Biomedical AI:
Its Roots, Evolution, and Early Days at Stanford

Edward H. Shortliffe, MD, PhD
Chair Emeritus and Adjunct Professor
Department of Biomedical Informatics
Columbia University

Department of Biomedical Data Science Seminar
Stanford Medicine
Stanford, California
2:30pm – 4:50pm – February 4, 2021

Seinfeld’s recent comments on Zoom....

Energy, attitude and personality cannot be “remoted” through even the best fiber optic lines

Jerry Seinfeld: So You Think New York Is ‘Dead’ (It’s not.)
Aug. 24, 2020
Disclosures

- No conflicts of interest with content of presentation
- Offering a historical perspective on medical AI, with an emphasis on US activities in the early days and specific work I know personally
- My research career was intense until I became a medical school dean in 2007
- Current research involvement is largely as a textbook author and two decades as editor-in-chief of a peer-reviewed journal (Journal of Biomedical Informatics [Elsevier])

Goals for Today’s Presentation

- Show that today’s state of the art in medical AI is part of a 50-year scientific trajectory that is still evolving
- Provide some advice to today’s biomedical AI researchers, drawing on that experience
- Summarize where we are today in the evolution, with suggestions for future emphasis

More details on slides than I can include in talk itself – Full deck available after the talk
Origins of AI

• Term “artificial intelligence” coined by John McCarthy at a Dartmouth conference in 1956
• Then a professor at MIT, McCarthy later moved to Stanford where he served on the faculty until his retirement
• Turing never actually used the AI term

Origins of Machine Learning ~1959

• Arthur Samuel (IBM Research)
• Sought to program a computer to play checkers but discovered the limits of his own expertise
• Encoded the rules but then had the program learn strategy by playing lots of games
• Ultimately had two versions of the program play one another
• Program became unbeatable, even by experts at the game
Key AI Leaders in the 1960s (CMU, MIT, Stanford)

Herb Simon  Allen Newell  Marvin Minsky  John McCarthy

1960’s-70’s

- Substantial AI work on problems familiar to us today:
  - Machine learning, neural networks
  - Natural language processing
  - Speech understanding
  - Simulation of human problem solving
- Emergence of applications of artificial intelligence in medicine (knowledge-based systems)
The Physician as Decision Maker

1950’s

• Earliest formal recognition of statistical issues in diagnosis and the potential role of computers
• Earliest formal recognition of statistical issues in diagnosis and the potential role of computers

Reasoning Foundations of Medical Diagnosis

Symbolic logic, probability, and value theory aid our understanding of how physicians reason.

Robert S. Ledley and Lee B. Lusted

Early AI and Biomedicine – The Dendral Project (late 1960s)

Joshua Lederberg
Carl Djerassi
Ed Feigenbaum
Bruce Buchanan
Early AI and Biomedicine – The Dendral Project (late 1960s)

- Studied hypothesis formation and discovery in science
- Helped organic chemists to identify unknown organic molecules by analyzing their mass spectra
- Used encoded knowledge of chemistry
- Meta-Dendral: machine learning system to propose a set of rules for mass spectrometry interpretation from examples

Edward Feigenbaum – “Knowledge is Power”

“The key empirical result of DENDRAL experiments became known as the knowledge-is-power hypothesis (later called the Knowledge Principle), stating that knowledge of the specific task domain in which the program is to do its problem solving was more important as a source of power for competent problem solving than the reasoning method employed.”


- Stanford University Medical Experimental Computer for Artificial Intelligence in Medicine – global users
- Funded by NIH (Division of Research Resources) and later by the National Library of Medicine
- First non-DOD computer on the ARPAnet
- AIM Workshops in early years
- PIs over the years: Josh Lederberg, Ed Feigenbaum, Stan Cohen, Ted Shortliffe

Example Medical AI Programs from 1970s

- Internist-1 / QMR
  Task: Diagnosis in internal medicine and neurology

- CASNET
  Task: Diagnosis and explanation using causal networks for ophthalmic physiology (glaucoma)

- The MYCIN System
  Task: Advise clinicians on the selection of antimicrobial regimens in critical settings (especially before culture results)

- Approaches/methods broadly adopted outside of medicine
Internist-1 – Pople and Myers (Univ of Pittsburgh)


CASNET – Kulikowski and Amarel (Rutgers Univ.)

The MYCIN Project (1972-1979)

- My doctoral dissertation work (completed 1976) while I was an MD/PhD student at Stanford Medical School
- Dissertation advisor: Stanley N. Cohen, MD
- Principal mentor and collaborator: Bruce G. Buchanan

MYCIN: An Overview

- Clinical Information Provided by the Clinician
- Ongoing Record of the Current Consultation
- Consultation System
- Explanation System
- Corpus of Decision Rules
- Rule-Acquisition System for use by Experts
<table>
<thead>
<tr>
<th>Sample MYCIN Rule</th>
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<tbody>
<tr>
<td>PREMISE: ($AND (SAME CNTXT GRAM GRAMPOS) (SAME CNTXT MORPH COCCUS) (SAME CNTXT CONFORM CLUMPS)) ACTION: (CONCLUDE CNTXT IDENT STAPHYLOCOCCUS TALLY 700)</td>
</tr>
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or (translated into English):

IF: 1) The gramstain of the organism is grampos  
2) The morphology of the organism is coccus  
3) The growth conformation of the organism is clumps  

THEN: There is suggestive evidence (.7) that the identity of the organism is staphylococcus.

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<table>
<thead>
<tr>
<th>Dissertation Revised and Published as Book</th>
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| • American Elsevier 1976  
• Now out of print, but entire volume available for download on my web site at http://shortliffe.net |
A Common Perspective at the Time

Prevailing Frequent Assertion: Clinicians will use AI systems if the programs can be shown to function at the level of experts

JAMA 242:1279-82 (1979)

Antimicrobial Selection by a Computer

A Blinded Evaluation by Infectious Diseases Experts

Victor L. Yu, MD; Lawrence M. Fagan; Sharon M. Wraith; William J. Glancey; A. Carlisle Scott, MS; John Hannigan, MS; Robert L. Blum, MD; Bruce G. Buchanan, PhD; Stanley N. Cohan, MD

- An evaluation of a computer-based consultation system called MYCIN was made. Eight independent evaluators with special expertise in the management of meningitis compared MYCIN’s choice of antimicrobials with the choices of nine human prescribers for ten test cases of meningitis. MYCIN received an acceptability rating of 66% by the evaluators; the corresponding ratings for acceptability of the regimen prescribed by the five faculty specialists ranged from 42.3% to 62.3%. The system never failed to cover a treatable pathogen while demonstrating efficiency in limiting the number of antimicrobials prescribed. The study design may be useful in assessing the performance of other computer-based clinical decision-making systems.

(JAMA 242:1279-1282, 1979)
Cognitive Science in the Clinical Context during the 1970s

• Studies of clinical reasoning were voraciously studied by medical AI researchers
• Work of Elstein, Shulman, and Sprafka was particularly influential
• Work of Jerry Kassirer (Tufts) and Kuipers (MIT)
• Important simulation work by Tony Gorry (MIT), Steve Pauker (Tufts), Jerry Kassirer (Tufts) and Bill Schwartz (Tufts)
• Later work by Vimla Patel (McGill University)


Theoretical Foundations for Medical Descriptions

The “Blois Funnel”

Artificial Intelligence (AI)

The study of ideas that enable computers to do the things that make human beings seem intelligent:

The ability to reason symbolically
The ability to acquire and apply knowledge
The ability to manipulate and communicate ideas

Taken from Patrick Winston's AI Textbook (1982; cover: 3rd edition 1992)
https://www.google.com/books/edition/AI/9780262611028?hl=en&gbpv=1
Biomedical AI at Stanford Flourishes: HPP and KSL

- Involved faculty and students from both Computer Science (engineering school) and Medical Informatics (medical school)
- Many clinician or bioscience collaborators
- Many students cross-trained in CS/informatics and biomedicine (PhD or MD)
- Feigenbaum and Buchanan led from CS side

Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project

Out of print, but entire book is available online for free download or perusal at http://shortliffe.net. Also available on AAAI Web Site
Readings in Medical AI: The First Decade

- Published in 1984 by Addison Wesley
- Co-edited by Bill Clancey and myself
- Entire volume (now out of print) is freely available on my web site at http://shortliffe.net or on AAAI web site.

Changing Technology Affects AIM Work

- Key changes in late 1970s and early 1980s:
  - Microprocessors and personal computers
  - Local area networking
  - Specialized machines for AI (LISP Machines)
  - General purpose workstations (e.g., Unix boxes)

ONCOCIN Interface When Program Ran on Time-shared Mainframe
Changing Technology Affects AIM Work (2)

- Graphical interface
- Mouse pointing device
- Less typing
- More intuitive for clinicians
- More responsive (no time sharing)

ONCOCIN Interface When Program Ran on Stand-alone LISP Machine

Internist-1 → QMR
Explosive Interest in AI

- Expert systems heavily covered in lay press, with medical examples prominent
- Cover stories in leading magazines and newspapers
- Investment by companies in learning about AI and its potential application in their businesses

Medical World Became More Interested in the Possibilities

Western Journal of Medicine devoted most of an issue (1986) to medical informatics, with an emphasis on AI and decision support.
1980’s and 90’s

• Disappointment that applied AI had not rapidly lived up to predictions for impact
• Perceived “overselling” of artificial intelligence
• Avoidance of use of the term by AI researchers

The AI Hype Cycles

Source: https://www.actuaries.digital/2018/09/05/history-of-ai-winters/
The adolescence of AI in Medicine: Will the field come of age in the ’90s?*

Edward H. Shortliffe

Abstract


2000-2010

• Integration of decision support with workflow viewed as a central requirement
• Further stimulated by concerns regarding patient safety and error reduction (NAM: “To Err is Human”)
• Increasing incorporation of decision-support functionalities (mostly warnings and alerts) in commercial products
AI in Medicine 2009;46:5-17

Artificial Intelligence in Medicine (2009) 46, 5–17

POSITION PAPER

The coming of age of artificial intelligence in medicine

Vimla L. Patel a,*, Edward H. Shortliffe a, b, Mario Stefanelli c, Peter Szolovits d, Michael R. Berthold e, Riccardo Bellazzi c, Ameen Abu-Hanna f

Fascination with Role of Technology and Computing in Health Care Persisted
Medical Stimulus to Machine Learning: “Make it Deep”

- Loads of patient data
- EHR investments helped to move away from paper as we made records digital
- New capabilities due to visionary work of computer scientists such as Geoffrey Hinton and others at University of Toronto (and later Google)
- Huge opportunity to learn from literally millions of cases

Privacy: A concern to some patients.....
QUESTIONS?

JAMA 2018;320(21):2199-2200

Clinical Decision Support in the Era of Artificial Intelligence

Clinicians and researchers have long envisioned the day when computers could assist with difficult decisions in complex clinical situations. The first article on this subject appeared in the scientific literature about 60 years ago, and the notion of computer-based clinical decision support has subsequently been a dominant topic for informatics research. Two recent Viewpoints in JAMA highlighted the promise of deep learning in medicine. Such new data analytic methods have much to offer in interpreting large and complex data sets. This viewpoint is focused on the subset of decision support systems that are designed to be used interactively by clinicians as they seek to reach decisions, regardless of the underlying analytic methodology that they incorporate.

CDSS = Clinical Decision-Support System
Principal Types of Clinical Decision Support

- Medical Device Data Interpretation
  - Often visual data (EKGs, X-ray images, EEGs, path slides, etc.)
  - Physician receiving report can often verify interpretation
From the article:

- The reason for the predictions? AI’s tantalizing power to identify patterns and anomalies and to examine pathologies that look certain ways.

- Radiologists are being trained to recognize AI’s shortcomings and capitalize on its strengths; most comparisons between algorithms and radiologists are too simplistic. AI is impressive in identifying horses, but is a long way from recognizing zebras.
**Principal Types of Clinical Decision Support**

- **Medical Device Data Interpretation**
  - Often visual data (EKGs, X-ray images, EEGs, path slides, etc.)
  - Physician receiving report can often verify interpretation
- **Event Monitoring and Alerts**
  - Typically in EHR environments
  - Simple logic that clinician can quickly interpret
- **Direct Consultation with Clinical User (CDSS)**
  - Major challenges in gaining acceptance and demonstrating utility

**Criteria for CDSS Acceptance and Integration into Workflow**

- Black boxes are unacceptable:
  - A Clinical Decision-Support System (CDSS) requires transparency so that users can understand the basis for any advice or recommendations that are offered.
Criteria for CDSS Acceptance and Integration into Workflow

- Time is a scarce resource:
  - A CDSS should be efficient in terms of time requirements and must blend into the workflow of the busy clinical environment.

Criteria for CDSS Acceptance and Integration into Workflow

- Complexity and lack of usability thwart use:
  - A CDSS should be intuitive and simple to learn and use so that major training is not required and it is easy to obtain advice or analytic results.
Users vote with their feet….

Criteria for CDSS Acceptance and Integration into Workflow

- Relevance and insight are essential:
  - A CDSS should reflect an understanding of the pertinent domain and the kinds of questions with which clinicians are likely to want assistance.
### Criteria for CDSS Acceptance and Integration into Workflow

- **Delivery of knowledge and information must be respectful:**
  - A CDSS should offer advice in a way that recognizes the expertise of the user, making it clear that it is designed to inform and assist but not to replace a clinician.

\[
(\text{brain} + \text{computer}) > \text{brain}
\]

### Criteria for CDSS Acceptance and Integration into Workflow

- **Scientific foundation must be strong:**
  - A CDSS should have rigorous, peer-reviewed scientific evidence establishing its safety, validity, reproducibility, usability, and reliability.
Staging from Laboratory to Naturalistic Settings

Some Observations as a Journal Editor

- JBI has been published for more than 50 years (formerly Computers & Biomedical Research)
- Published under current title for 20 years
- Emphasizes novel methodology, driven by biomedical problems
- About half of submissions now deal with machine/deep learning (including NLP/text mining)
- Increase in numbers of articles coming from engineering schools and computer scientists
Some Key Issues: Stressing BMI and AI as Science

- Novel methods (often driven by applications) rather than novel applications
- Need to convey how a contribution generalizes to other problems (and range of applicability)
- “I used familiar method X to address a new problem Y and got great results.” → desk rejection
- Rather: “I tried to address problem Y and in order to do so I had to develop new method X which I believe (or have shown) can also be used in problems such as A, B, and C”

The Current Decade

- Explosion of interest in AI broadly, and medical AI in particular
- Confusion in terms: AI, machine learning, data analytics, and data science are not synonyms
  - Articulation with BMI needs better definition
- Deep learning too often viewed as the full solution
  - What does a deep learning program "know" when it is performing well?
  - How should we best merge traditional knowledge representation for a domain with programs that use machine learning methods to solve problems in that domain?
- Many of the early challenges persist (integration, interoperability, terminology standardization, data ownership, and many others)
### The Key Lessons

- Do not be too quick to reject the “knowledge is power” aphorism
- Incorporate an understanding how human beings, and especially acknowledged experts, solve the problem
- Promulgation and acceptance of medical AI solutions will depend on much more than decision making or analytic performance
- AI projects must be driven in part by a deep understanding of the biomedical issues → collaboration!
- The future is bright, but we are still in mid-stream

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**Thank You**

- ted@shortliffe.net
- http://shortliffe.net