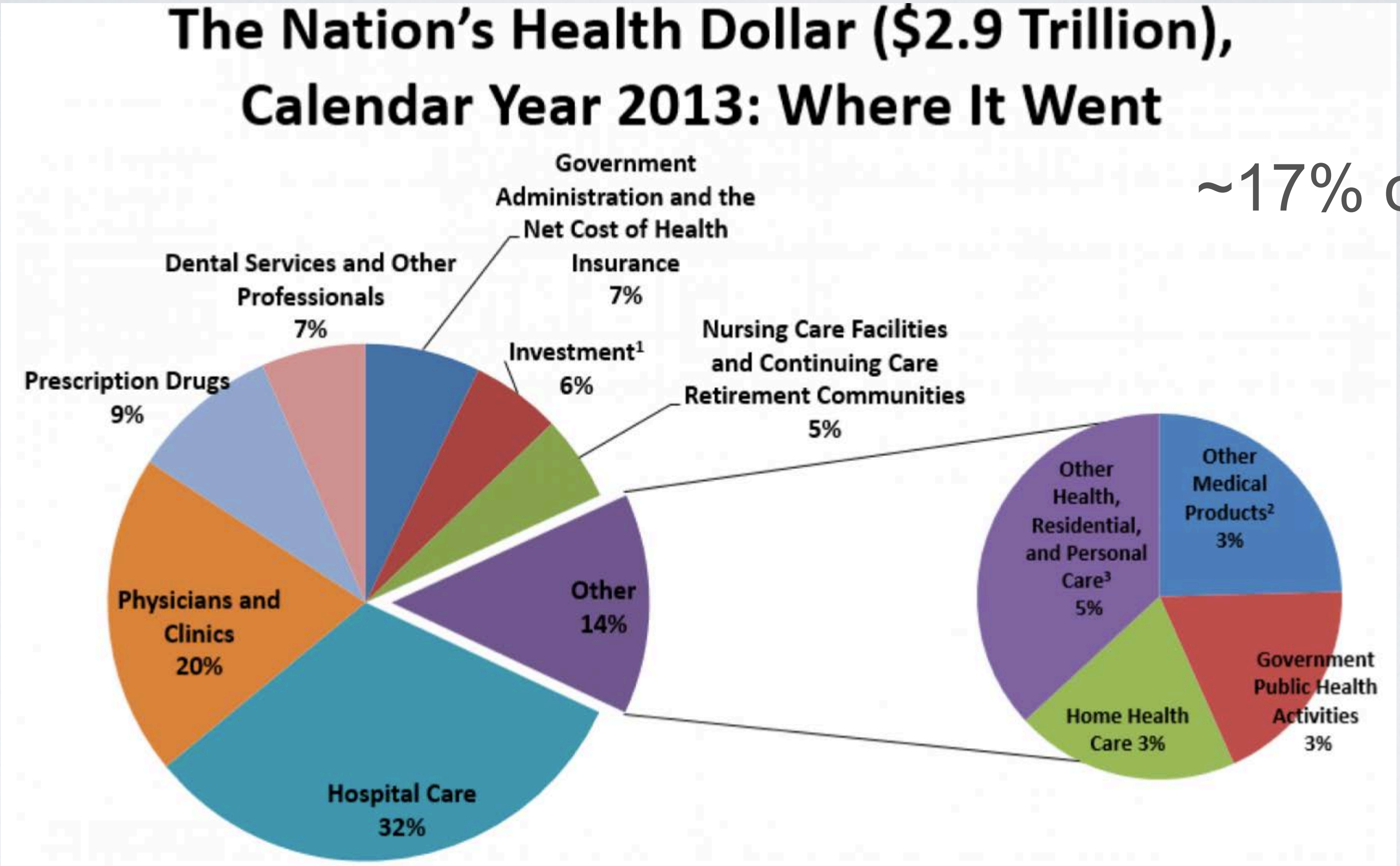
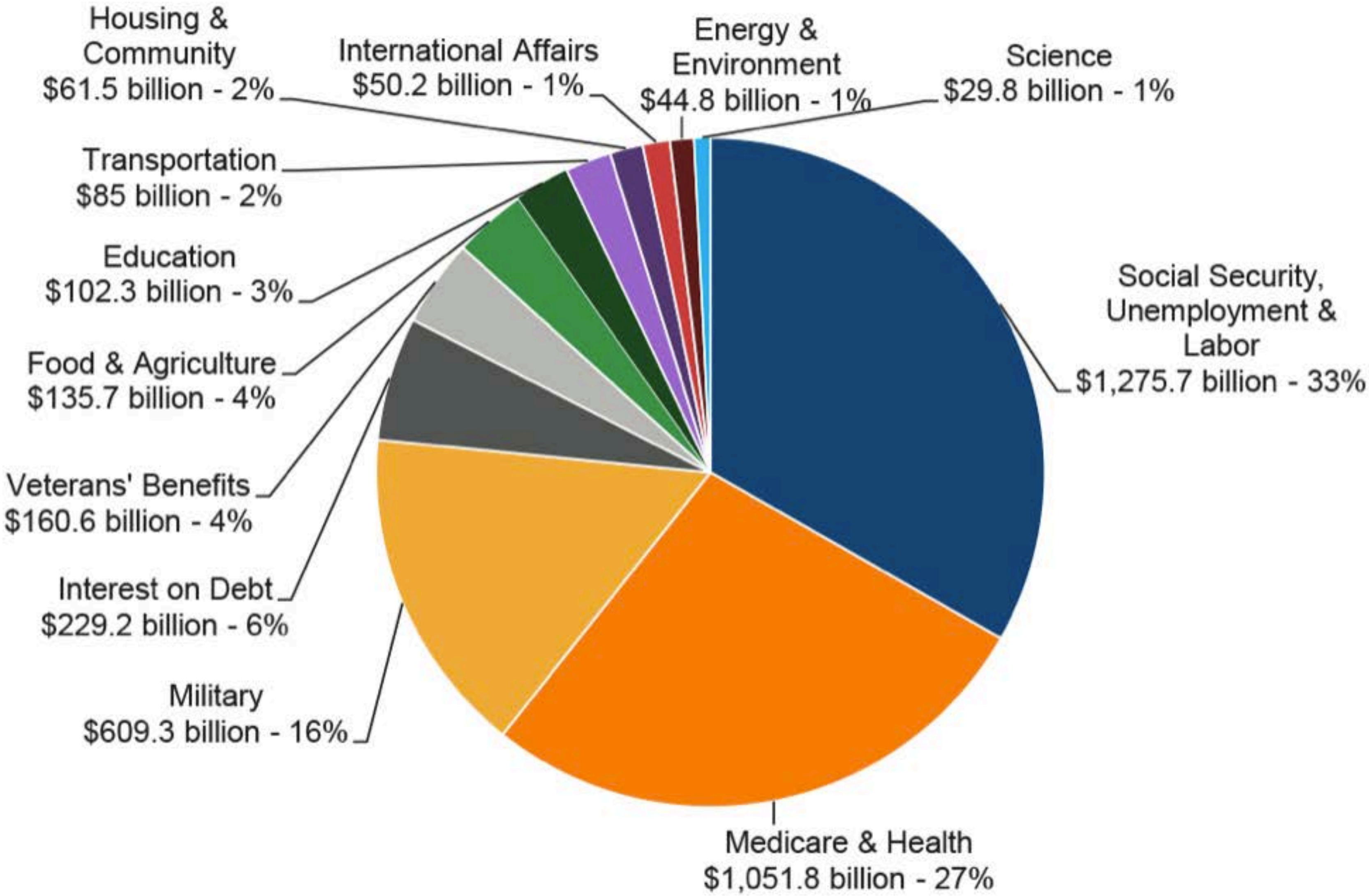
PURE RATIONALITY



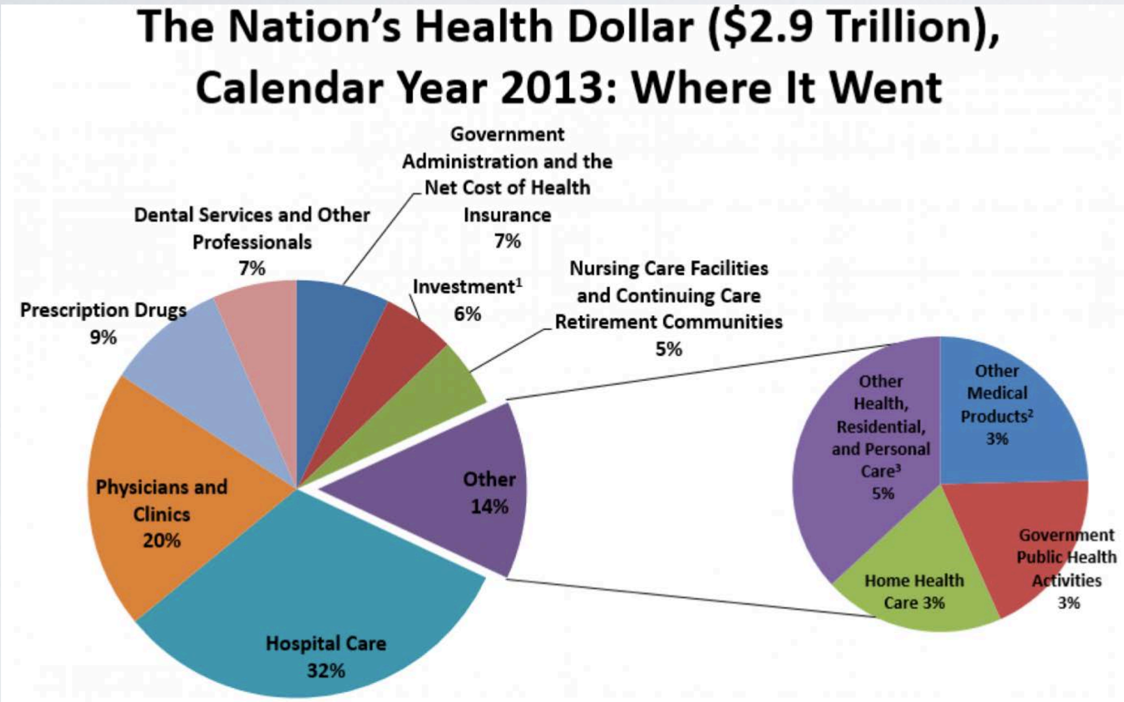
~17% of GDP

- Where do the dollars go and what can we do to use them better!

Total Federal Spending 2015: $3.8 Trillion



DO YOU HAVE IDEAS OF HOW TO SAVE $$ OR BETTER ALLOCATE EXISTING SPENDING?



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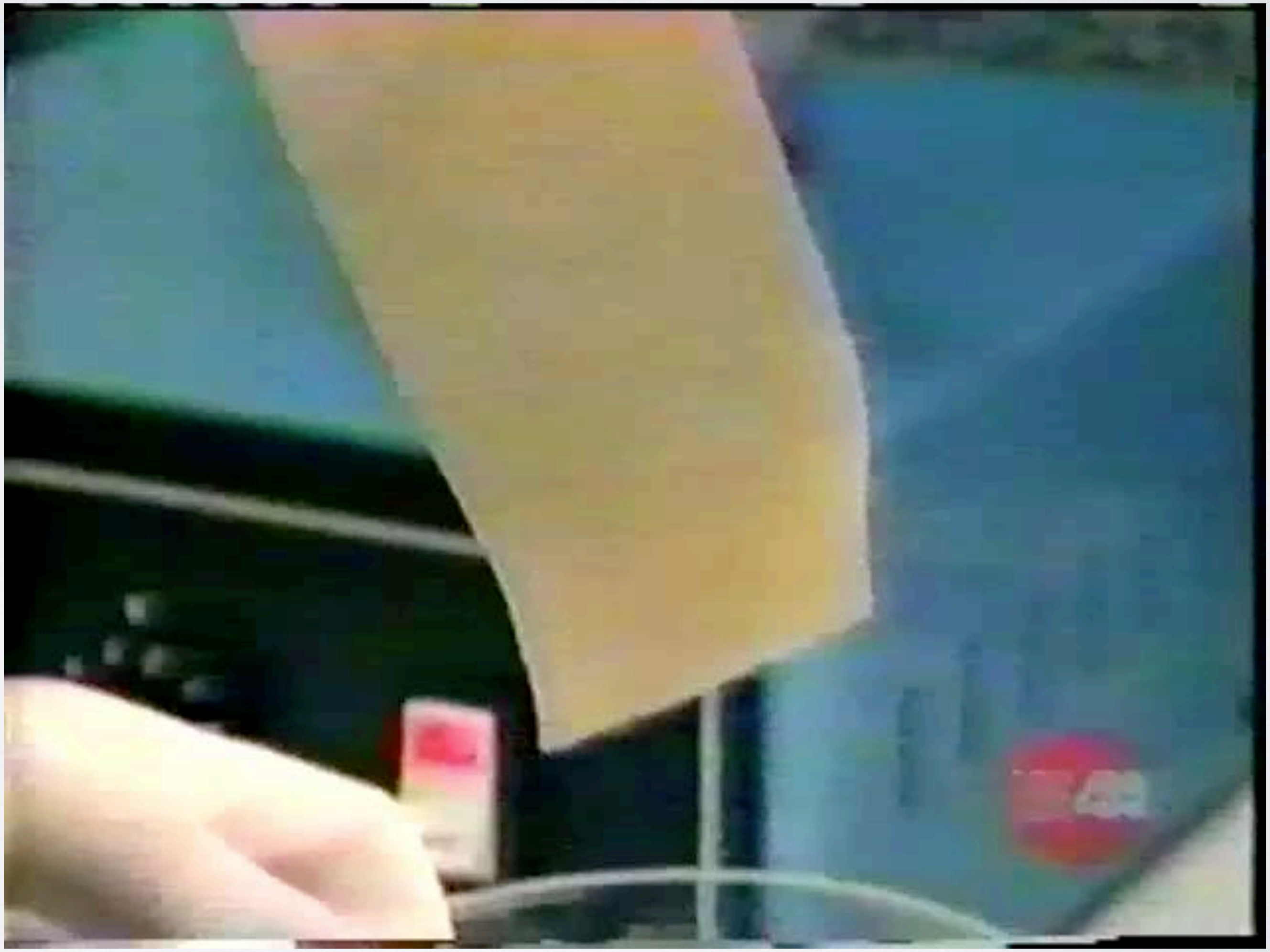
TISSUE ENGINEERING

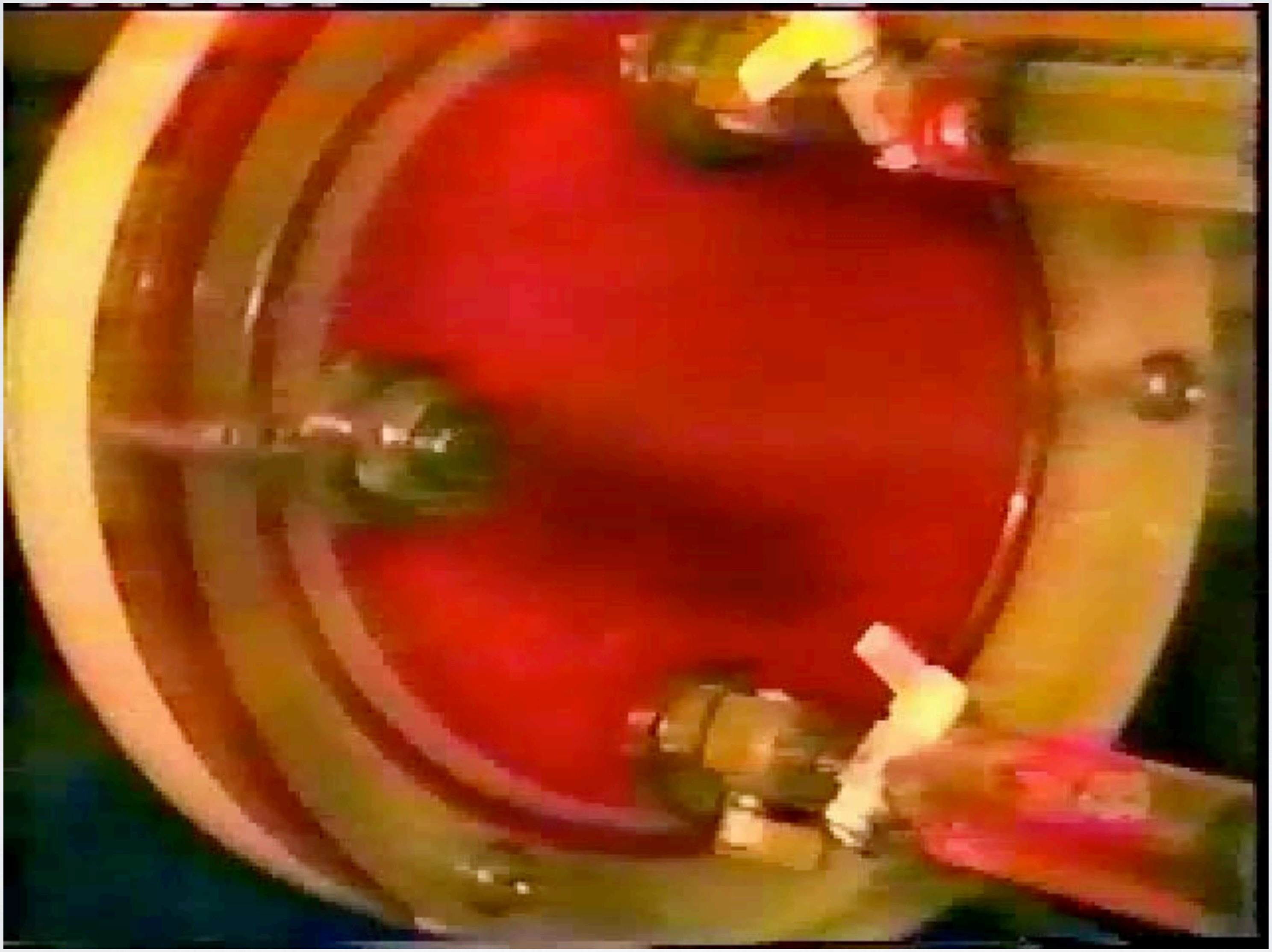
- Can we grow cells outside of person and transplant inside?
- Can we regenerate tissue inside of people?
- What other options exist?

ORIGINALLY: WE THOUGHT IT WOULD BE EASY! SYNTHESIS OF REPLACEMENT PARTS FOR PEOPLE

- Bob Langer, Chemical Enginering Professor at MIT
- Alan Alda,
  One of Langer's students
- Video from Scientific American Frontiers

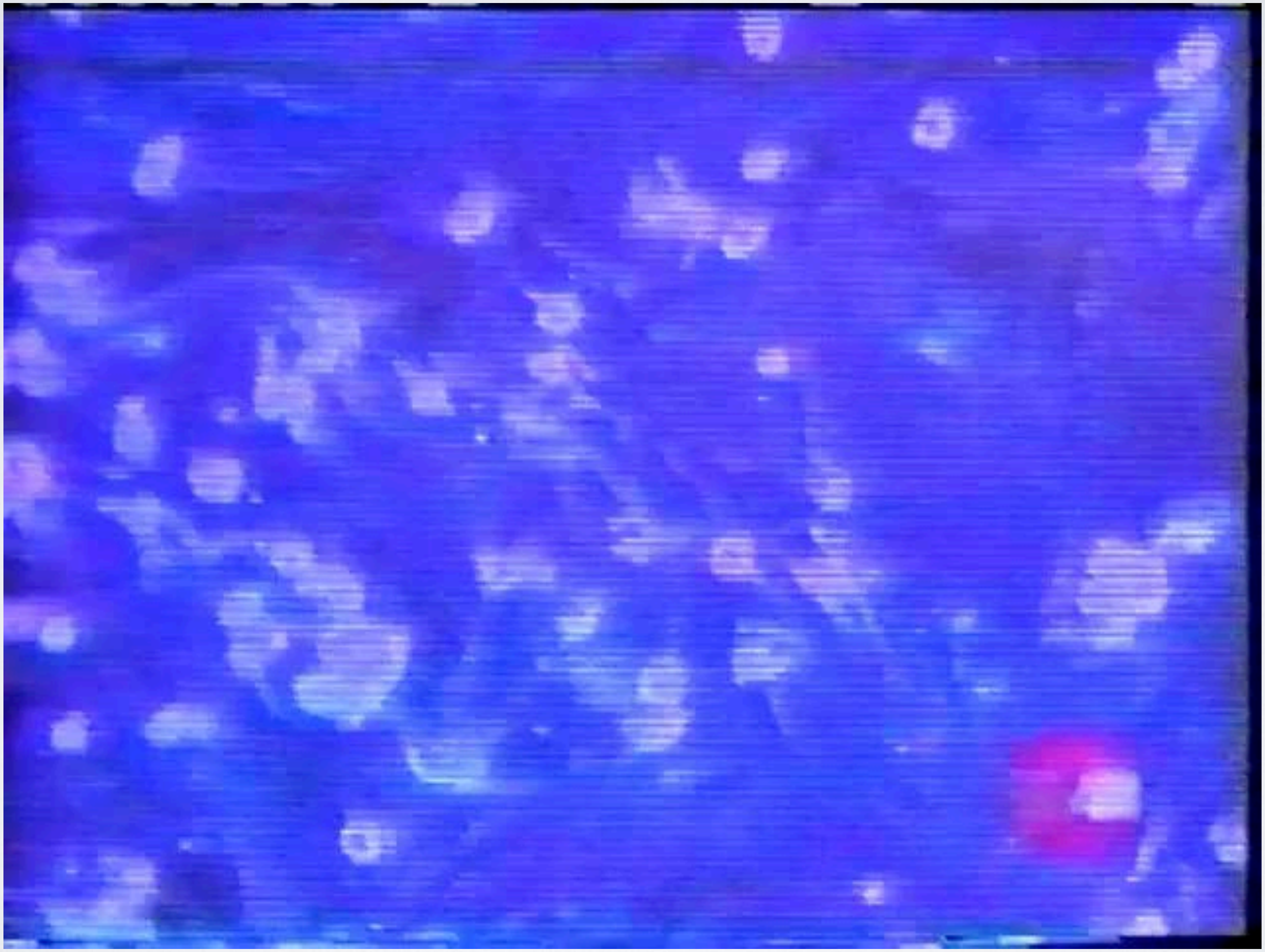


CHEMICAL REACTOR FOR GROWING HEART TISSUE



SYNTHETIC HEART CELLS

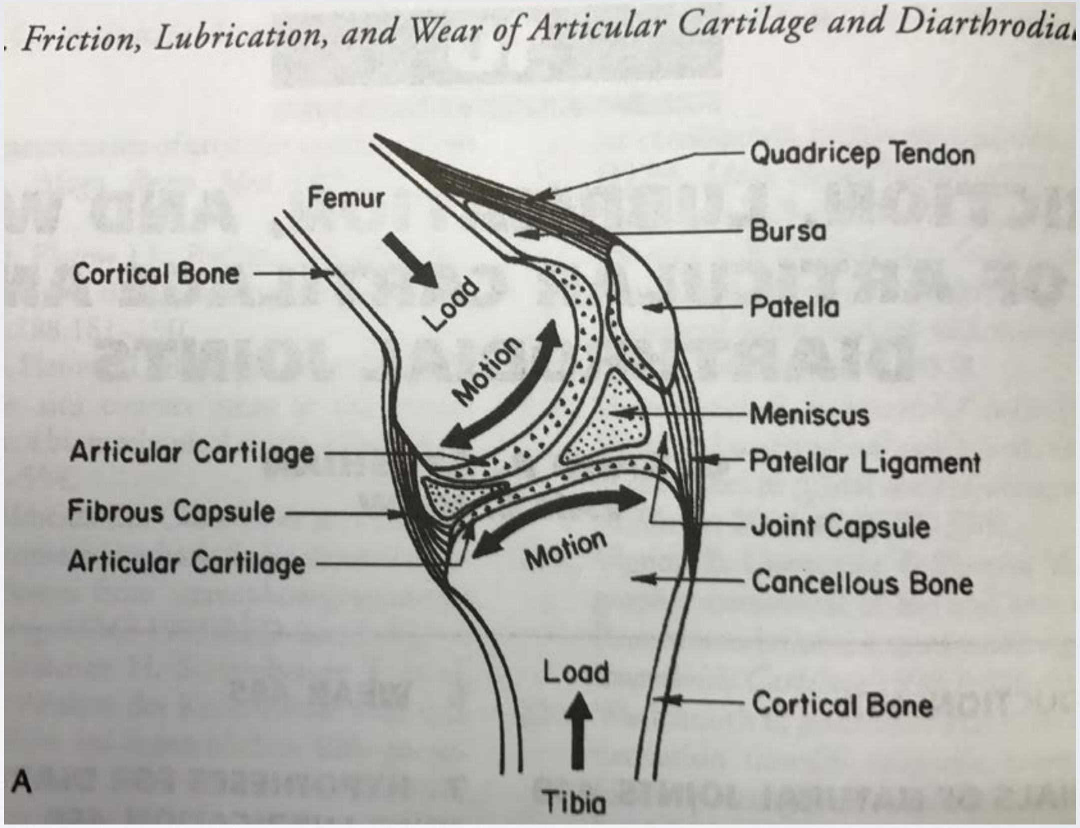
SYNTHETIC HEART CELLS



20 YEARS LATER

- Limited success 😔
- Can’t figure out how to vascularize tissue
    - blood flow essential for nutrient transport
- Can’t make complex structures
    - e.g., a heart or kidney

VASCULARIZATION NOT NEEDED



- Cartilage
- Cornea
- Thin layers of tissue: skin for burn victims

VASCULARIZATION: DIFFUSION LENGTH SCALE

- All cells need oxygen and other nutrients
- This needs to be refreshed on a time scale of ~100 sec, τ
- Oxygen “diffuses” through the cell membranes (fast) but much more slowly through the interstitial liquid between cells
    - We can figure out how far from a blood vessel (capillary) this distance can be.
        - (same dimensional reasoning we discussed last week)
    - The physical variable, *D*, is called the “molecular diffusivity”. It has a value of about 10^{-5} cm^2/s.
        - To make a “length” we need $\sqrt{D\tau}$
        - This is about 300 μm

SCIENTIFIC REFERENCE

The Pivotal Role of Vascularization in Tissue Engineering

François A. Auger,[1,2,*] Laure Gibot,[3,4,*] and Dan Lacroix[1]

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*Both first authors have contributed equally to the manuscript.

Keywords

regenerative medicine, microvascularization, angiogenesis, lymphangiogenesis

Abstract

Vascularization is one of the great challenges that tissue engineering faces in order to achieve sizeable tissue and organ substitutes that contain living cells. There are instances, such as skin replacement, in which a tissue-engineered substitute does not absolutely need a preexisting vascularization. However, tissue or organ substitutes in which any dimension, such as thickness, exceeds 400 μm need to be vascularized to ensure cellular survival. Consistent with the wide spectrum of approaches to tissue engineering itself, which vary from acellular synthetic biomaterials to purely biological living constructs,

ARTIFICIAL VASCULARIZATION

- This problem is largely unsolved
  - Microlithography: The science and “art” of making small scale electronic circuits is very advanced and it is possible to use the masking, radiating and etching to make a pattern of holes or bumps on which to grow “blood vessels”.
    - There is a vast literature on variations of this idea
  - Another approach is to use fibers in a construct and then *dissolve* out the fibers as conduits.
  - A third approach is to use stem cells to try to get the blood vessels to form.

The Pivotal Role of Vascularization in Tissue Engineering

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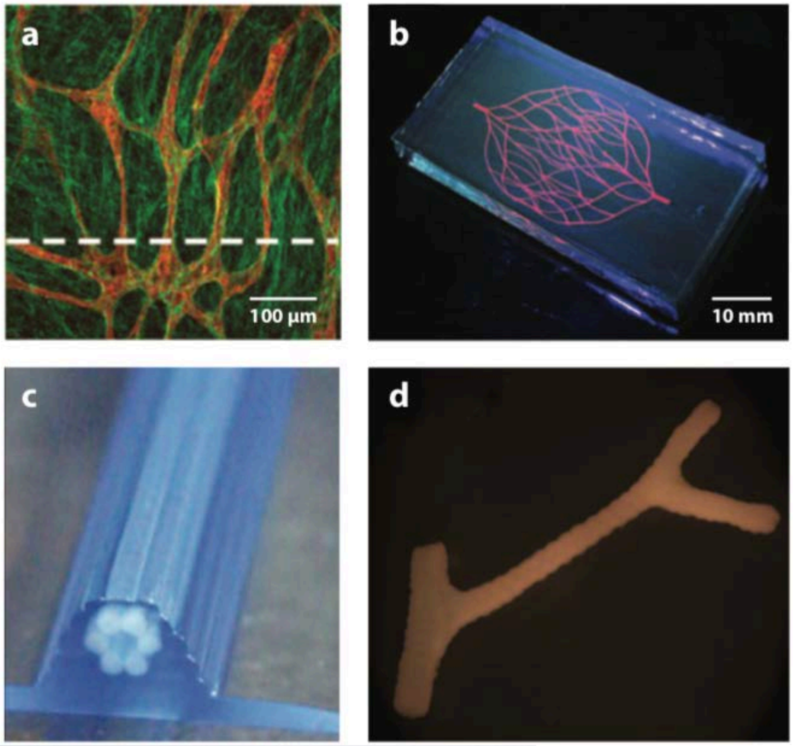


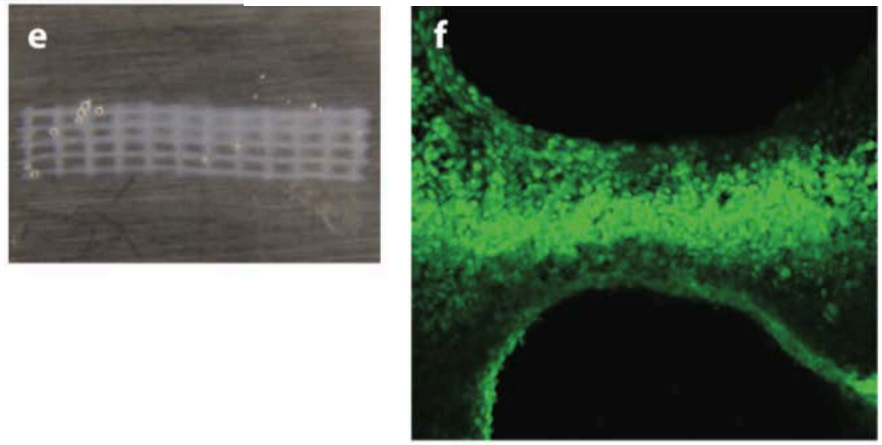
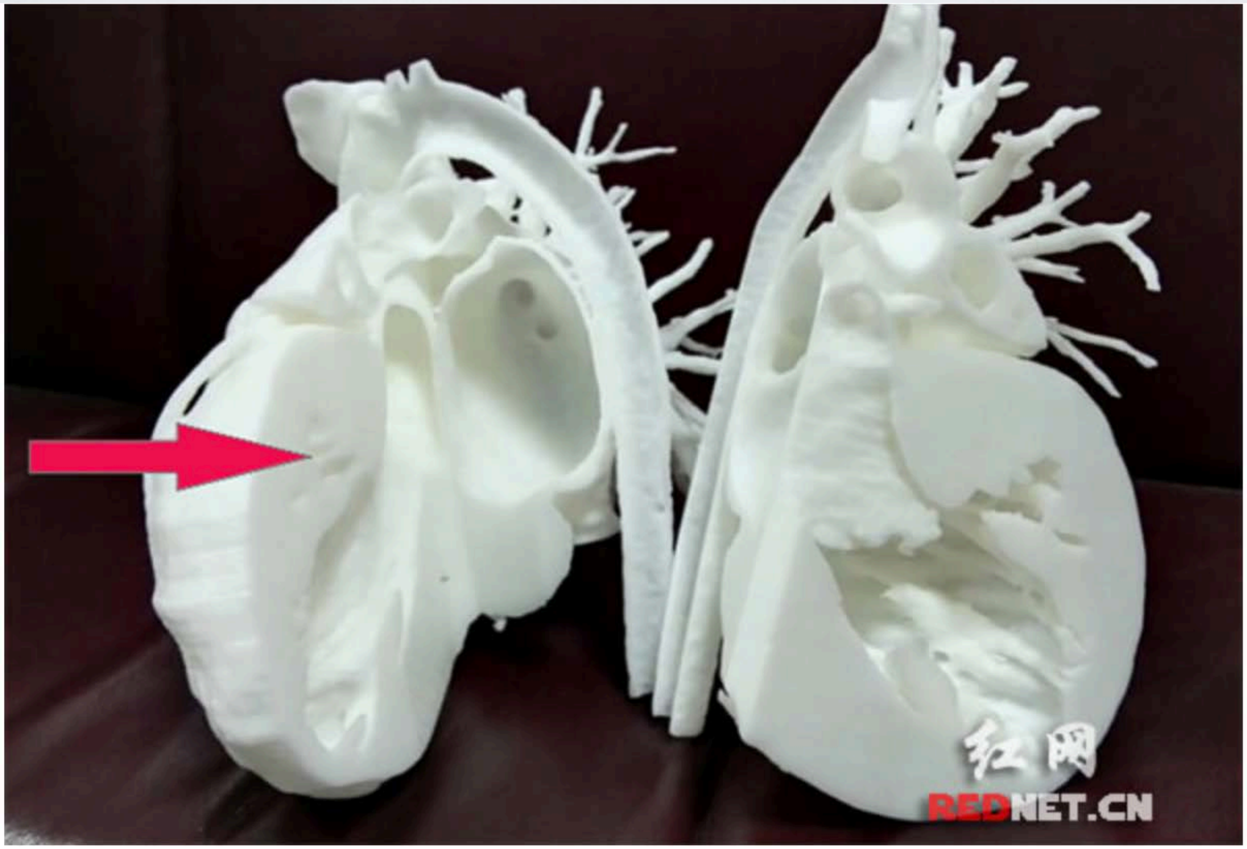


Figure 1

(*a*) Multilayered prevascularized tissue that, using thermoresponsive cell culture surfaces, combined micropatterned HUVECs with human fibroblast monolayer sheets. The white dotted line indicates where a cross-sectional picture, shown in the original article, was taken. (*b*) Three-dimensional biomimetic microvascular network constructed by omnidirectional printing. (*c*) Tubular structure generated by bioprinting using a scaffold-free approach based on the use of agarose rods as building blocks of a molding template. (*d*) Branching pattern generated with agarose and multicellular rods that were bioprinted layer by layer using the template shown in panel *c*. (*e*) Printed fibrin scaffold generated using modified inkjet printer. (*f*) Fluorescent stained HMVECs, which aligned inside the fibrin scaffold on day 0 (as shown in panel *e*), formed an aligned tubular structure after 21 days of culture. (Panels *a*, *b*, *c*–*d*, and *e*–*f* were reproduced with permission from References 72, 75, 76, and 79, respectively.)

(ASIDE) 3-D PRINTING FOR DIAGNOSIS



A 1:1 scale 3D printed heart replica. Image via Rednet.cn.

W NE?

MEDICAL

3D Printed Heart Models Helping Doctors Optimize Surgical Plans for Complex Operations

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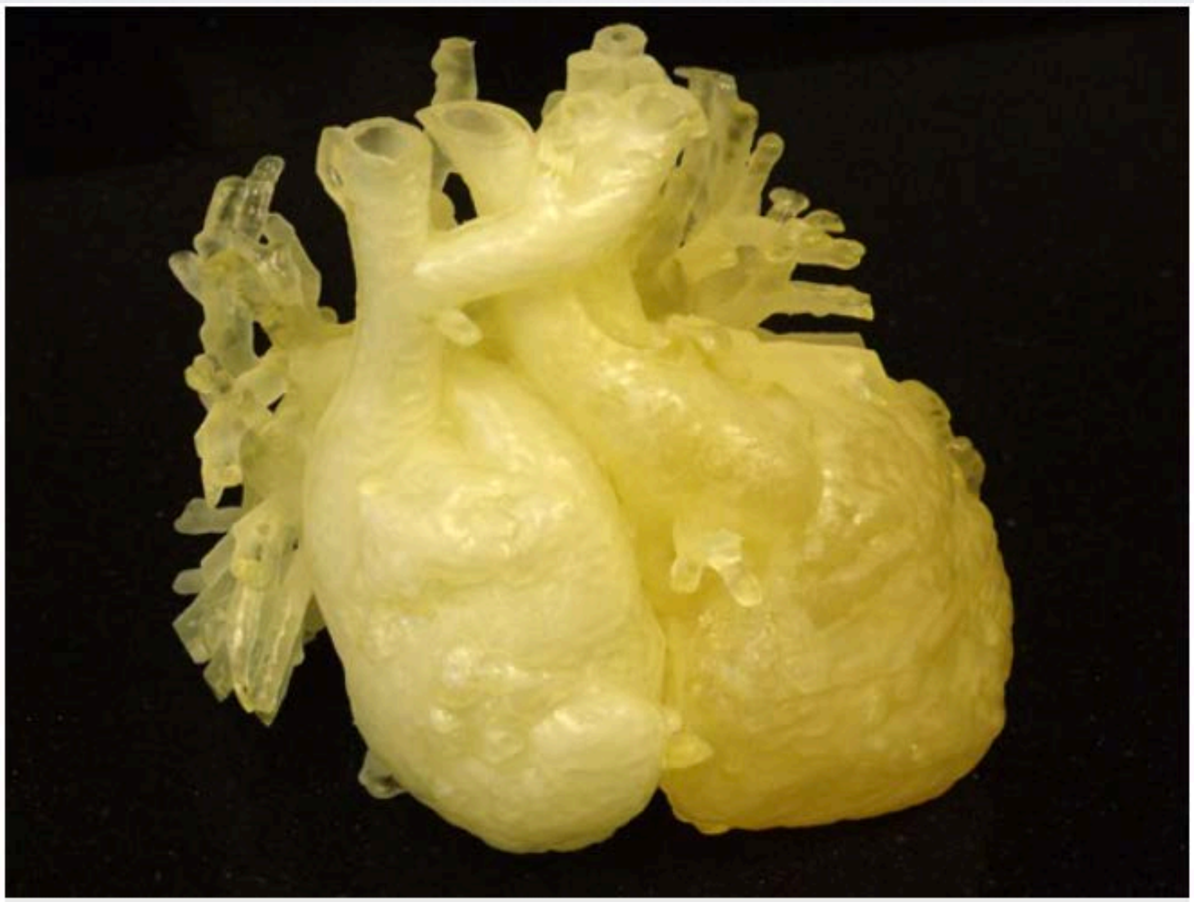
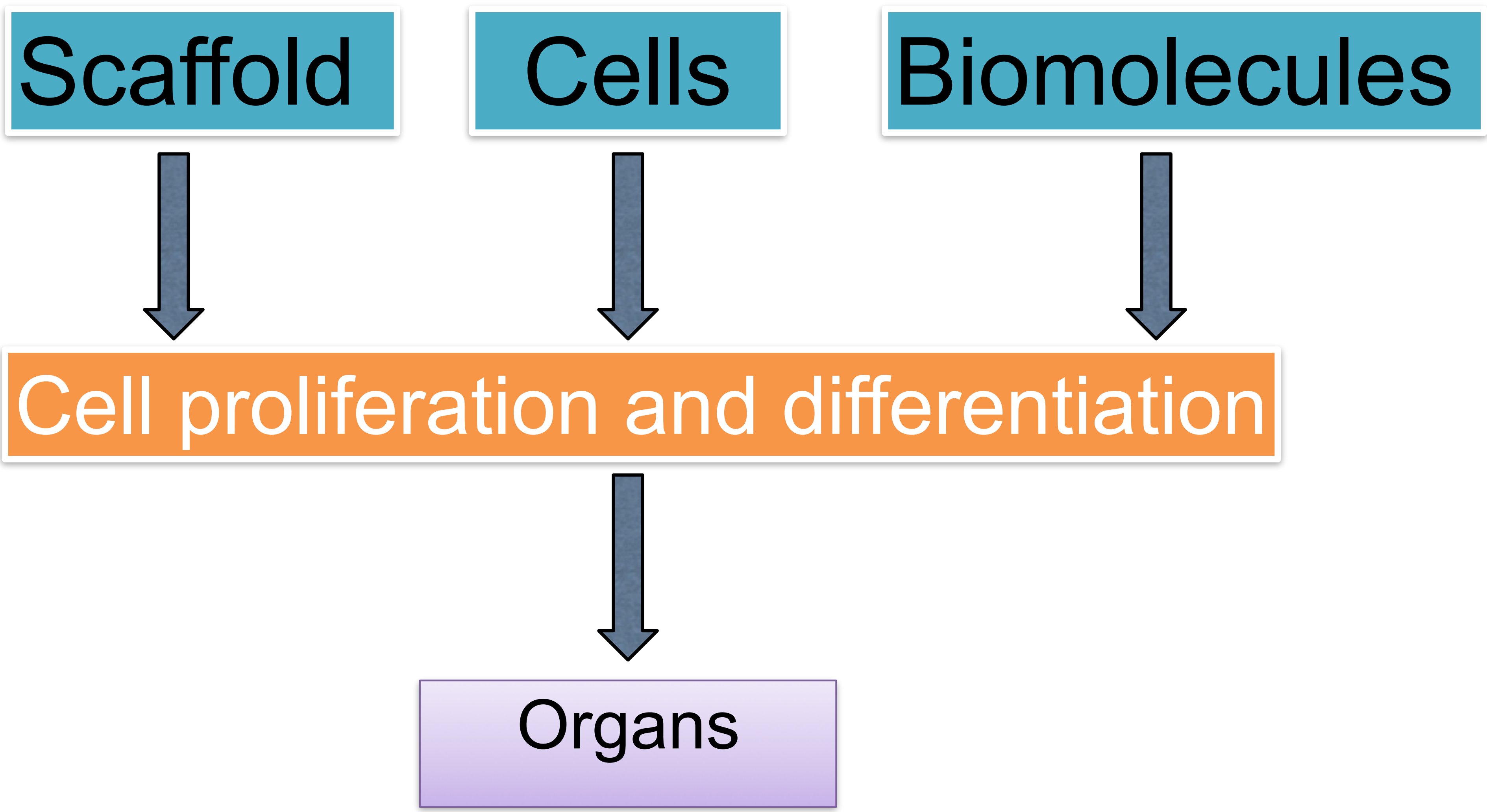


Whole organ decellularization: a penultimate biomaterial?

Slide by Jeremy Zartman

“The heart makers”
http://www.youtube.com/watch?v=pd3TFB0wOI0

Tissue engineering



Slide by Jeremy Zartman

Modified from Moreno-Borchart, Alexandra. 2004. “Building organs piece by piece.” EMBO Rep 5 (11) (November): 1025-1028. doi:10.1038/sj.embor.7400287.

Stem cells: key players in TE

- Stem cells: Cells that proliferate while maintaining a primitive state (self-renewal) and are able to differentiate into one or more specialized lineages
  - Unipotent (can produce one cell type)
  - Pluripotent (can produce many cell types)
  - Totipotent (can produce all cells types)
- Example: Lethally irradiated mice can be rescued with select stem cells which rebuild the multi-lineage of hematopoiesis (formation of blood cells)

Slide by Jeremy Zartman

“HEALTH” ENGINEERING AT NOTRE DAME

- https://www.youtube.com/watch?v=RAQBEN3lFPE#t=43
- https://www.youtube.com/watch?v=a0_er0YYwaU
- http://newsinfo.nd.edu/news/31468-multifunctional-nanoparticles-promise-to-improve-blood-cancer-treatment/

RECAP

- While Engineers have long been involved in medical problems, “engineering” has not fully infused the practice of medicine and we can expect many new, interesting and valuable contributions in the future (more than traditional fields)
- Part of this comes from rapidly increasing understanding of molecular biology (which is a much younger field than, say, organic chemistry)
- Engineers can be expected to contribute
  - new systems and devices, better targeting for treatments, new ways to regenerate and hopefully replace tissue and organs
  - general and personalized diagnostics and treatments

BLANK SLIDE

SCAFFOLDS

- Either on the scale of blood vessels (but capillaries are too small) or for larger scale structures, one avenue of research is to “print” a scaffold out of a structural (inert) material then then infuse a mixture of cells and active biological molecules to try and initiate tissue growth or regeneration.
  - some success at regenerating existing damaged tissues has been seen with stem cell injections.

Challenges

- Scalability (oxygen transport)
- Control of cell source and scaffold material
- Integration into the host

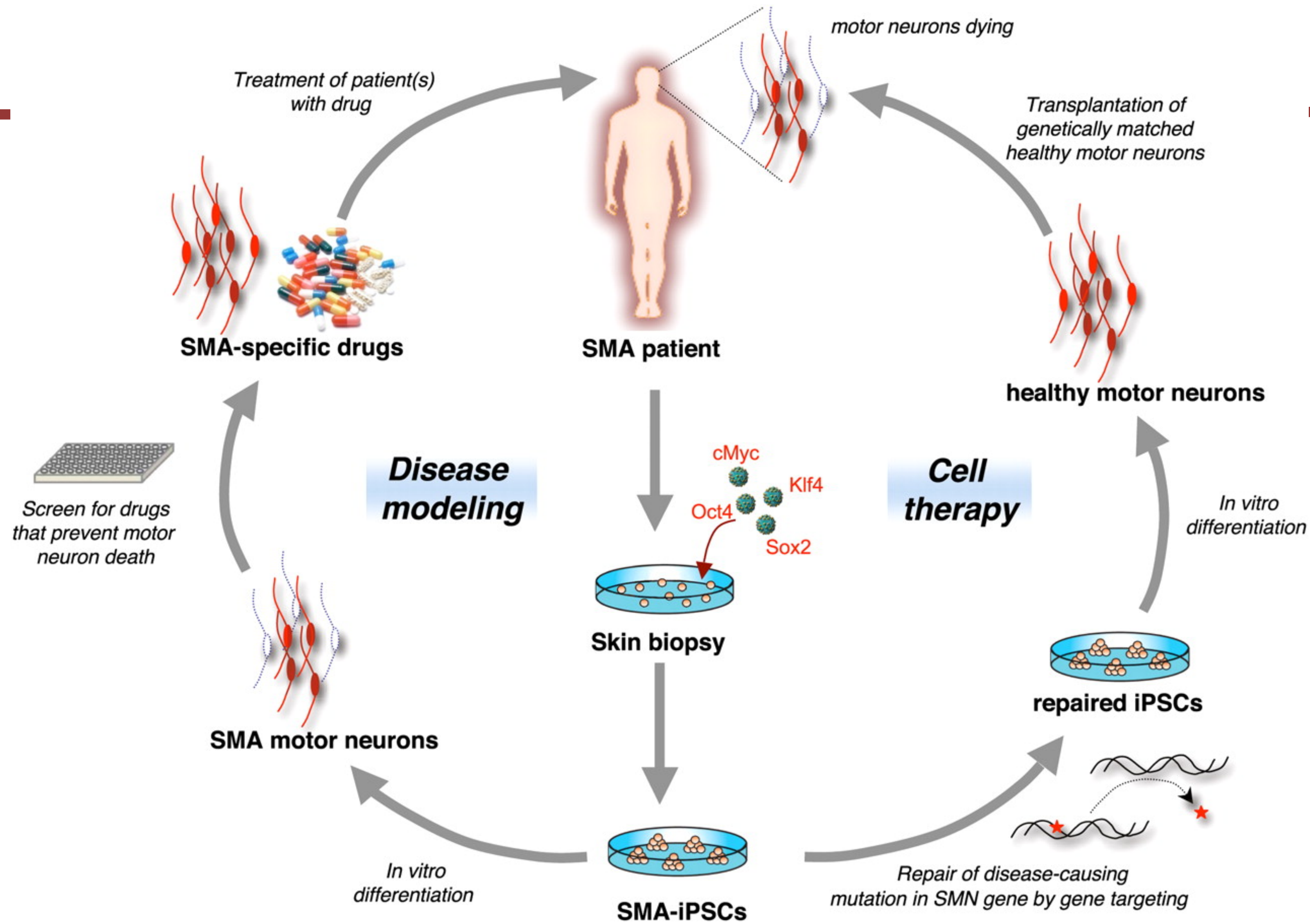
Other tissues?

- Big problem for many TE solutions is lack of vasculature connected to and perfused by blood system of host.
- Advances in some tissues: bladder, cornea, and bronchial tubes
- Challenges for blood vessels, heart, and liver
- Industry decline in early 2000s
- New emphasis on stem cell technology
- Important connections between tissue engineering, drug delivery and genetic engineering

Properties

- Stem cells are isolated using surface markers (ex. Hematopoietic stem cells are $CD34^+$ and $CD38^-$)
- Most cells are differentiated cells. 1 in 100,000 cells in the bone marrow are stem cells.
- Adult stem cells are found in the adult and are more limited. Embryonic stem cells are derived from the embryo prior to commitment to a given germ layer.

Induced pluripotent stem cells (iPSCs)



Stadtfeld M, and Hochedlinger K Genes Dev. 2010;24:2239-2263

In spinal muscular atrophy (SMA) patients, motor neurons are afflicted and die, causing the devastating symptoms of the disease.

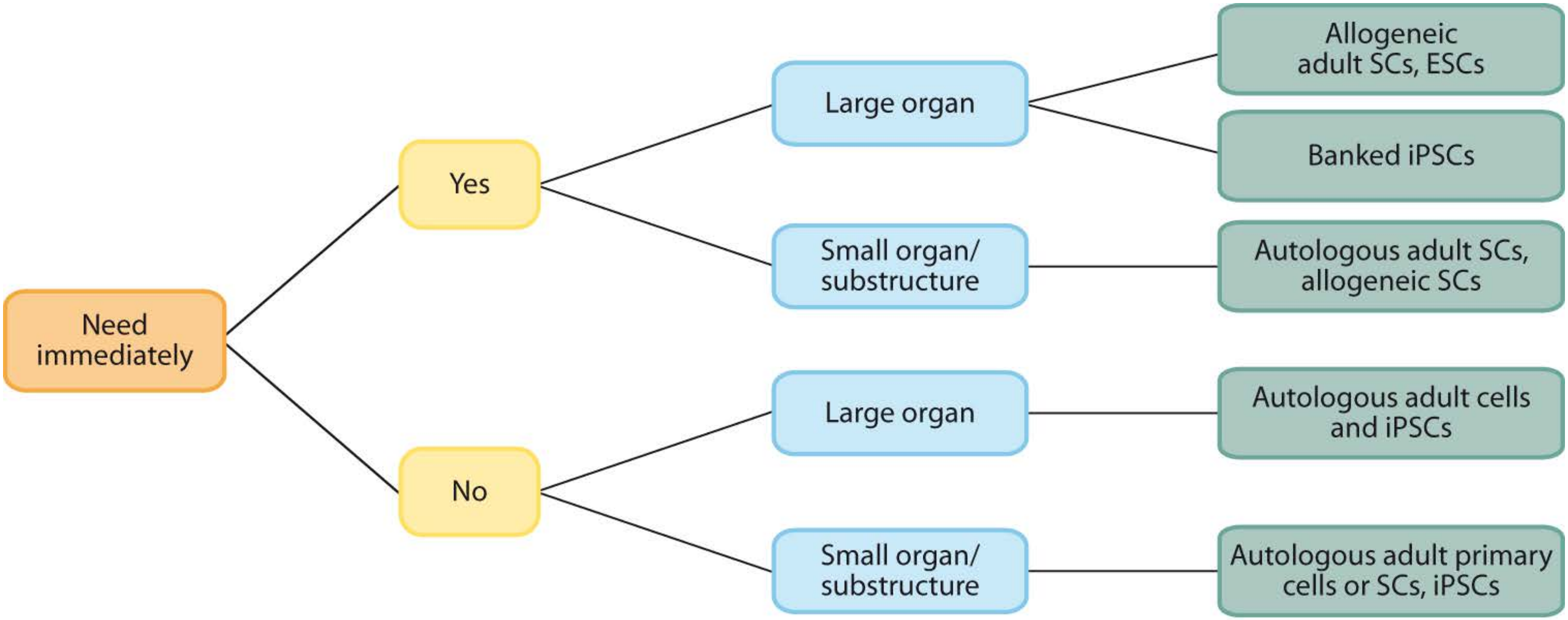
Techniques to decellularize an organ

Decellularization of tissues and organs

Physical	Enzymatic	Chemical
Mechanical agitation	Trypsin	Alkaline/acid Hypotonic and hypertonic solutions
Freeze/thaw	Endonucleases	EDTA, EGTA
Sonication	Exonucleases	**~Nonionic detergents** Triton X-100
		~Ionic detergents Sodium dodecyl sulfate (SDS) Triton X-200
		~Zwitterionic detergents CHAPS Sulfobetaine-10 and -16 (SB-10, SB-16) Tri(n-butyl)phosphate

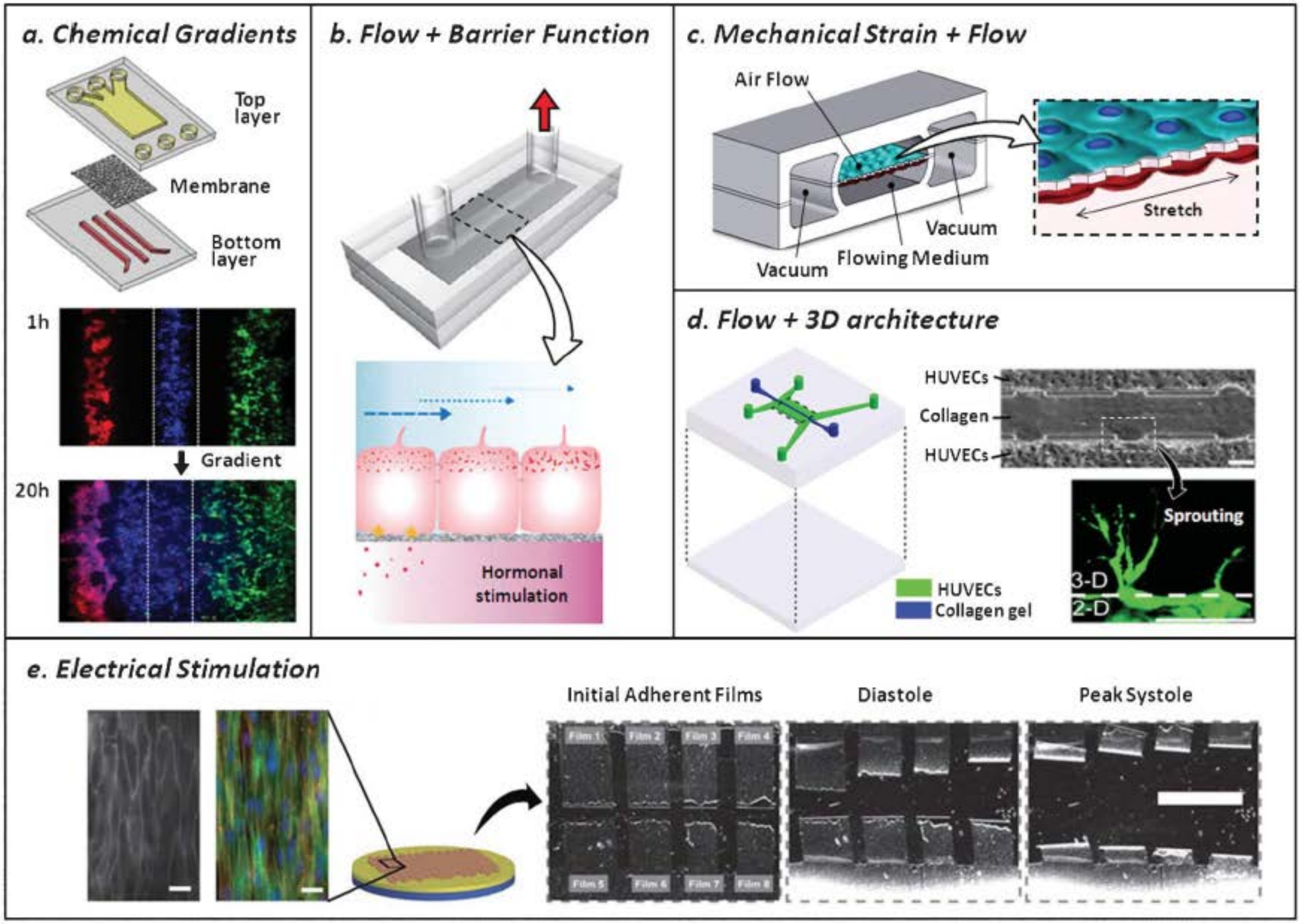
Badylak SF, et al. 2011.
Annu. Rev. Biomed. Eng. 13:27–53

Decision algorithm for choosing seeding cells



Badylak SF, et al. 2011.
Annu. Rev. Biomed. Eng. 13:27–53

Organ-level function on a chip



Huh D, Torisawa Y, Hamilton GA, Kim HJ, Ingber DE. Microengineered physiological biomimicry: Organs-on-Chips. Lab on a Chip 2012;12(12):2156.

Designing a tissue construct

From Homework assignment:

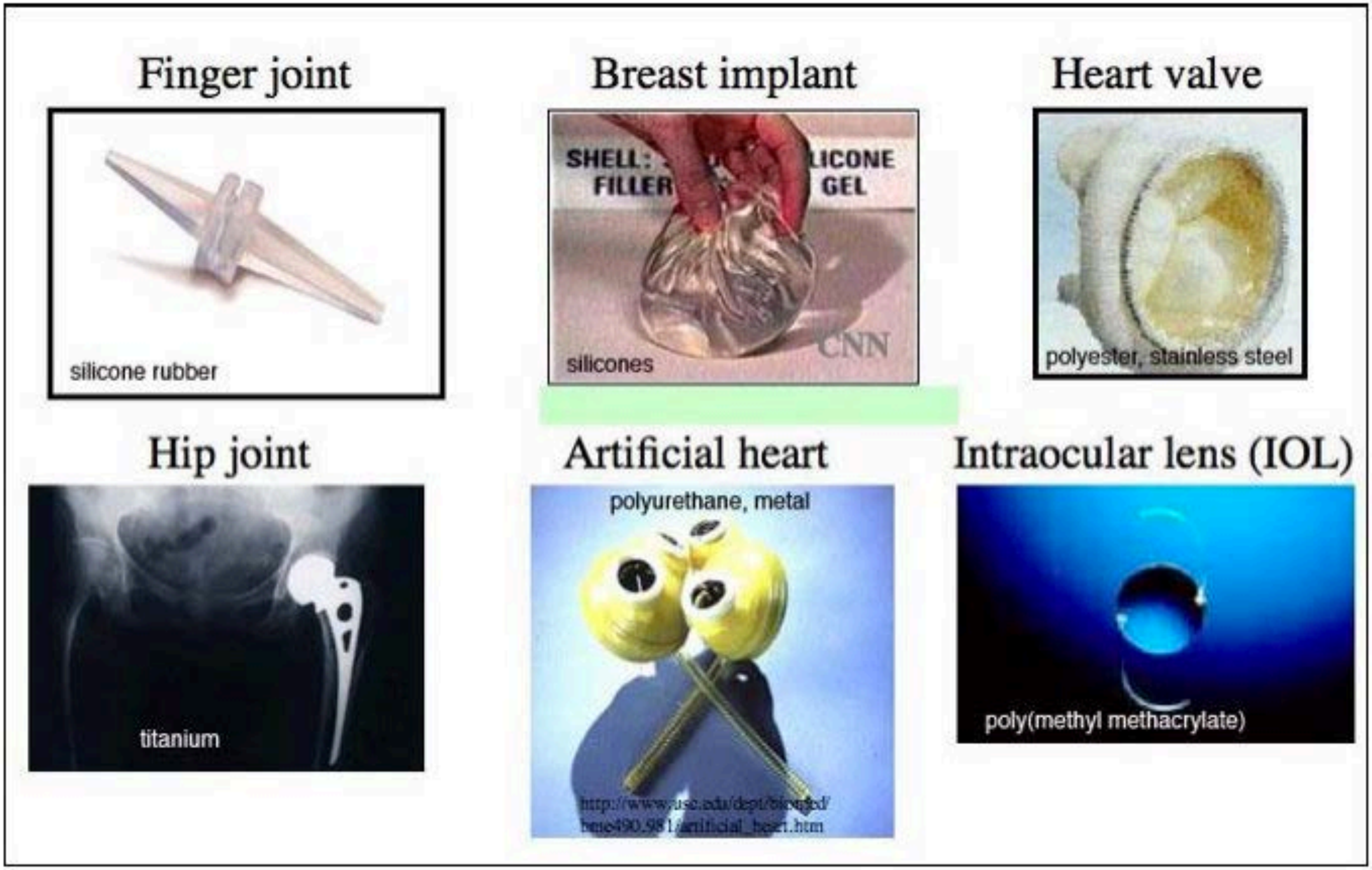
You wish to design a cellular construct to be implanted into the body to provide a therapeutic role. When considering geometries for your construct, your main concern is for all cells in the construct to receive enough oxygen to survive. Determine the maximum-size sphere, slab, and cylinder that would allow all cells to survive. You may assume that cell death occurs at half of the bulk oxygen concentration. You may also assume that the slab is thin compared with its length and width (infinite slab) and that the radius of the cylinder is small compared to its length (infinite length)

(A) Express R_{max} or L_{max} in terms of the bulk concentration (c_B [mol/mL]), diffusivity of oxygen through the construct (D[cm^2/s]), and maximum consumption rate (V_m [mol/mL/s]). You may assume zero-order oxygen-uptake kinetics. State your model assumptions.
(B) Which geometry allows the largest size construct while keeping cells alive?
(C) Which geometry is least efficient? By what factor?
(D) What parameters might you manipulate experimentally to alter the critical size of the given construct? Give two specific examples.

RECAP

- Engineers use understanding of the situation and mathematical analysis to get quantitative answers that tell how to design and build all of the technologies of the world!
- It is within your choice to find a role that provides the personal fulfillment you desire!

Biomaterials



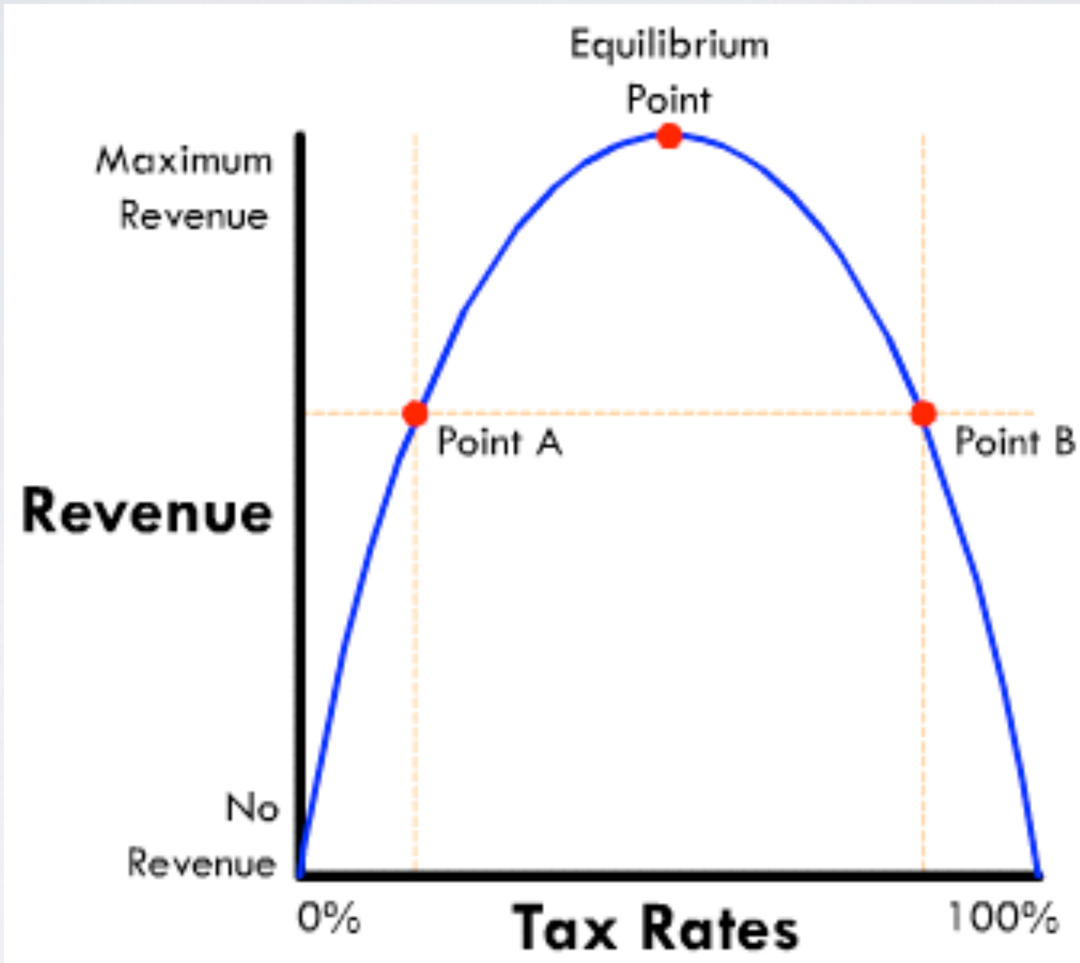
http://www.uweb.engr.washington.edu/research/tutorials/introbiomat.html

SUCCESS IN LIFE

- Skills, knowledge and ability to learn
- dedicated to task and career
- have the capacity and inclination to determine how "other people" will think and why

TAXES: LOOK AT LIMITS...

Recall "Extreme value theorem" or Rolle's Theorem from Calculus



Laffer tax-revenue curve

FOR MANY YEARS, WE HAVE BEEN TOLD TO RAISE OUR HDL LEVELS BUT..

- http://www.nytimes.com/2012/05/17/health/research/hdl-good-cholesterol-found-not-to-cut-heart-risk.html
- http://www.cbn.com/health/naturalhealth/drsears_heartattack.aspx

RELATIONSHIP BETWEEN SALT AND HEALTH?

- http://www.nytimes.com/2011/07/12/health/research/12nostrums.html?ref=health
- http://www.nytimes.com/2013/05/15/health/panel-finds-no-benefit-in-sharply-restricting-sodium.html?pagewanted=all

IT IS OK TO CHALLENGE ACCEPTED THINKING!

- Some things we thought we knew:
    - Margarine was considered a health food
    - Left-handed people die sooner because of the hazards of the right-handed word
    - Stomach Ulcers are caused by stress
    - Plants absorb CO2 and emit O2
    - The adult brain has no capacity to regenerate itself
    - Komodo Dragons bit their prey and waited for them to succumb to bacterial infections

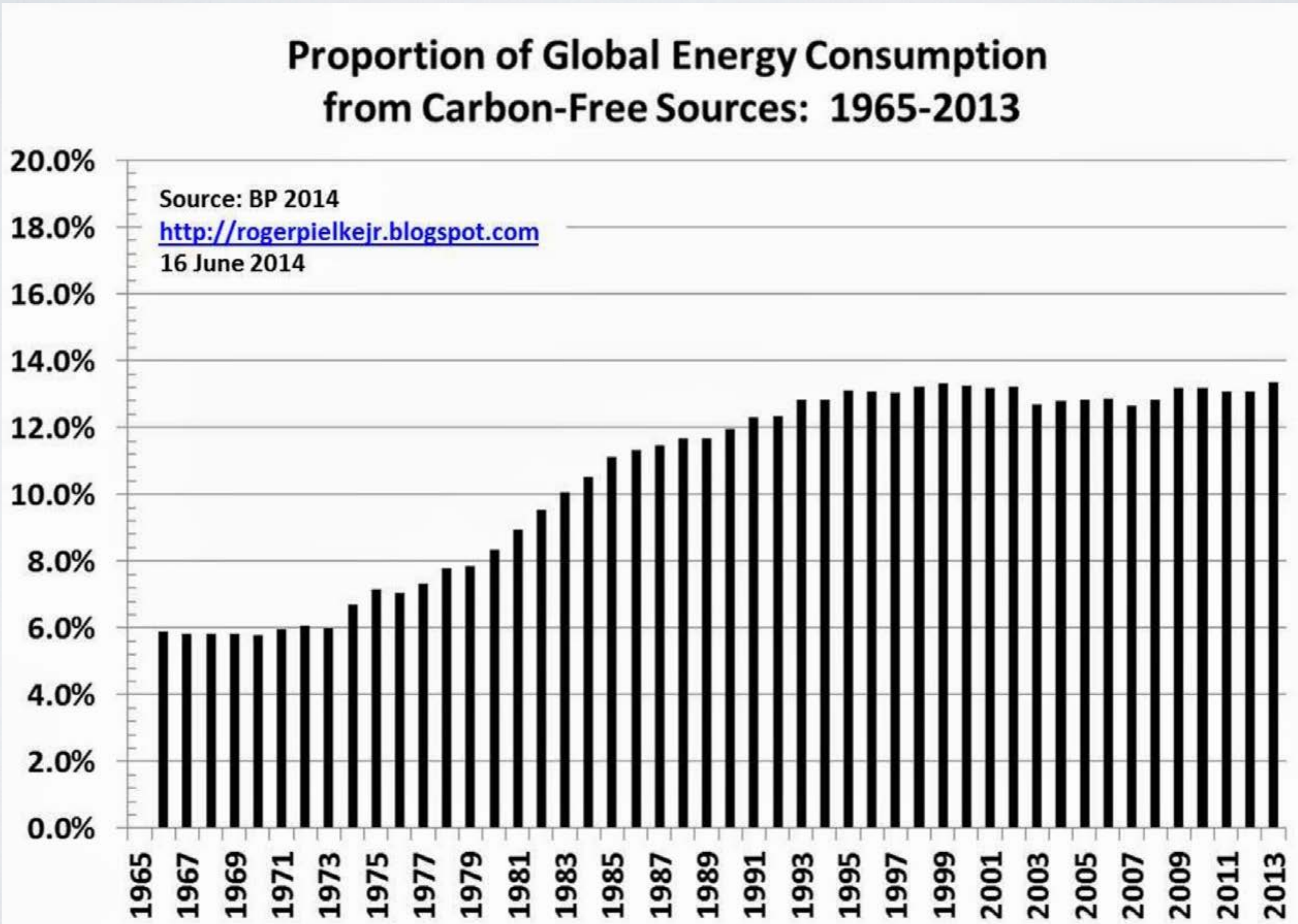
TOPICS OF THE MOMENT

- Healthcare
- Energy
- The Environment
- The Economy
- Engineers are critically involved in all of these and will chart the future course
- "Society" may call these issues "problems", engineers see these as challenges to be met!
  - Major advances in all of these areas will require engineering!

ENGINEERING IN MEDICINE

- http://www.flukebiomedical.com/Biomedical/usen/products/default.htm
  - http://www.washingtonpost.com/blogs/innovations/wp/2014/06/17/google-and-apple-want-to-be-your-doctor-and-thats-a-good-thing/

“RENEWABLES” ARE NOT GAINING GROUND



ENERGY PER POUND

substance	food calories	kW-hours	compared to TNT
bullet (1000 ft/s)	4.5	0.005	0.015
car battery	14	0.016	0.046
computer battery	45	0.053	0.15
alkaline battery	68	0.079	0.23
TNT	295	0.343	1
PETN	454	0.538	1.5
Chocolate chip cookie	2,269	2.6	7.7
Coal	2,723	3.2	9.2
Butter	3,176	3.7	11
Ethanol	2,723	3.2	9
Gasoline	4,538	5.3	15
Natural gas	5,899	6.9	20

New construction: Electricity Cost

Type	Cost per megawatt-hour
Coal	100.1
Natural Gas[16]	65.6
Nuclear	108.4
Geothermal	89.6
Biomass	111.0
Non-dispatchable Technologies	
Wind (Onshore)	86.6
Wind (Offshore)	221.5
Solar Photovoltaic	144.3
Solar Thermal	261.5
Hydroelectric	90.3

When all costs are factored in—transmission, capital, operations and maintenance, etc.—natural gas continues to be the fuel of choice for electricity production in the United States because it is Cheaper than other sources. *Source*: Energy Information Administration, Annual Energy Outlook 2013.[17]

CHALLENGES OF RENEWABLE ENERGY

- Let’s consider
  - Wind
  - Solar
  - Biomass

WIND

- Roughly, it takes 350-450 square miles of windmills (approximately 13000 wind turbines) to produce the electrical equivalent of a large coal or nuclear plant: 1000MW.
- This is the size of St. Joseph Co. IN
- 300,000 people live here and we use about 600 MW
- We don’t have very good wind here (so it would not work) and it would seem a bit inconvenient to cover 1/2 of the county with windmills

TO REPLACE JUST THE COAL…

If You Want to Replace US Coal-fired Capacity with Wind, Then Find a Land Area the Size of Italy

ENERGY DENSITY OF WIND AND SOLAR

- If we work out the numbers, the power density of wind is about
  - 0.004 MW/acre
- What could we compare this to (Engineers always want to make comparisons!)
- How about solar flux?
  - We can capture only part of the solar flux for useful heat, much less for electricity
    - What are these numbers?
- Solar flux averaged over the earth is ~350 W/m^2
- While nothing more energetic than a tree "runs" directly on solar, this gives a value of about
  - 0.3 MW/acre

TO GET 20% OF ENERGY FROM BIOMASS

Faster, Lighter, Denser, Cheaper:How Proving the Catastrophists Wrong: Robert Bryce

Source: Author calculations, based on land-productivity calculations for biofuels published by Oak Ridge National Laboratory.

WHAT ELSE TO COMPARE

- 1000 MW power plant using coal might occupy 100 acres
  - This is enough power for 1 Million people in the US
- 1 really good oil well could produce 100,000 bbl/day
  - This is an equivalent amount of power
    - Footprint could be just a few acres

RECAP

- One way to compare potential utility of energy systems is to look at power produced per acre of land
  - Coal to Electricity: 1000 MW
  - Solar to Electricity: 30 MW
  - Wind to Electricity: 0.4MW
  - Corn to liquid fuel: 0.1 MW
  - 10 oil wells (surface footprint): 10 GW
- We breath air and use oxygen in metabolism because this is 17 times more energetic than a non-aerobic digestion reaction

RECAP

- Successful engineering requires an understanding of the detailed device or process but must be practiced in the larger context of all of society

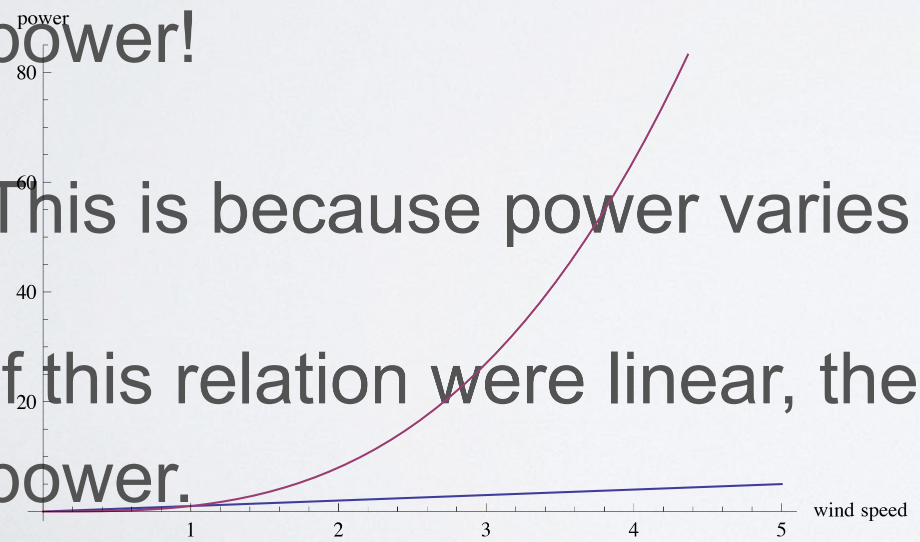
- This general knowledge and understanding is also important for engineers.

RECAP CONTINUED

- Current energy sources are ultimately unsustainable and cause at least some degree of extra forcing on climate stability
- Solar could provide all of the power society needs, but current costs are much too high and current storage technologies inadequate
- This is just one critical technology that needs more new ideas and people to push the efforts forward
    - It is a good time to be an engineer!

WIND POWER (HOMEWORK)

- Suppose that I design a wind turbine to work perfectly for 25 mph wind
- If the wind speed drops to 15 mph, I get only 22% of the power!
- This is because power varies as the cube of the wind speed
- If this relation were linear, then we would get 60% of the power.



PROBLEM DEFINITION

- Every aspect of engineering relies on us knowing what problem we are trying to solve
- We may have to produce an “answer” (design) when we don’t know a lot about the fundamental science or other underlying phenomena, but
- We can never produce a result when we don’t know the problem!
- This is not the case in society in general!

IMPERFECT UNDERSTANDING

- **6.1 The Ideal solution**

- The history of modern science has shown repeatedly that a quantitative description of nature can often be achieved most successfully by first idealizing natural phenomena, i.e. by setting up a simplified model, either physical or mathematical, which crudely describes the essential behavior while neglecting details. **(In fact, one of the outstanding characteristics of great contributors to modern science has been their ability to distinguish between what is essential from what is incidental)** ..."

- From: Molecular Thermodynamics of Fluid Phase Equilibria

- John M. Prausnitz 1969.

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- **This statement describes how an engineer often must do her job. You cannot waste your time on details that don't matter !!!!**

MEDAL OF SCIENCE CEREMONY

SOME REALITIES OF THE WORLD

- I am wont to say, “I hate it when facts get in the way of my opinions!”, but this is what we must face as engineers
    - Let’s do green energy!
- Let’s do the simplest analysis to quantify our thinking

THIS ONE WILL BE INTERESTING?

- http://www.telegraph.co.uk/foodanddrink/foodanddrinknews/9340712/Coca-Cola-not-to-blame-for-US-obesity.html
- http://www.advisory.com/Daily-Briefing/2013/03/20/Pepsi-health-challenge-Sugary-drinks-linked-to-obesity-related-deaths

It is OK (sometimes) to change your mind

Corporations act in their own best interest

Clifton Garvin
CEO Exxon circa 1980

Garvin and Exxon were enthusiastic proponents and participants in "synfuels" in the 1970's

In a stunning reversal of thinking, at the last minute, Garvin pulled the plug and stopped the project before it was built!

He saved Exxon and other oil companies Billions of dollars!

LEADERSHIP MATTERS!

ce 2000:
Vin Percentage
pearances (12-5)
Bowl Victories

Since 2
42.77% Win I
2 Playoff Appea
No Supe

"Qui tacet consentiret"

"Silence gives consent"

Saint Thomas Moore
Lord Chancellor of England
when
Henry VIII was king

ENGINEERS LIKE TO COMPARE THINGS

- If I asked: ".. how far is it to Chicago?"
  - would you answer
    - "a couple of hours" or...
    - "about 90 miles"
- If I asked: ".. is a meter a long distance?" what would you say
  - "No", compared to the distance to Chicago
  - "Yes", compared to a micron

IMPORTANCE OF DIMENSIONLESS NUMBERS

- Reynolds number:

$$\frac{Inertia \quad forces}{Viscous \quad forces}$$

- Another number

$$Cr \equiv \frac{How \quad Smart \quad You\, Are}{How \quad Smart \quad You \quad Think \quad You \quad Are}$$

-

DIMENSIONLESS CONFUCIUS PROVERB

$$Cr \equiv \frac{How \;\; Smart \;\; You\, Are}{How \;\; Smart \;\; You \;\; Think \;\; You \;\; Are}$$

- He who knows not and knows he knows not is a child, teach him, Cr~1
- He who knows not and knows not he knows not is a fool, shun him, Cr<<1
- He who knows and knows not he knows is asleep, awaken him, Cr>>1
- He who knows and knows he knows is wise, follow him Cr~1