Intelligent systems to support patient management

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Artificial Intelligence

- Many motivations, from computational theory of (human) intelligence through engineering, much debate and definitions
- McCarthy: “Today’s AI is tomorrow’s CS”
- AI techniques are real!
  - Deep blue, backgammon, …
  - Genome project & protein structure discovery
  - Mars rover robots & mobile robots
  - …
Fundamental observation about intelligence

• Experts effortlessly and routinely mobilise vast quantities of knowledge
• They are unreliable witnesses when explaining how they do what they do
• Much of an expert’s knowledge is tacit, deeply ingrained
• It is difficult to elicit the knowledge that is being used by an expert
Core concepts in AI

- Ontology & knowledge representation
  - XML and the “semantic” web

- Intelligent search
  - Massive search spaces
  - Game playing

- Inference
  - Rule-based systems & case-based reasoning
  - Reasoning under uncertainty

- Perception & motor control
Inference

- Rule-based system: MYCIN
- Case-based reasoning
- The Cancer Research UK systems
  - **PROforma**: computer-understandable notation for describing clinical & other processes
  - **Tallis**: tools for creating & distributing PROforma systems on the web
  - **CREDO**: using AI to support the National Cancer plan
MYCIN

• Provide consultative advice on diagnosis and therapy for infectious disease
  – eg. TB, pneumonia, meningitis, …

• Advice on identifying bacterial infection:
  – E.coli, klebsiella, enterobacter, …

• Advice on therapies:
  – “Give Gentamicin 119mg q8h IV for 10 days”

• Developed in late 1970s at Stanford by Shortliffe & Buchanan
Interaction with Mycin 1 - Patient

1) Patient’s name: Fred Smith

2) Sex
   Male

3) Age
   55

4) Have you been able to obtain positive cultures from a site at which Fred Smith has an infection?
   yes
Interaction 2: Infection

5) What is the infection?
   Primary bacteremia

6) Please give the date & approximate time when signs or symptoms of the primary bacteria (infection-1) first appeared
   May 5, 1980

The most recent positive culture associated with the primary bacteria (infection-1) will be referred to as culture-1
Interaction 3: Culture

7) From what site was the specimen for culture-1 taken?
    Blood

8) Please give the date & time when culture-1 was obtained
    May 9, 1980

The first significant organism from culture-1 will be referred to as organism-1
Interaction 4: Organism

9) Enter the identity of organism-1
   Unknown
10) Is organism-1 a rod, coccus, …
   Rod
11) The gram stain of organism-1:
    Gramneg
12) Have there been any positive cultures from sites which are not associated with infections about which you are seeking advice?
    No
13) Did organism-1 grow aerobically?
    Yes (0.8)
14) Did organism-1 grow anaerobically?
    yes
15) What is the suspected portal of entry of organism-1 into the sterile site?
    GI (0.6)

..... Etc gathering sufficient information for inferring possible identities of the infecting organisms
Mycin’s basis for advice

My therapy recommendation will be based on the following probable infection(s) and potential causative organism(s):

Infection-1 is PRIMARY-BACTERIA

The identity of organism-1 may be:
1. PSEUDOMONAS-AERUGINOSA
2. KLEBSIELLA-PNEUMONIAE
3. E.COLI
4. BACTEROIDES-FRAGILIS
5. ENTEROBACTER
6. PROTEUS-NON-MIRABILIS
Final questions ...

46) On a scale of 0-4 (higher indicates increasing severity), how would you rate Fred Smith’s degree of sickness?
   3

47) Does Fred Smith have a clinically significant allergic reaction to any microbial agent?
   No

48) Fred Smith’s weight in Kg
   70
My preferred therapy recommendation is:
To cover for \{1,2,3,5,6\}, give GENTAMICIN 119mg q8h IV or IM for 10 days; modify dose in case of renal failure
To cover for item 4, give CLINDAMYCIN 595mg q6h IV/IM for 14 days; if diarrhea or other GI symptoms develop, patient should be evaluated for possible pseudomembranous colitis

Do you wish to see the next choice therapy?
   Yes
Which of the above drugs do you wish to eliminate from consideration?
   Clindamycin
Alternative therapy recommendation

To cover for \{2, 3, 4, 5, 6\} give
CHLORAMPHENICOL 1gm q6h IV for 14 days; monitor patient’s white count

To cover for 1, give GENTAMICIN 119mg IV/IM for 10 days; modify dose in case of renal failure
Mycin’s medical knowledge is encoded as rules

Premise: (AND (SAME Cntxt Infect primary-bacteremia)
(MEMBF Cntxt Site Sterilesites)
(SAME Cntxt Portal GI))

Action: (Conclude Cntxt Ident Bacteroides 0.7)

If 1) infection is primary-bacteremia
2) site of the culture is one of the sterile sites
3) suspected portal of entry is GI

Then there is suggestive evidence (0.7) that the organism is bacteroides
Mycin’s rules run “backwards”

• One possibility: all the premises of a rule match items in the database, so fire the rule to draw the conclusion

• Alternative: it is desired to know whether or not the conclusion is satisfied – set up the satisfaction of the premises as subgoals of showing this

Mycin uses the second of these – it gives it a more “goal oriented” behaviour, rather than jumping about from topic to topic
Object Hierarchy

Patient

Culture
- Positive culture
- Known organism

Susppected infection
- Pending culture
- Organism on smear

Therapy
- Current therapy
- Prior therapy
How does Mycin work?

- There is a database of facts culled from the interaction
- There is an evolving set of deductions, obtained by inference, by “firing” rules that apply
- There is a database of rules encapsulating clinical knowledge
- There is an inference engine that chooses which rule to fire at each step
At each cycle, a rule is picked whose **action part** *matches* the database, in which case the rule is *fired* and this either sets up a list of new things that need to be found out, or are known, …and this cues additional rules that could be fired…
Uncertainty management

**BOTH** the knowledge and the data are:

- incomplete
- redundant
- noisy
- erroneous
- potentially voluminous
Certainty factors

- CF = degree of confirmation
- one-number calculus
  “How much more certain are you with the new evidence than you were before?”
- Evidence gathering
  – accumulate evidence
  – weigh positive and negative evidence
CF calculus

Previous CF(X) = 0.6

Apply Rule:
  A & B, X (0.5)
  [ A and B both true]

New CF(X)  = 0.6 + (0.5 *(1-.6))
           = 0.8
CF calculus II

Previous CF(X) = 0.6

Apply Rule:

A & B, X (0.5)

[ CF(A) = 0.5, (CF(B) = 1.0]

Use min CF of premise clauses

New CF(X) = 0.6 + (0.25 * (1-.6))

= 0.7
Alternatives to CF calculus

- Categorical reasoning (no uncertainty)
- Simple counts of positive and negative factors
- Weighted sum
- Fuzzy logic
- Bayes’ rule
- Belief networks
Is blood a sterile site?

Yes. Blood is one of those sites that are normally sterile.

What organisms are likely to be found in the throat?

The likely pathogens associated with throat are: Streptococcus-pneumoniae, streptococcus-group-a, ...
More on descriptive explanations from MYCIN

- How do you decide that an organism might be pseudomonas aeruginosa?

*Rules which conclude that the identity of the organism is pseudomonas-a. generally use one or more of the following pieces of information:* 
- the site of the culture,
- the gram stain of the organism,
- the morphology of the organism.

etc
The Cancer Research UK* systems

• **CREDO:**
  – using AI to support the National Cancer plan

• **PROforma:**
  – computer-understandable notation for describing clinical & other processes

• **Tallis:**
  – tools for creating & distributing PROforma systems on the web

*Advanced Computation Laboratory, headed by Professor John Fox
http://www.acl.icnet.uk/lab/
Supporting clinical practice and the NHS cancer plan

- Improving prevention
- Cutting waiting times
- Better detection
- Improving treatment
- Better palliative care
- Empowering the patient
- Preparing for the genetics revolution
The software architecture for all the applications

John Fox refers to this organisation as the *domino*
Example: Prescribing drugs

- Treat condition
- Diagnosis
  - Clinical goals
  - Patient data
  - Actions
  - Options
  - Evidence & arguments
  - Protocols & pathways

- Drugs
  - Cost, contraindications, side-effects, interactions...
  - Recommend (prescribe)
EMPOWERING THE PATIENT

Patients “want support in making their own choices about timing, to consider options for treatment … and they want the arrangements to be personalised around their own circumstances and particular clinical needs”
Zooming in on the plan portion

<table>
<thead>
<tr>
<th>Plan 1</th>
<th>Plan 2</th>
<th>Plan 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>pregnancy</td>
<td>breastfeeding</td>
<td>self examination</td>
</tr>
<tr>
<td>mammographic screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tamoxifen</td>
<td></td>
<td>oophorectomy</td>
</tr>
<tr>
<td>bilateral mastectomy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Now aged 30
Zooming in on the recommendations portion

There are good reasons to act to reduce risk

There are a number of reasons to start Tamoxifen
  - Tamoxifen has major benefits for women who have had surgery for breast cancer
    - REASON: reduces recurrence by more than a third (43%)
    - REASON: reduces deaths by nearly a quarter (22%)
    - REASON: reduces cancer in other breast by nearly a half (47%)
    - By analogy Tamoxifen may work to prevent breast cancer in a healthy at-risk woman
  - There are a number of incidental health benefits

There are a number of reasons to consider not starting Tamoxifen
  - Side effects: Hot flushes, vaginal bleeding, secretions
  - Increased risk of endometrial cancer
    - BUT: Mainly post-menopausal
    - BUT: rare (1 in 10,000 per annum rises to 6–9 in 10,000 p.a.)
    - BUT: treatable (hysterectomy) if symptoms are reported
  - Risk of blood clots
  - Risk of eye problems

= reasons in support of a recommendation
= reasons against a recommendation
Risk assessment in genetics

- Assess risk
- Clinical goals
- Options
- Risk levels

- Worried patient
- Patient data
- Evidence & arguments

- Recommend (accept)
- Actions
- Protocols & pathways

- Genetics, epidemiology & other knowledge
The following information applies ONLY to the highlighted path.

This patient is at moderate risk of being a gene carrier because, on the highest-risk path of inheritance found by the program:

* The mother of the presenting patient is affected, which indicates an increased risk level.
* One first-degree relative (FDR) is affected (Each affected FDR indicates an additional risk factor).
* One affected FDR has an onset age under 50, indicating a moderate increase in risk
* The combination of one breast and one ovarian cancer indicates a moderate increase in risk level.

However, this is balanced to some extent by the following factors which indicate lower risk level:

* The oldest affected second-degree relative has an age of onset over 60. Genetic predisposition is more likely to be associated with lower ages of onset, and this age indicates a considerable reduction in risk level.
* Genetic predisposition is less likely in a person over 40 who has not developed cancer.

Overall, the likelihood that this patient is a gene carrier is moderate.
The CREDO system for the *patient journey* in breast cancer

**Detection**
- GP Screening
- Family history
- Other

**Work up**
- Risk (genetics etc.)
- Diagnosis
- Staging
- Pathology
- Imaging

**Therapy**
- Chemo-therapy
- Radio-therapy
- Surgery

**Follow-up**
- Palliative care
- Psycho-Social
- Home and Community services

**Database**

**Pathway**:
- Refer
- Info

**Process**:
- Detection → Work up → Therapy → Follow-up
Proforma Tasks

• 4 Task types used to build up a guideline in PROforma
  - Actions
e.g. Surgical Resection
  - Enquiries
e.g. Patient History
  - Decisions
e.g. Treatment Options
  - Plans
  Used to group other tasks
PROforma: process as object

Tallis

- Authoring tool using the PROforma language
- Tallis suite enables fast prototyping systems
- Customisation of the final user interface is possible
Tallis
Tallis
Tallis

Tallis Web Enactment

CRC Patient Journey

Active Tasks:
- First Step

Available Services:
- No services available

View Data Summary

Refresh Engine

View Current Process

View Current Task Tree

First Step

Decision: Click on the plus signs to view arguments for and against each decision option

Decision Options

- Surgery
- Symptoms include "Bowel obstruction by the tumor"
- Stage 2 or 3 Cancer

- Palliative_Care
- Age >= 80

- Symptoms include "Bowel obstruction by the tumor"

- Chemo

Symptoms include "Bowel obstruction by the tumor"

commit
The “MDT Suite”

- Information integration
  - Image analysis, image fusion (and signals)
  - Efficient access to that information
  - Integration with patient information
  - Integration with genetics information (eg microarray)
  - More informed decision making
- Remembering what was decided, and why
  - More information patient management decisions
  - Deepening appreciation by pathologists and radiologists of each other’s images
  - “Closing the loop” for the surgeon
    - circumferential resection margin (CRM) for successful outcome
  - Basis for a teaching tool for the MDM
MDT first observations

- Commitment and astonishing expertise of the members of the team
- Openness of the specialists and welcome that we have had
- Scale of the challenge
- Cost of bringing all that expertise together
  - Make the best use of it while it’s available!
  - Supporting decision making not automating it
- Decision making under uncertainty
  - Encapsulating and mobilising knowledge
  - Elicitation of that knowledge
- Images + clinical information ➔ patient management options
  - Surgery or (or HIFU) or palliative care
  - Radiotherapy or chemotherapy to downstage
Observations of the MDT

- Rudimentary support for image display
- Image fusion (MR-MR, CT-PET) is rarely used (and software has “limited” capabilities)
- Computer-based image analysis not used
- Discussions of images “qualitative”, not quantitative
- Gulf between pathology and radiology
- Need for more functional information earlier (but watch cost)
- Patient information reported and integrated “informally” in the patient management decisions
- Decisions recorded but contingencies mostly implicit
- Volumetric information needed
- No explicit representation of what the decision last time depended upon, hence how the new information changes contingencies
- Limited kinds of information mobilised in decision making
- Skeletal nature of some of the data makes integration challenging
- Errors of omission more likely than errors of commission
- Not possible to restrict discussion only to the liver!
- Audit trail of decisions?
- …
**Tallis**: publishing Proforma systems on the web

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**ISIS-4**: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. **ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group.**

58,050 patients entering 1086 hospitals up to 24 h (median 8 h) after the onset of suspected acute myocardial infarction (MI) with no clear contraindications to the study treatments (in particular, no cardiogenic shock or persistent severe hypotension) were randomised in a ”2 x 2 x 2 factorial” study. The treatment comparisons were: (i) 1 month of oral captopril (6.25 mg initial dose titrated up to 50 mg twice daily) versus matching placebo; (ii) 1 month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg once daily) versus matching placebo; and (iii) 24 h of intravenous magnesium sulphate (8 mmol initial bolus followed by 72 mmol) versus open control.

There were no significant "interactions" between the effects of these three treatments, and the results for each are based on the randomised comparison of about 29,000 active versus 29,000 control allocated patients. Captopril There was a significant 7% (SD 3) proportional reduction in 5-week mortality (2088 [7.19%] captopril-allocated deaths vs 2231 [7.69%] placebo; 2p = 0.02), which corresponds to an absolute difference of 4.9 SD 2.2 fewer deaths per 1000 patients treated for 1 month. The absolute benefits appeared to be larger (perhaps about 10 fewer deaths per 1000) in certain higher-risk groups, such as those presenting with a history of previous MI or with heart failure. The survival advantage appeared to be maintained in the longer term (5.4 [SD 2.8] fewer deaths per 1000 at 12 months). Captopril was associated with an increase of 52 (SD 2) patient severe 1000 in hypotension considered severe enough to require termination of study treatment, of 5 (SD 2) per 1000 in reported cardiogenic shock, and of 5 (SD 1) per 1000
Fundamental observation

• IT is increasingly pervasive in healthcare delivery (and other complex applications)

• As more imaging and signal modalities become available to clinicians, communications become faster, and computers more powerful, doctors are drowning in data; but what they want is information to guide patient management.

• To do this, systems need to become smarter. Here we examine two currently complementary (though fundamentally linked) aspects to achieving this:
  – Systems capable of reasoning, understanding & offering advice
  – Systems capable of analysing signals and images