Biomedical Physics

Physics provides medical imaging techniques.

Wilhelm Röntgen, first recipient of the Nobel Prize in Physics

print of Röntgen's first "medical" X-ray, of his wife's hand, taken on December 22, 1895

brain activity measurements:
- EEG, electroencephalography
- MEG, magnetoencephalography
- PET, positron emission tomography
- MRI, magnetic resonance imaging
- fMRI, functional magnetic resonance imaging
- CT, computer tomography
- SPECT (single-photon emission computed tomography with gamma-emitting radioisotope)

Also fluorescence techniques, atomic force microscopy, etc.
Lasers and optics in medicine and biomedical science: an enormous area

Steven Chu, United States Secretary of Energy
Nobel Prize for Physics (1997)
professor of physics; professor of molecular and cell biology
quantum optics, general relativity;
single molecule biology, biophysics, and biomedicine

Charles Munnerlyn, cofounder of VISX, with his wife Judy.

By 2002, about two thirds of laser vision correction procedures in the U.S. were performed with VISX equipment.

His degrees are in physics and optics, from Texas A&M and Rochester. He has also been an avid amateur astronomer since age 13.


Nuclear medicine is also an enormous area, for imaging and treatment.
Table 1: A Partial Nanomedicine Technologies Taxonomy

<table>
<thead>
<tr>
<th>Raw nanomaterials</th>
<th>Cell simulations and cell diagnostics</th>
<th>Biological research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticle coatings</td>
<td>Cell chips</td>
<td>Nanobiology</td>
</tr>
<tr>
<td>Nanocrystalline materials</td>
<td>Cell stimulator</td>
<td>Nanoscience in life sciences</td>
</tr>
<tr>
<td>Nanostructured materials</td>
<td>DNA manipulation, sequencing, diagnostics</td>
<td>Drug delivery</td>
</tr>
<tr>
<td>Cyclic peptides</td>
<td>Genetic testing</td>
<td>Drug discovery</td>
</tr>
<tr>
<td>Dendrimers</td>
<td>DNA microarrays</td>
<td>Biopharmaceutics</td>
</tr>
<tr>
<td>Detoxification agents</td>
<td>Ultrafast DNA sequencing</td>
<td>Drug encapsulation</td>
</tr>
<tr>
<td>Drug encapsulation</td>
<td>DNA manipulation and control</td>
<td>Smart drugs</td>
</tr>
<tr>
<td>Fullerene</td>
<td>Tools and diagnostics</td>
<td>Molecular medicine</td>
</tr>
<tr>
<td>Functional drug carriers Smart drugs</td>
<td>Bacterial detection systems</td>
<td>Genetic therapy</td>
</tr>
<tr>
<td>MRI scanning (nanoparticles)</td>
<td>Biosensors and biodetection</td>
<td>Pharmacogenomics</td>
</tr>
<tr>
<td>Nanobarcode</td>
<td>Diagnostic and defense applications</td>
<td>Artificial enzymes and enzyme control</td>
</tr>
<tr>
<td>Molecular medicine</td>
<td>Endoscopic robots and microscopes</td>
<td>Enzyme manipulation and control</td>
</tr>
<tr>
<td>Nanoemulsions</td>
<td>Fullerene-based sensors</td>
<td>Nanotherapeutics</td>
</tr>
<tr>
<td>Nanofibers</td>
<td>Imaging (cellular, etc.)</td>
<td>Antibacterial and antiviral nanoparticles</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>Monitoring</td>
<td>Fullerene-based pharmaceuticals</td>
</tr>
<tr>
<td>Nanoshells</td>
<td>Lab on a chip</td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>Nanosensors</td>
<td>Radiopharmaceuticals</td>
</tr>
<tr>
<td>Noncarbon nanotubes</td>
<td>Point of care diagnostics</td>
<td>Synthetic biology and early nanodevices</td>
</tr>
<tr>
<td>Quantum dots</td>
<td>Protein microarrays</td>
<td>Dynamic nanoparticle nanosome</td>
</tr>
<tr>
<td>Artificial binding sites</td>
<td>Scanning probe microscopy</td>
<td>Tecto-dendrimers</td>
</tr>
<tr>
<td>Artificial antibodies</td>
<td>Intracellular devices</td>
<td>Artificial cells and liposomes</td>
</tr>
<tr>
<td>Artificial enzymes</td>
<td>Intracellular biocomputers</td>
<td>Polymeric micelles and polyemersomes</td>
</tr>
<tr>
<td>Artificial receptors</td>
<td>Intracellular sensors/reporters</td>
<td>Biotechnology and biobotics</td>
</tr>
<tr>
<td>Molecuraly imprinted polymers</td>
<td>Implants inside cells</td>
<td>Biologic viral therapy</td>
</tr>
<tr>
<td>BioMEMS</td>
<td>BioMEMS</td>
<td>Virus-based hybrids</td>
</tr>
<tr>
<td>Control of surfaces</td>
<td>Implantable materials and devices</td>
<td>Stem cells and cloning</td>
</tr>
<tr>
<td>Artificial surfaces-adhesives</td>
<td>Implanted bioMEMS, chips, and electrodes</td>
<td>Tissue engineering</td>
</tr>
<tr>
<td>Artificial surfaces—nonadhesive</td>
<td>MEMS/Nanomaterials-based prosthetics</td>
<td>Artificial organs</td>
</tr>
<tr>
<td>Artificial surfaces—regulated</td>
<td>Sensory aids (artificial retina, etc.)</td>
<td>Nanobiotechnology</td>
</tr>
<tr>
<td>Biocompatible surfaces</td>
<td>Microarrays</td>
<td>Birobotics and biobots</td>
</tr>
<tr>
<td>Biofilm suppression</td>
<td>Microcantilever-based sensors</td>
<td>Nanorobotics</td>
</tr>
<tr>
<td>Engineered surfaces</td>
<td>Microfluidics</td>
<td>DNA-based devices and nanorobots</td>
</tr>
<tr>
<td>Pattern surfaces (contact guidance)</td>
<td>Microneedles</td>
<td>Diamond-based nanorobots</td>
</tr>
<tr>
<td>Thin-film coatings</td>
<td>Medical MEMS</td>
<td>Cell repair devices</td>
</tr>
<tr>
<td>Nanopores</td>
<td>MEMS</td>
<td></td>
</tr>
</tbody>
</table>
The chemists also have something to say.
1. A hormone binds to the receptor.

2. The receptor alters shape. Inside the cell, the G-protein binds and is activated.

3. Activated G-protein breaks apart. The free α-subunit will trigger a chain of reactions that alters the cell’s metabolism.

4. A new G-protein binds. The receptor can activate hundreds of G-proteins before the hormone on the outside detaches.

Figure 2. When a hormone, olfactory molecule or a taste molecule couples with a receptor on the cell surface, a chain of reactions inside the cell is triggered.
What about theory?

One dream for the future:

Set up and solve the $N$ coupled equations for the most relevant $dx_k/dt$, where $x_k$ is the concentration of a specific biochemical molecule in a specific region, and $dx_k/dt$ is its rate of change.

But large-scale quantitative simulations will be an enormous task for a world-wide community, with $N \sim 100, 1000, \text{or much more}$ for significant problems, even after they are drastically reduced with maximum cleverness.

The hardest part will be getting reliable parameters, such as reaction rates.

Note that the pathways for various processes and diseases (e.g. cancers, heart diseases, and diabetes) are sure to be rather strongly coupled.
The principal paradigm of how to simplify the equations: Michaelis–Menten kinetics (1913)

\[ E + S \xrightleftharpoons[ k_r ]{ k_f } ES \xrightarrow{ k_{\text{cat}} } E + P \]

The enzyme E catalyzes the reaction to substrate product P, and the reaction rate increases with substrate concentration S.

German biochemist Leonor Michaelis  
Canadian physician Maud Menten

from http://en.wikipedia.org/wiki/Michaelis–Menten_kinetics

But the coupled equations for all relevant pathways are still enormously complicated, even at this “mesoscopic” level.
Every cell is complicated, and miraculous in its performance.
Your body has trillions of cells, of many different kinds in many different organs, each performing incredibly sophisticated functions on short time and length scales.

from http://emedtravel.wordpress.com/2012/06/25/how-neurons-pass-signals-through-the-nervous-system/

from http://www.3dscience.com/Resources/3d_Human_Anatomy.php
The most simplistic view: Signaling molecules trigger a change in gene expression, so that proteins are ultimately produced. But the reality is vastly more complex.
Signaling transcription (in nucleus) ➔ translation (in cytoplasm) ➔ functioning protein

-- extremely complicated!

from http://ebbailey.wordpress.com/general-information/dna-to-protein/
The genome is beautifully structured but amazingly complex.
Each protein can be very complicated.

http://en.wikipedia.org/wiki/Histone

a core histone:
Protein H2AFJ PDB
DNA replication is different, but related to DNA ➔ RNA ➔ protein.

from http://serc.carleton.edu/microbelife/research_methods/genomics/transcrip.html
The proteins have to fold into their native states.
Amyloids, insoluble fibrous protein aggregates, arise from at least 18 inappropriately folded versions of proteins and polypeptides.

Diseases featuring amyloids:

- Alzheimer's disease
- Parkinson's disease
- Huntington's Disease
- Rheumatoid arthritis
- Type 2 diabetes
- Atherosclerosis
- Bovine spongiform encephalopathy
- Medullary carcinoma of the thyroid
- Cardiac arrhythmias, Isolated atrial amyloidosis
- Aortic medial amyloid
- Prolactinomas
- Familial amyloid polyneuropathy
- Several forms of amyloidosis
- Lattice corneal dystrophy
- Cerebral amyloid angiopathy
- Dialysis related amyloidosis
- Finnish amyloidosis
- Systemic AL amyloidosis
- Sporadic Inclusion Body Myositis

from http://en.wikipedia.org/wiki/Amyloid
from http://sierram.web.unc.edu/
ALS heroes

from http://www.lougehrig.com/

from http://www.pbs.org/

MS heroes

from www.wellsphere.com

from http://www.thefind.com/gifts/

Annette Funicello

http://multiplesclerosis-relief.com/

Structure of GNNQQNY. Carbon atoms are colored in purple or grey/white, oxygen in red, and nitrogen in blue.

“We selected the yeast protein Sup35 for X-ray diffraction analysis.”

“Its fibril-forming tendency had been traced to the N-terminus of the prion-determining domain, and from this region we isolated a 7-residue, fibril-forming segment with sequence GNNQQNY.”

Example of theory: a molecular dynamics simulation

Levels of theory:

“microscopic” – e.g., quantum chemistry and molecular dynamics simulations

“mesoscopic” – e.g., modeling of molecular pathways in cell

“macroscopic” – e.g., modeling of processes in whole body

“formal” – e.g., searching for new principles (often without much success)

We have developed a general method for calculating the biochemical response to medications or other medical interventions, and applied it in trying to understand a scientific mystery:

Why do people usually show immediate remission of type 2 diabetes when they have bariatric surgery, in which food bypasses most of the stomach and small intestine?

With understanding, perhaps the surgery can be replaced with pharmaceuticals.
We constructed and solved a simple macroscopic model for the effect of bariatric surgery on type 2 diabetes.

Consequences of type 2 diabetes:

Diabetes is responsible for more than half of lower limb amputations performed in the U.S. Diabetes is the leading cause of new cases of blindness in adults age 20 – 74. Risk of heart disease and stroke, nerve damage, vascular injuries, kidney failure. Increased risk for hearing loss, dementia, respiratory and urinary tract infections, colorectal cancer, uterine cancer, periodontal disease, nonalcoholic fatty liver disease.
insulin → glucose enters cell

Normal absorption of glucose by muscle and fat cells requires insulin.

exercise → glucose enters cell

Glucose absorption in muscle cells due to exercise is insulin-independent.

from http://diabetesmanager.pbworks.com/w/page/17680187/Exercise and the Regulation of Blood Glucose
Two tests of the hypothesis that an increase in incretin concentration alone can explain the fall in glucose level and insulin resistance immediately after surgery. The three lower curves show the scaled glucose concentration as a function of the factor $r$ by which incretins are increased. (Observed values of $r$ range from 1 to 5, with a clustering below 2.) They correspond to three assumptions regarding the incretin contribution to insulin production: 50% for the top curve, 67% for the middle curve, and 100% for the bottom curve. Even in the most favorable scenarios, the decrease is insufficient to explain all the observations. The horizontal line at the top is the scaled insulin resistance $= \text{glucose} \times \text{insulin}$ for all scenarios -- i.e., for all values of $r$ and all percentages for the incretin contribution. As found above, it is constant. In other words, the incretin mechanism alone predicts no decrease whatsoever in insulin resistance. The observations, on the other hand, show a substantial drop in insulin resistance soon after surgery.

The most popular hypothesis is that bariatric surgery causes an increase in incretins -- biochemicals that combine with glucose to stimulate insulin production.

Then more insulin would cause a faster absorption of glucose by the cells.

This is a 2\textsuperscript{nd} order process, since the glucose must be absorbed twice: by the pancreas to stimulate insulin production, and again by the cells.
We propose that the bariatric surgery also causes production of some substance which opens an alternative insulin-independent pathway for glucose absorption.

This is a 1st order process, since it is insulin independent.

The drop in glucose level is therefore much larger, and there is now the same drop in insulin resistance, in agreement with the observations.

Glucose concentration as a function of the increase $r$ in a substance which opens an alternative insulin-independent pathway for glucose absorption. The top and middle curves are respectively for $c_a = 1$ and 2, where $c_a$ is the strength of this alternative pathway relative to the normal insulin-dependent pathway in a patient with strong insulin resistance. The bottom curve represents the limit of extreme insulin resistance. The scaled insulin resistance is given by exactly these same curves, since the insulin level is constant in this case. If the present mechanism and that of the preceding figure are both operative, there is, of course, an even larger drop in glucose level, and also a substantial drop in insulin resistance.
We have addressed the amazing fact that remission of type 2 diabetes is usually achieved immediately after bariatric surgery, long before any appreciable weight loss.

This result is ordinarily attributed to a dramatic increase in incretins, but our model indicates that this mechanism alone is not sufficient to explain the largest declines in glucose levels or measured values of insulin resistance.

The most robust additional mechanism would be production of a substance which opens an insulin-independent pathway for glucose transport into cells, analogous to the established insulin-independent pathway associated with exercise.

If such a substance could be identified, it might be possible to replace the surgery by medication.

These ideas and results were also presented in talks by Jia Ng and Roberto Ortiz at the Fall 2012 meeting of the Texas Section of the American Physical Society.

Other collaborators: At Texas A&M, Tyler Hughes; at TAMU Qatar, Michel Abou Ghantous and Othmane Bouhal; at Qatar Biomedical Research Institute, Philippe Froguel and Abdelilah Arredouani.
Life in the Higgs condensate, where electrons have mass!

Note: If the electron had no mass, there would be no atoms and no us. So we need the Higgs condensate!

The Higgs boson, field, and condensate – but should it be called the *London mechanism* for giving mass to fundamental particles, after Fritz and Heinz London?

In 1935, they effectively showed that the photon – the particle of light – has a mass in a superconductor.

The magnetic field falls to zero in a superconductor for the same basic reason that the weak nuclear force has a very short range: the force-carrying particle has a mass.
The Higgs condensate is responsible for the masses of both
(1) the W and Z particles which carry the weak nuclear force
(responsible for radioactive beta decay) and
(2) fermions like electrons, but in different ways.

W and Z particles ↔ photon in superconductor, for which

mass \propto \frac{1}{\lambda}, \quad \lambda = \text{penetration depth for magnetic field}

fermions like electrons:

mass \propto \text{coupling to Higgs field} ↔ \text{coupling to field of snow}

zero or small coupling to Higgs field, as for neutrino: sliding across snow on skis
moderate coupling to Higgs field, as for electron: walking atop snow with snowshoes
large coupling to Higgs field, as for top quark: plodding through snow wearing boots
Which theorists deserve the Nobel Prize? The Swedish Academy will decide!

We have to use some terminology, and the following seems fair:
London-Anderson-Englert-Brout-Higgs-Guralnik-Hagen-Kibble
(LAEBHGHK) mechanism
but Higgs boson

Phil Anderson (1963) – mechanism
Robert Brout and Francois Englert (August 1964) – mechanism
Peter Higgs (October 1964) – mechanism and boson [with more discussion of boson later]
Gerald Guralnik, Dick Hagen, and Tom Kibble (November 1964) – mechanism

Higgs field ↔ field of snow
⇒ discovering Higgs boson ↔ freeing a snowflake

When you walk across a room, you are walking through an incredibly massive condensate.
The mass of your electrons (and quarks) results from this condensate.

However, about 99% of the mass of your body results from \( E=mc^2 \), as the quarks
and gluons whiz around relativistically inside your protons and neutrons.
From *More and Different, notes from a thoughtful curmudgeon*:

In 1962 I set out to make my gauge symmetry ideas into a relativistic field theory, and wrote a brief article … which caught the eye of Peter Higgs, who translated it into more acceptable “particlese” and thereby became famous.

To calibrate this statement, you will have to evaluate the modesty of the author, by reading the rest of this fascinating book!
what we now know!

12 spin \( \frac{1}{2} \) fermions
4 types of spin 1 bosons
and now the spin 0 Higgs boson

But the Higgs discovery appears to require new physics, most likely supersymmetry, for consistency.

Without protection from new physics, virtual processes should drive the mass of the Higgs up to an enormous (ridiculous) energy scale.
Direct evidence for susy: coupling constants of the 3 fundamental forces are unified at the natural energy scale for grand unification. Without susy, the 3 curves fail to intersect at a common point, so no unification.
Why do we need grand unification?

Because another rather recent discovery – neutrino masses – appears to require it.

The neutrino mass requires one of two extensions, either of which upsets the delicate requirements for the Standard Model to be mathematically consistent:

For a *Dirac* mass, an extra field has to be added for each generation of fermions. For a *Majorana* mass, lepton number conservation has to be broken.

But both are natural with grand unification.

So now the electron has a mass.
And the weak nuclear is very short range because the force-carrying particles have very large masses.
All this because the Higgs field condensed as the universe cooled after the Big Bang.
The Higgs seems to point toward supersymmetry.


Neutrino masses seem to point toward grand unification of forces, with symmetry-breaking as the universe cooled after the Big Bang.

E.g., $SO(10) \rightarrow SU(5) \times U(1) \rightarrow SU(3)_C \times SU(2)_L \times U(1)_Y$.
Blue: matter (ordinary and dark) mapped by gravitational lensing
Red: hot gas, representing ordinary matter

The clear separation of dark matter and gas clouds is considered direct evidence that dark matter exists.

A beautiful theory, a great experiment, and a landmark in human intellectual history, as the internet clearly reveals.