Electrobiology and Electronics: Converging Disciplines

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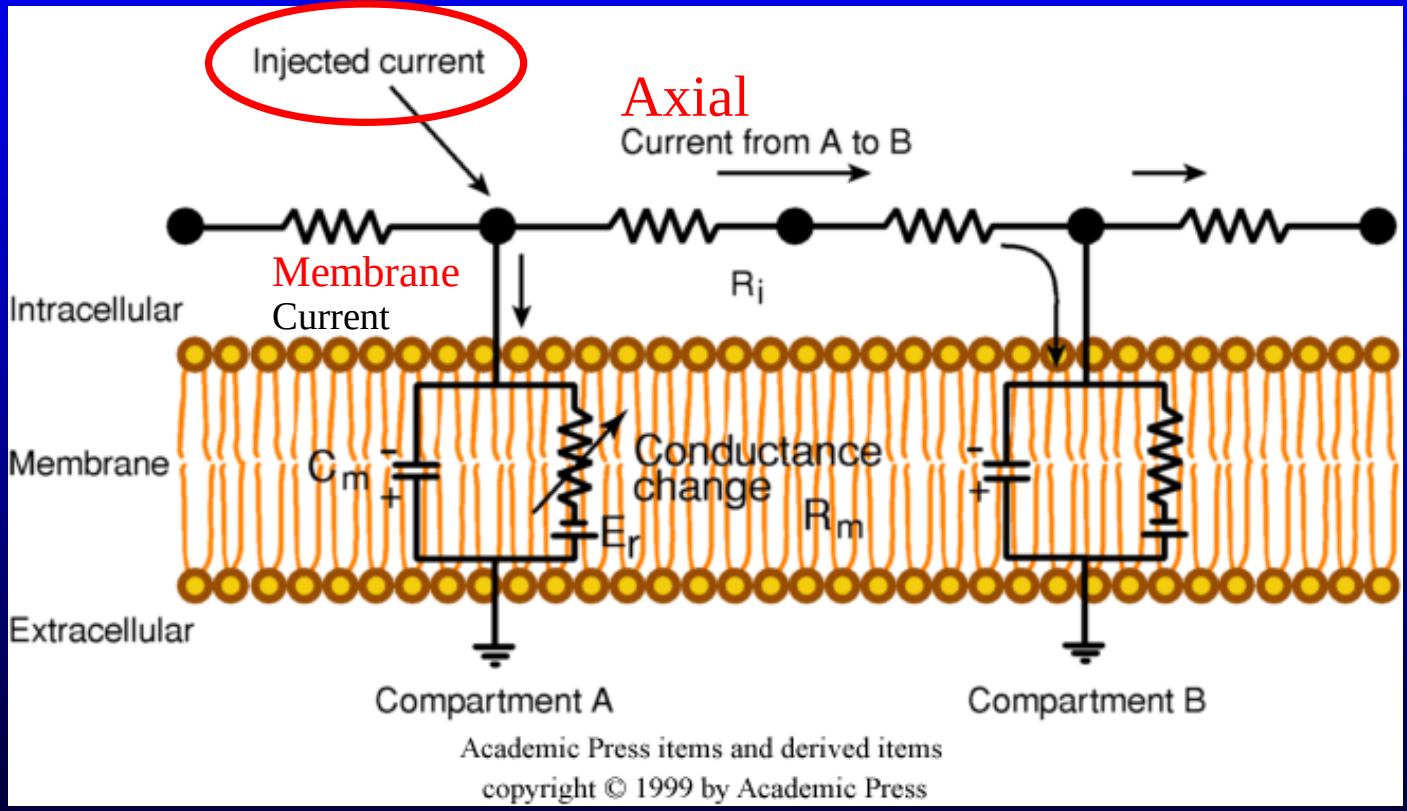
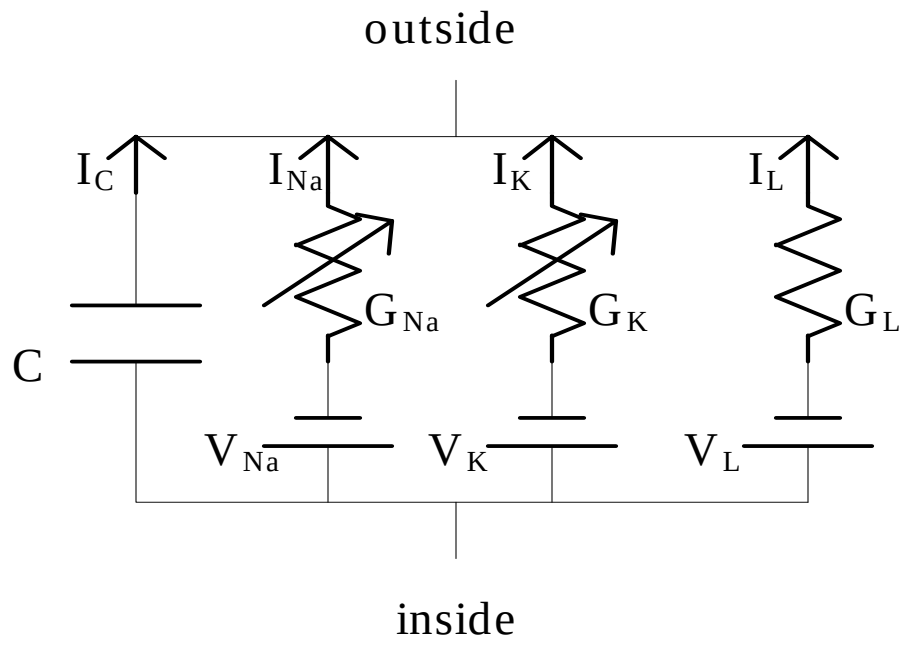
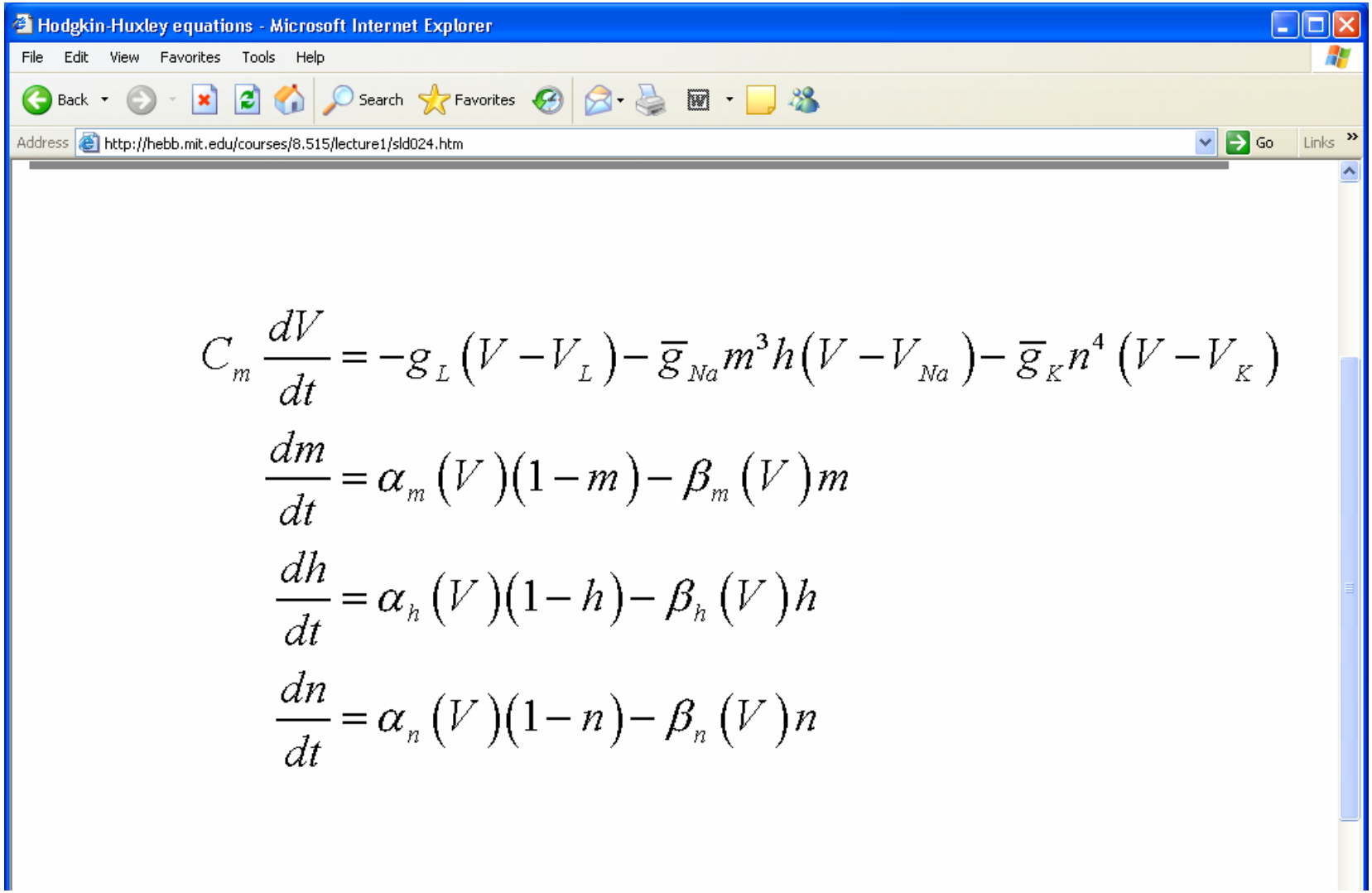
Transient Signals - Two Segments





A patch of nerve membrane as described by Hodgkin and Huxley in 1952. The capacitance of the membrane is C, the V's are the reversal potential for ion-selective conductances, and the G's are the conductances

The Hodgkin-Huxley equations for the voltage-dependent variation of specific ionic conductances that underly electrical



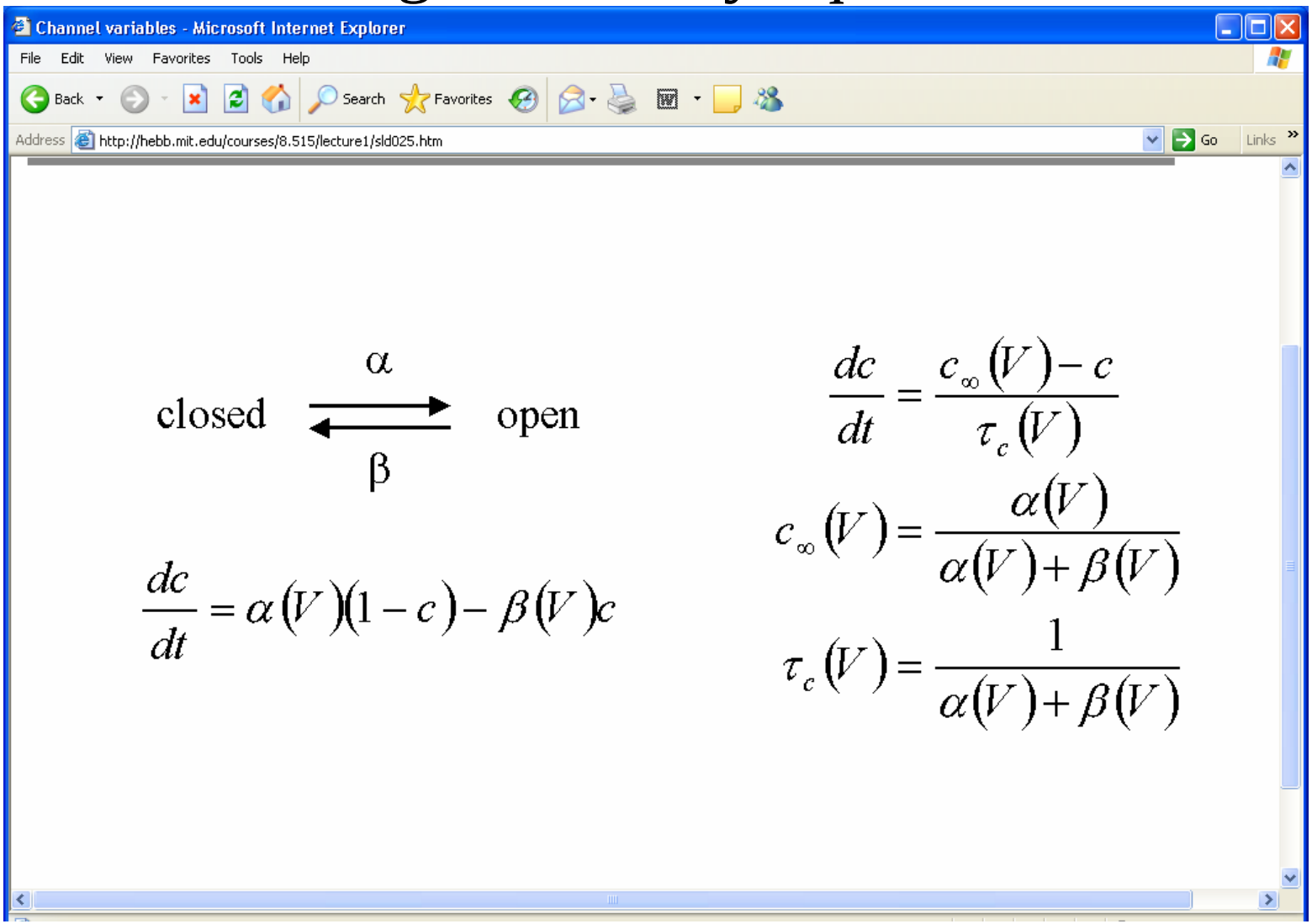
$$C_m \frac{dV}{dt} = -g_L (V - V_L) - \overline{g}_{Na} m^3 h (V - V_{Na}) - \overline{g}_K n^4 (V - V_K)$$

$$\frac{dm}{dt} = \alpha_m (V)(1 - m) - \beta_m (V) m$$

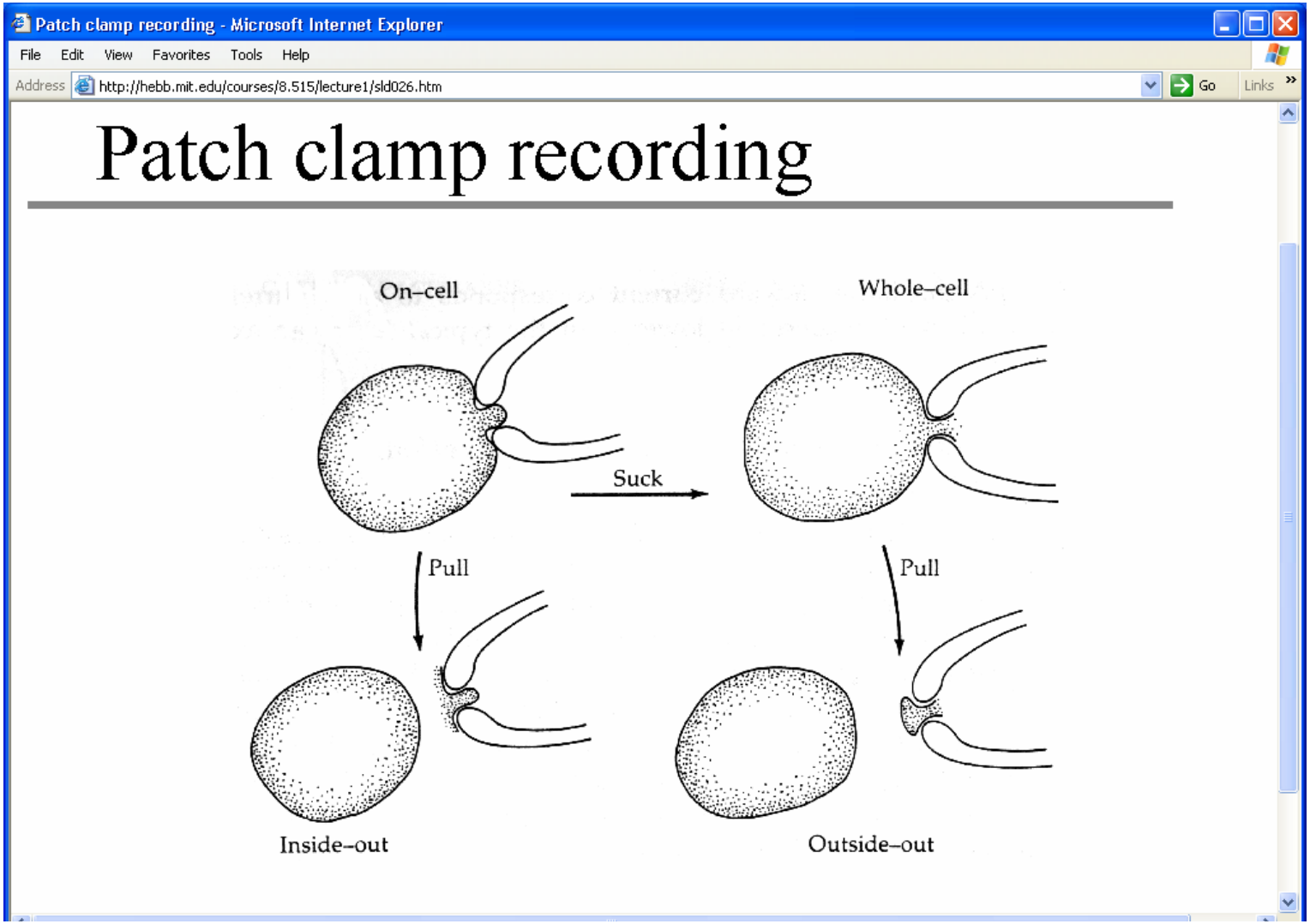
$$\frac{dh}{dt} = \alpha_h (V)(1 - h) - \beta_h (V) h$$

$$\frac{dn}{dt} = \alpha_n (V)(1 - n) - \beta_n (V) n$$

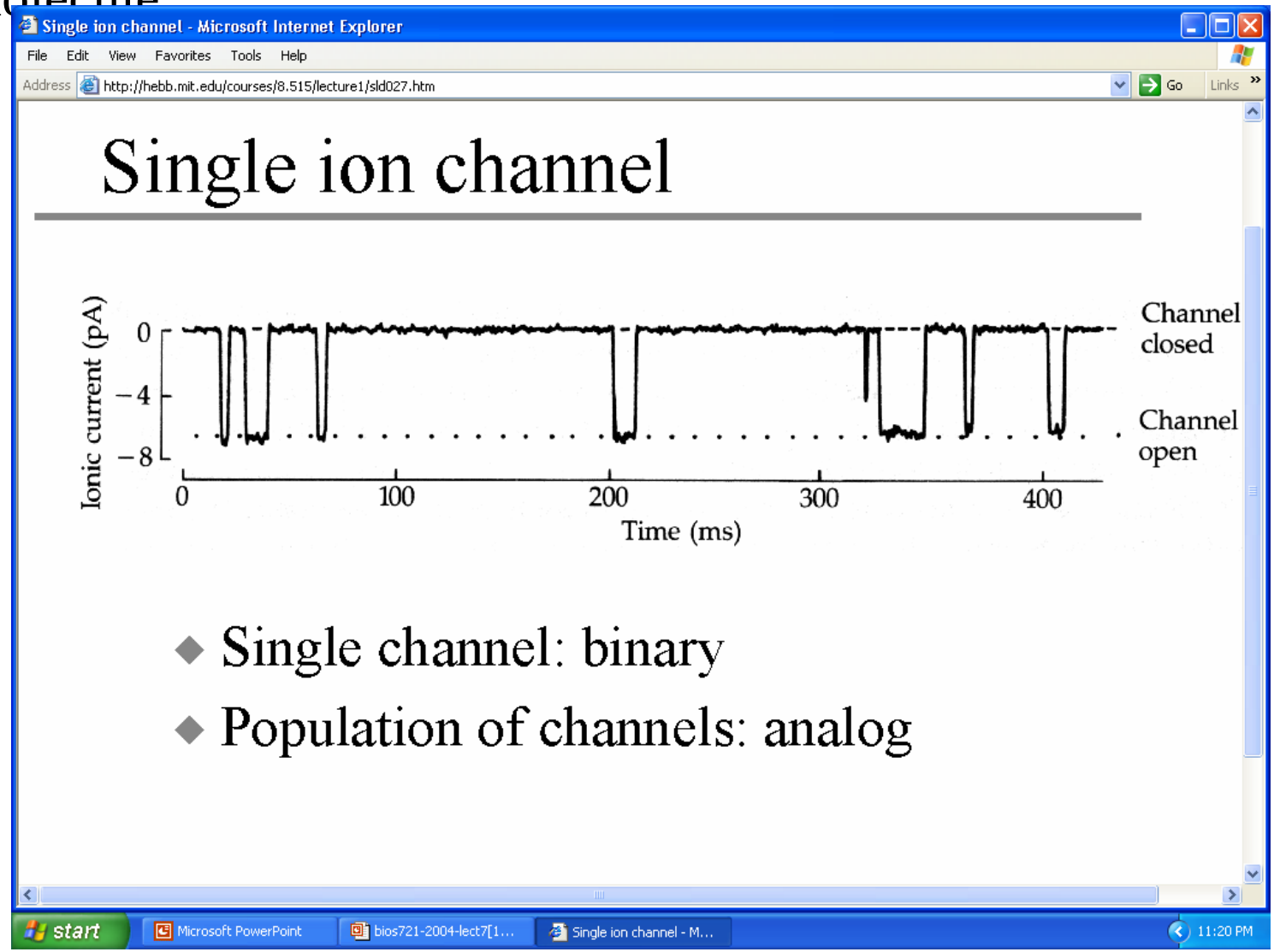
Kinetic Interpretation of the gating in the Hodgkin-Huxley equations



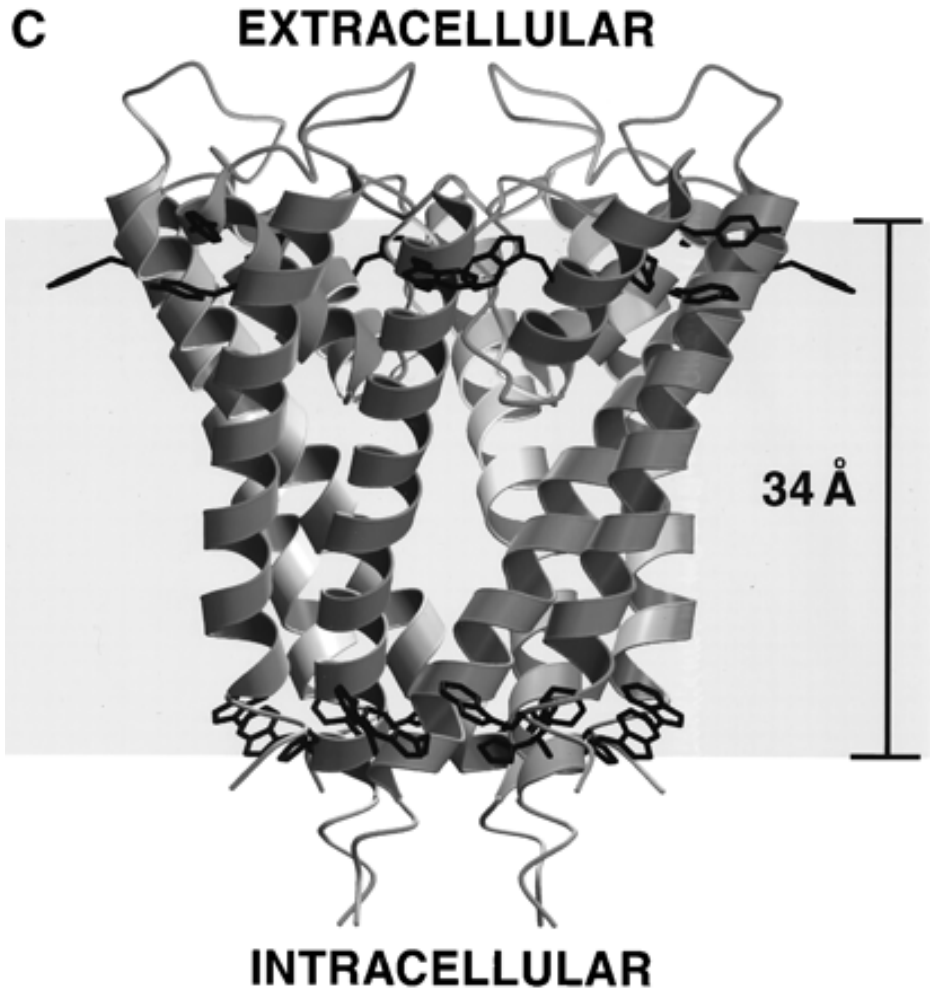
Fast forward to 1976—Neher and Sakmann invent the patch clamp



The patch clamp records permit us to see single channels opening and closing—functional properties of a single protein molecule



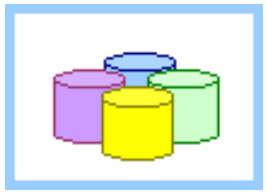
Fast forward to 1998—The structure of the permeation pathway of the potassium channel.

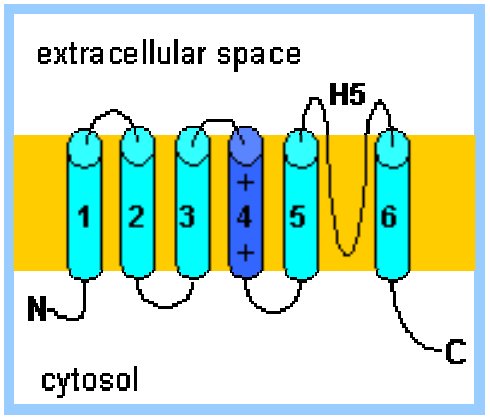


So, in three Nobel Prize efforts, spaced about ¼ century apart:

- Hodgkin and Huxley quantitatively describe the excitable membrane as an equivalent electrical circuit with properties governed by electric-field dependent kinetics (1952)
- Neher and Sakmann make it possible to study the function of individual protein channels, the emf's and the resistors (1976)
- Mackinnon lab solves the structure of the permeation pathway of the channel (1998) [In 2003, the Mackinnon lab obtains a structure for the channel including the voltage sensor, but the structure is controversial.]

We now know there is a common molecular topology for the voltage-gated ion channels: 4 domains, 6 transmembrane segments for each domain, selectivity filter between the 5th and 6th TM segment, charged residues for the voltage sensor in the 4th TM segment. In H-H terms, the emf is in H5, the activation (m) gate sensor is in S4, and it effects opening by moving the intracellular ends of the 6th TM, and inactivation (h) is by an inactivation "ball" at the N terminus of the domain.





So….H-H variables are now neatly mapped on to the channel molecule, except……

The properties are not quite as localized as I said; that is, mutations in the permeation pathway can modify gating properties, mutations outside the permeation pathway can modify conductance, etc. A single mutation can modify more than one of the H-H model parameters.

The protein is only approximately modular.

A difference between design by humans and
design by biology:

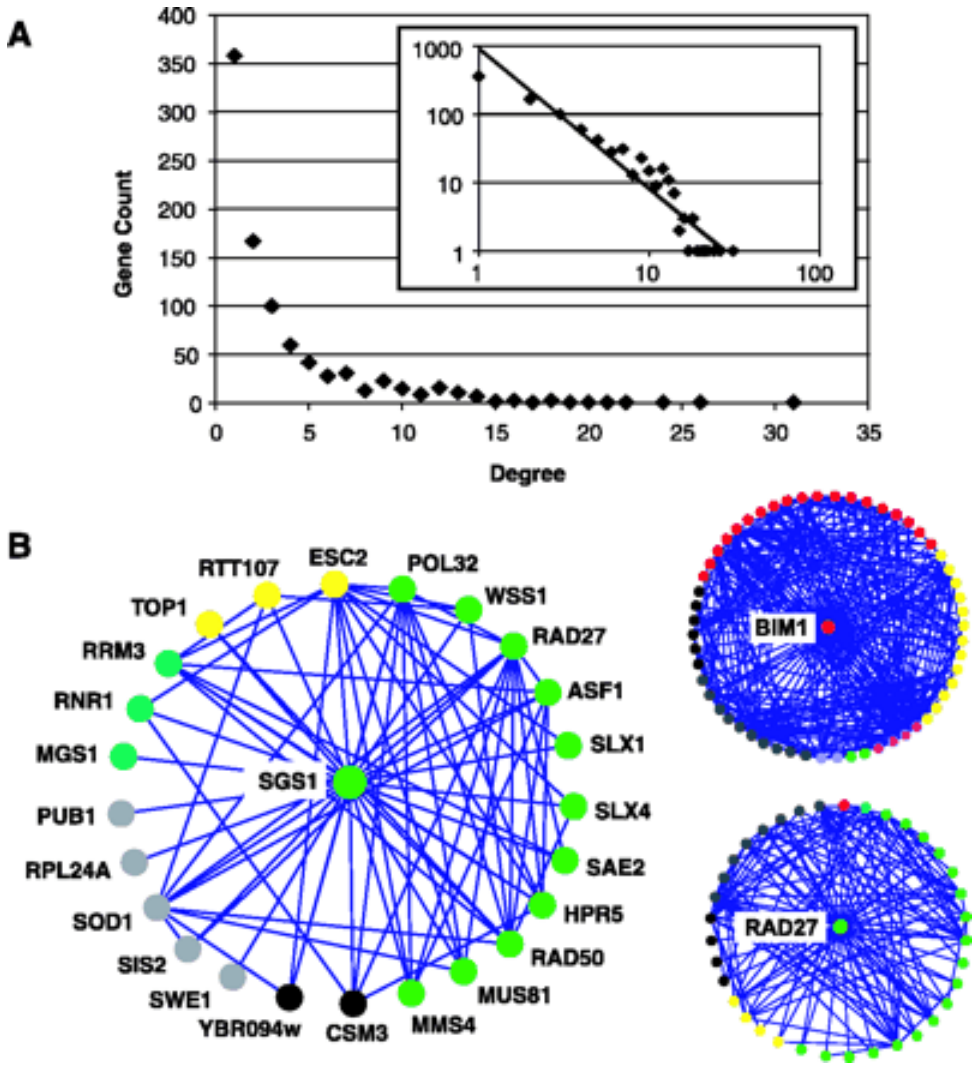
Human-designed systems tend to be modular—the parts in one subsystem are different from the parts in another subsystem.

Biological systems are semi-modular: Their function can usefully be analyzed as consisting of specialized subsystems, but the subsystems share parts. This is true at all levels of organization, from molecules to ecosystems.

The corollary to semi-modularity of biological systems: Assignment of function is meaningful only in context.

Voltage-gated potassium channels, for example, are critical for both electrical signaling and osmoregulation.

More generally (from Tong et al, Global mapping of the yeast genetic interaction network, *Science*, *2-6-04*…)

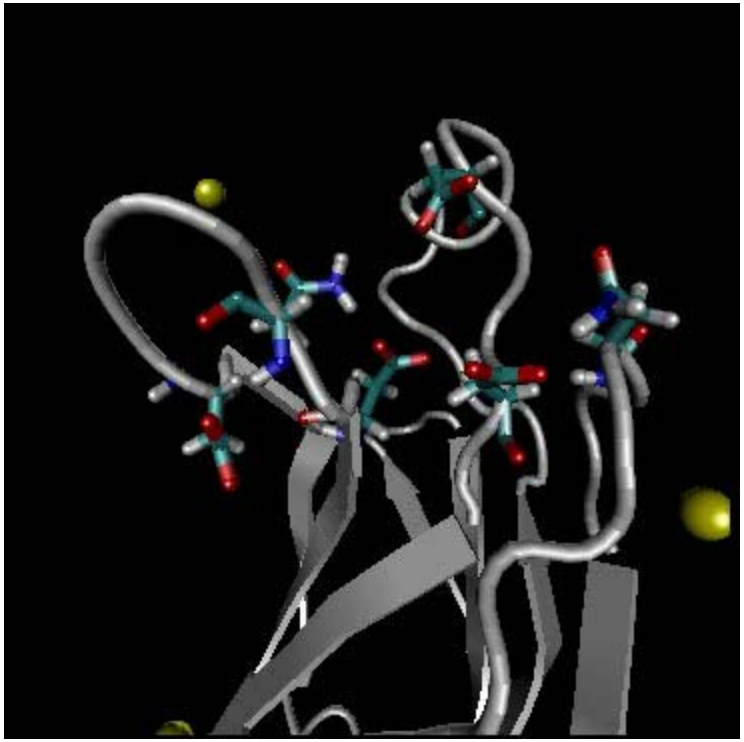


Possible relevance to biomimetic nanodesign

- Biological design is guided by some optimizing principles that we do not yet understand clearly.
- While we certainly want to understand biological design, and want to use some of its principles, we don’t want to emulate it completely.

Specific nanodesign thoughts: Consider the Fokker-Planck equation: First term on the rhs is deterministic and irreversible, second term is stochastic and reversible. For macrosystems, first term dominates, for nanosystems, the second term dominates.

$$d\mathbf{x}_t = \mathbf{f}(\mathbf{x}_t, t)dt + g(\mathbf{x}_t, t)d\mathbf{w}_t$$



For Nanoscientists Looking at the NIH for support I: General Issues

- First Principle: NIH is a mission-driven agency. We support basic science (lots of it) and technology and infrastructure development (on an increasing trend line), but it all must be justifiable by a payoff down the line in improving the health of the American people.
- Corollary Principle: We understand that the payoff may not be immediate, so we support work where the payoff is a decade or more in the future. It is better to present an justification for a reasonable but long-term payoff than an unrealistic short-term payoff.

For Engineers, Physical Scientists, and Computational Scientists Looking at the NIH for support II: Perspectives on the Role of Engineering and Physical Science in Biomedical Research and Health Care Delivery

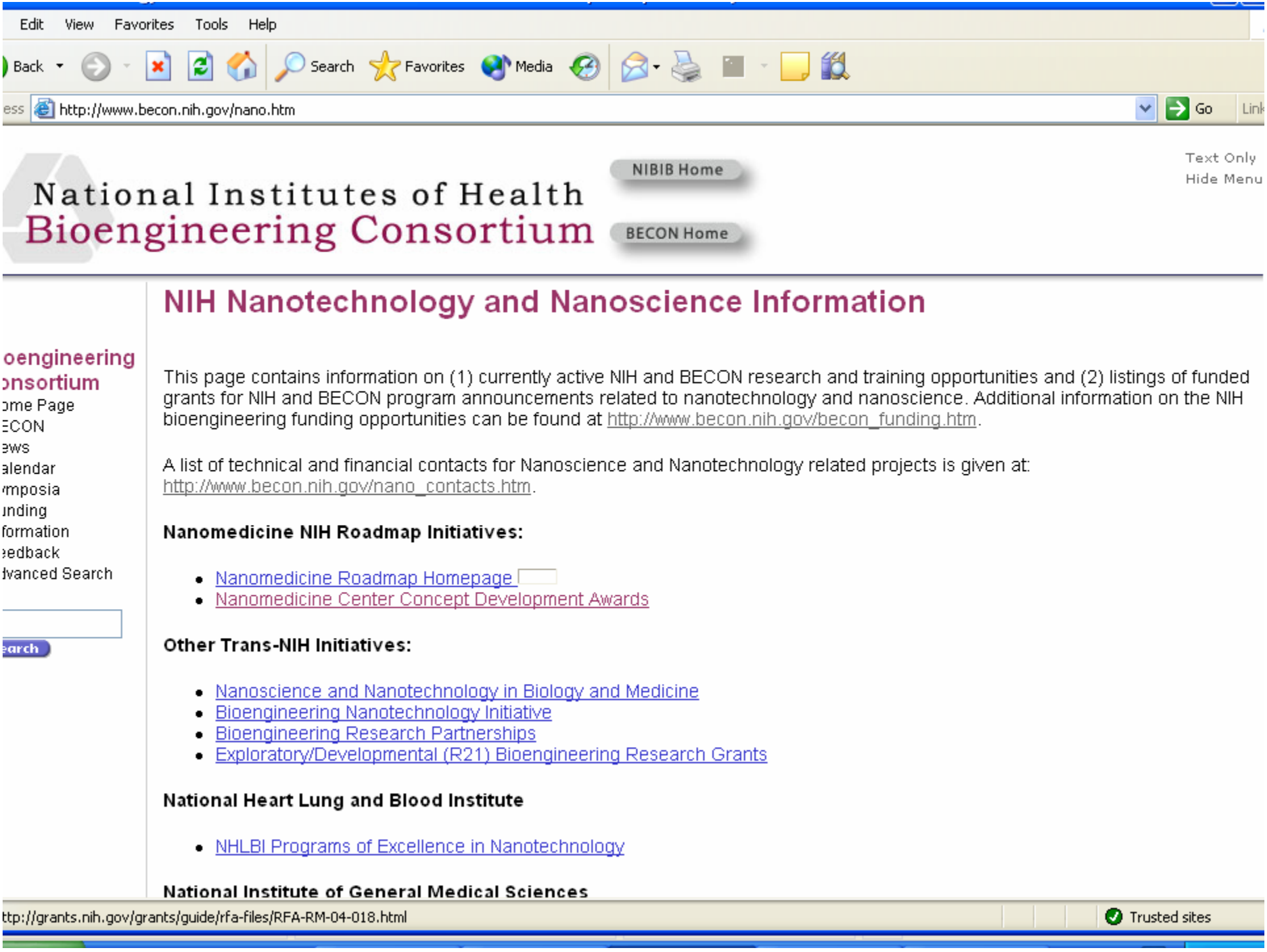
- We see that in the 20th Century, molecular biology became a branch of applied physics, in the sense that every page of any molecular biology text has information that could not have been obtained or even imagined with the knowledge of physics that pertained at the beginning of the 20th Century. Recent advances have also required significant computation.
- The corollary is that engineering based on physical science coupled with appropriate computation is critical to every aspect of our mission, from the most basic research to the efficient and effective delivery of health care in all venues.
- We need engineers, physical scientists, computer scientists, and computational scientists to be partners with NIH in determining what quantitative science we should support to move our mission forward.

For Quantitative Scientists Looking at the NIH for support III: Finding out what NIH actually funds

- CRISP data base (Google “NIH CRISP” provides keyword-searchable database of all NIH-funded projects from 1972-2004
- Comprehensive access to publications by NIH grantees provided by author-searchable Pubmed literature database (Google “pubmed”)

For Quantitative Scientists and Engineers Looking at the NIH for support IV: Building on your knowledge of what we now do to what we might support you for doing

- First-stop (but not “one stop”) information source is the BECON web site (Google “NIH BECON”), button under “Funding”. For primarily computational work, also check the BISTI home page (Google “NIH BISTI”), again look under “Funding”.
- If you don’t find a funding announcement that fits your ideas/capabilities, but you feel you have something to contribute, don’t hesitate to send an unsolicited application. (Receipt dates February 1, June 1, and October 1 each year for new applications). Success rates for unsolicited applications are often as good as, in some cases better than, success rates for proposals submitted in response to specific funding announcements.
- Consult with an NIH Program Director at the concept development stage. This is easy if you are responding to a funding announcement—the right contact information is in the funding announcement. For an unsolicited application, you may need to browse through Web sites for many of the semi-autonomous 27 Institutes and Centers that comprise the NIH, as well as the NIH Roadmap site, that contains information on NIH-wide initiatives. But---NIH is a strongly interconnected community, so if you start calling program staff and the first person you call is not the right person, you will get good direction to the right person fairly quickly.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NIH Nanotechnology and Nanoscience Information
This page contains information on (1) currently active NIH and BECON research and training opportunities and (2) listings of funded grants for NIH and BECON program announcements related to nanotechnology and nanoscience. Additional information on the NIH bioengineering funding opportunities can be found at http://www.becon.nih.gov/becon_funding.htm.
A list of technical and financial contacts for Nanoscience and Nanotechnology related projects is given at: http://www.becon.nih.gov/nano_contacts.htm.
Nanomedicine NIH Roadmap Initiatives:
Nanomedicine Roadmap Homepage
Nanomedicine Center Concept Development Awards
Other Trans-NIH Initiatives:
Nanoscience and Nanotechnology in Biology and Medicine
Bioengineering Nanotechnology Initiative
Bioengineering Research Partnerships
Exploratory/Developmental (R21) Bioengineering Research Grants
National Heart Lung and Blood Institute
NHLBI Programs of Excellence in Nanotechnology
National Institute of General Medical Sciences
ttp://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-018.html
Trusted sites

For Quantitative Scientists Looking at the NIH for support IV: Building on your knowledge of what we now do to what we might support you for doing (continued)

- Research study sections as well as programs (Google NIH CSR), button under “Study Section Information.”
- On study section targeting, consult with Program Director and/or Scientific Review Administrator (Understand that program and review functions at NIH collaborate with each other but are independently accountable. This is different from NSF, where the same individuals are responsible for both creating program and overseeing review. With respect to NIH review issues, the AUTHORITATIVE information comes from the review side)
- FOLLOW THE RULES AND GUIDELINES! (Google “NIH 398” in addition to particular funding announcements.) That gives program and review staff more time to deal with your scientifically substantive concerns, because they won’t have to work around emergent procedural issues.

For Quantitative Scientists Looking at the NIH for support IV: Building on your knowledge of what we now do to what we might support you for doing (final)

- Develop an NIH “grant journal club” (or comparable structure) at your institution where colleagues read and critique each other’s NIH grant applications and progress reports in preparation.