Adventures of a Logician-Engineer: A Journey Through Logic, Engineering, Medicine, Biology, and Statistics

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Plan

- **Understanding query languages**
- **Engineering data integration systems**
- **Optimising disease treatments**
- **Recognizing DNA feature sites**
- **Discovering reliable patterns**

Understanding Query Languages

Nested Relational Calculus (NRC)

The complex object types are:

$$s, t ::= \mid bool \mid b \mid s \times t \mid \{s\}$$

The expression constructs are:

$$\frac{}{x^s : s} \qquad \frac{e_1 : s \quad e_2 : t}{(e_1, e_2) : s \times t} \qquad \frac{e : s \times t}{\pi_1\ e : s \quad \pi_2\ e : t}$$

$$\frac{}{true\ : bool} \qquad \frac{}{false\ : bool} \qquad \frac{e_1 : bool \quad e_2 : s \quad e_3 : s}{if\ e_1\ then\ e_2\ else\ e_3 : s}$$

$$\frac{}{\{\}^s : \{s\}} \qquad \frac{e : s}{\{e\} : \{s\}} \qquad \frac{e_1 : \{s\} \quad e_2 : \{s\}}{e_1 \bigcup e_2 : \{s\}}$$

$$\frac{e_1 : \{s\} \quad e_2 : \{t\}}{\cup\{e_1 \mid x^t \in e_2\} : \{s\}} \qquad \frac{e : \{s\}}{empty\ e : bool} \qquad \frac{e_1 : s \quad e_2 : s}{e_1 = e_2 : bool}$$

Explanation

- $\pi_1\ e$ **stands for the first component of the pair** e

  Eg: $\pi_1\ (o_1,o_2) = o_1$

- $\cup\{e_1 \mid x \in e_2\}$ **stands for the set obtained by combining the results of applying the function** $f(x) = e_1$ **to each element of** e_2

  Eg: $\cup\{\{x, x+1\} \mid x \in \{1,2,3\}\} = \{1,2,3,4\}$

Examples

- **Relational projection**

$$\Pi_2(R) := \cup\{\{\ \pi_2\ x\} \mid x \in R\}$$

- **Relational selection**

$$\sigma(p)(R) := \cup\{\text{if } p(x) \text{ then } \{x\} \text{ else } \{\} \mid x \in R\}$$

- **Cartesian product**

$$\otimes(R,S) := \cup\{\cup\{\{(x,y)\} \mid x \in R\} \mid y \in S\}$$

Conservative Extension Property

A language $\mathcal{L}$ has conservative extension property if

for every function f definable in $\mathcal{L}$,
there is an implementation of f in $\mathcal{L}$ such that

for any input i and corresponding output o,

each intermediate data item created in the course of executing f on i to produce o has nesting complexity less than that of i and o

Expressive Power of NRC

- Proposition 1 (Tannen, Buneman, Wong, ICDT92)

  NRC has the same expressive power as Schek&Scholl, Thomas&Fischer, etc.

- Theorem 2 (Wong, PODS93)

  NRC has the conservative extension property at all input/output types

- Corollary 3

  Every function from flat relations to flat relations expressible in NRC is expressible in FO(=)

Theoretical Reconstruction of SQL

Expressions of $\mathcal{NRC}(\mathbb{Q}, +, \cdot, -, \div, \Sigma, =, \leq^{\mathbb{Q}})$ are those of $\mathcal{NRC}$ plus the following

$$\frac{e_1 : \mathbb{Q} \quad e_2 : \mathbb{Q}}{e_1 + e_2 : \mathbb{Q}} \qquad \frac{e_1 : \mathbb{Q} \quad e_2 : \mathbb{Q}}{e_1 \cdot e_2 : \mathbb{Q}} \qquad \frac{e_1 : \mathbb{Q} \quad e_2 : \mathbb{Q}}{e_1 \div e_2 : \mathbb{Q}}$$

$$\frac{e_1 : \mathbb{Q} \quad e_2 : \mathbb{Q}}{e_1 - e_2 : \mathbb{Q}} \qquad \frac{e_1 : \mathbb{Q} \quad e_2 : \{s\}}{\Sigma\{\!|e_1 \mid x^s \in e_2|\!\} : \mathbb{Q}} \qquad \frac{e_1 : \mathbb{Q} \quad e_2 : \mathbb{Q}}{e_1 \leq e_2 : bool}$$

Semantics. $\Sigma\{\!|e_1 \mid x \in e_2|\!\} = f(o_1) + \ldots + f(o_n)$, where f is the function $f(x) = e_1$ $\{o_1, \ldots, o_n\}$ is the set e_2.

Example Aggregate Functions

- **Count the number of records**

  $\mathbf{count}(R) := \Sigma\{| \, 1 \mid x \in R \, |\}$

- **Total the first column**

  $\mathbf{total}_1(R) := \Sigma\{| \, \pi_1 \, x \mid x \in R \, |\}$

- **Average of the first column**

  $\mathbf{ave}_1(R) := \mathbf{total}_1(R) \div \mathbf{count}(R)$

- **A totally generic query expressible in SQL but inexpressible in FO(=)**

  $\mathbf{eqcard}(R,S) := \mathbf{count}(R) = \mathbf{count}(S)$

Expressive Power of NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$)

- Proposition (Libkin, Wong, DBPL93)

  NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$) captures "standard" SQL

- Theorem 4 (Libkin, Wong, PODS94)

  NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$) has the conservative extension property at all input/output types

- Corollary 5

  Every function from flat relations to flat relations is expressible in NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$) iff it is also expressible in SQL

Bounded Degree Property

A language $\mathcal{L}$ has bounded degree property if

for every function f, on graphs, definable in $\mathcal{L}$, and for any number k,

there is a number c such that

for any graph $\mathcal{G}$ with $\deg(\mathcal{G}) \in \{0, 1, \ldots, k\}$,

it is the case that $c \geq \text{card}(\deg(f(\mathcal{G})))$

That is, $\mathcal{L}$ cannot define a function that produces complex graphs from simple graphs

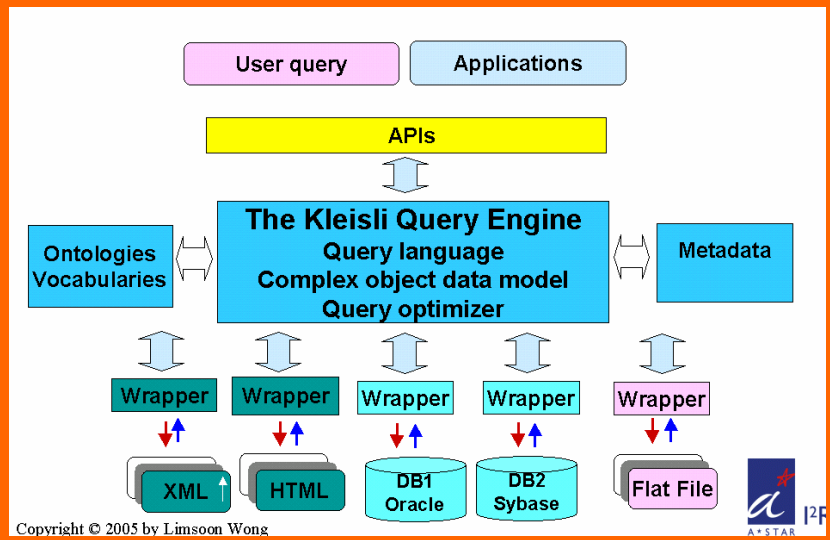
Expressive Power of NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$)

- Theorem 6 (Dong, Libkin, Wong, ICDT97)

  NRC(Q,+,•,–,÷,Σ,=, $\geq^Q$) has the bounded degree property

- Corollary 7
  - Transitive closure of unordered graphs cannot be expressed in SQL
  - Parity test on cardinality of unordered graphs cannot be expressed in SQL
  - Transitive closure of linear chains cannot be expressed in SQL
  - ...

Engineering Data Integration Systems



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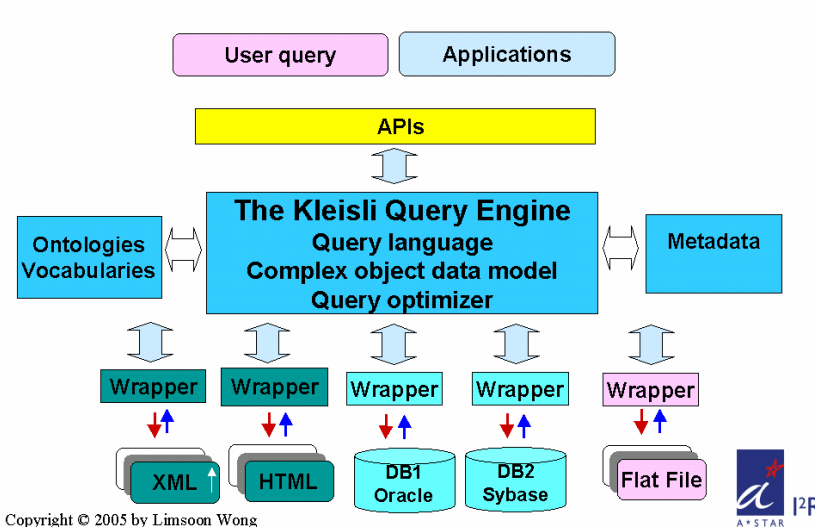
Integration: What are the problems?

A US DOE “impossible query”, circa 1993:

For each gene on a given cytogenetic band, find its non-human homologs.

source	type	location	remarks
GDB	Sybase	Baltimore	Flat tables SQL joins Location info
Entrez	ASN.1	Bethesda	Nested tables Keywords Homolog info

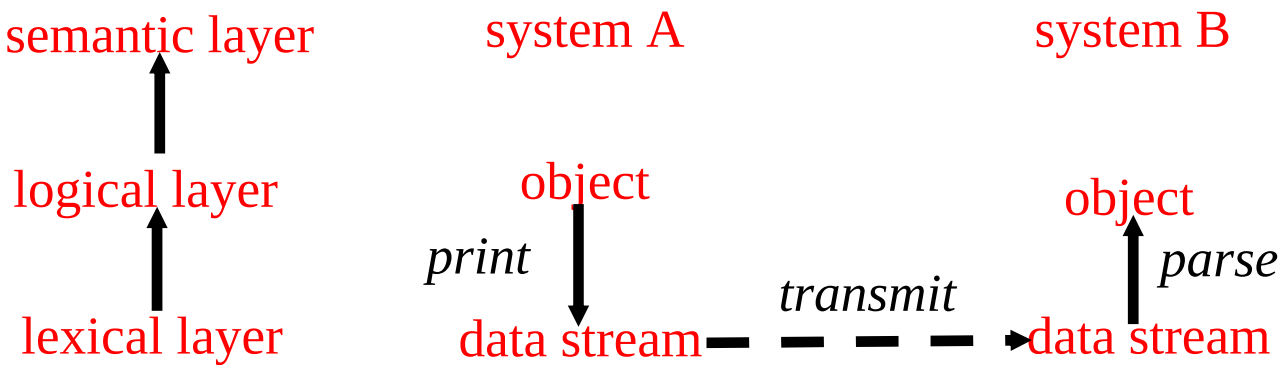
Integration Solution: Kleisli



Buneman, Davidson, Hart, Overton, Wong, VLDB95
Wong, ICFP00

- **Nested relational data model**
- **Self-describing data exchange format**
- **Thin wrappers & lots of them**
- **High-level query languages**
- **Powerful query optimizer**
- **Open "database" connectivity & API**
- **Nested relational data store**

Self-Describing Data Exchange Format



- **Logical & lexical layers are important aspects**
- **“Print” & “parse” to move between layers**
- **“Transmit” to move between systems**
- **Clear separation ⇒ generic parsers & “printers”**

GenPept: E.g. of Poor Format

```
LOCUS       T41727         577 aa          PLN       03-DEC-1999
DEFINITION  F-box domain protein Pof3p - fission yeast
ACCESSION   T41727
PID         g7490551
VERSION     T41727  GI:7490551
DBSOURCE    pir: locus T41727;
            summary: #length 577 #weight 66238 ...
KEYWORDS    .
SOURCE      fission yeast.
  ORGANISM  Schizosaccharomyces pombe
            Eukaryota; Fungi; Ascomycota; ...
REFERENCE   1  (residues 1 to 577)
  AUTHORS   Lyne,M., Wood,V., Rajandream,M.A., ...
  TITLE     Direct Submission
  JOURNAL   Submitted (??-JUN-1998) to the EMBL Data Library
FEATURES             Location/Qualifiers
     source          1..577
                     /organism="Schizosaccharomyces pombe"
                     /db_xref="taxon:4896"
     Protein         1..577
                     /product="F-box domain protein Pof3p"
ORIGIN
   1 mnnyqvkaik ektqqylskr kfedaltfit ktieqepnpt ...
```

- **Deeply nested structure**
- **No separation of logical vs. lexical layers**
- **Specialized parser is a must**

Kleisli's Data Exchange Format

logical layer	lexical layer	remarks
Booleans	True, false	
Numbers	123, 123.123	Positive numbers
	~123, ~123,123	Negative numbers
strings	"a string"	String is inside double quotes
records	$(\#l_1: v_1, \ldots, \#l_n: v_n)$	Record is inside round brackets
sets	$\{v_1, \ldots, v_n\}$	Set is inside curly brackets

- **Lexical layer matches logical layer**
- **Mirrors nested relational data model**
- **Avoids impedance mismatch**
- **Easier to write wrappers**

GenPept: In a Better Format

```
(#uid: 7490551,
 #title: "F-box domain protein Pof3p - fission yeast",
 #accession: "T41727",
 #common: "fission yeast.",
 #organism: (#genus: "Schizosaccharomyces",
        #species: "pombe",
        #lineage: ["Eukaryota", "Fungi", "Ascomycota", ...]),
 #feature: {(#name: "source", #start: 0, #end: 576,
        #anno: [(#anno_name: "organism",
                 #descr: "Schizosaccharomyces pombe"),
                (#anno_name:"db_xref", #descr:"taxon:4896")]),
       (#name: "Protein", #start: 0, #end: 576,
        #anno: [(#anno_name: "product",
                 #descr: "F-box domain protein Pof3p")])},
 #sequence: "MNNYQVKAIKEKTQQYLSKRKFEDALTFITKTIEQEPNPTID...")
```

- **Boundaries of different nested structures are explicit**
- **Logical vs. lexical layers no longer mixed up**
- **Specialized parser no longer needed**

Data Integration Results

- **Using Kleisli:**
  - Clear
  - Succinct
  - Efficient
- **Handles**
  - heterogeneity
  - complexity

```
sybase-add (#name:"GDB", ...);
create view  L from locus_cyto_location using GDB;
create view E from object_genbank_eref using GDB;
select
    #accn: g.#genbank_ref,   #nonhuman-homologs: H
from
    L as c,  E as g,
    {select u
     from g.#genbank_ref.na-get-homolog-summary as u
     where not(u.#title string-islike "%Human%") &
           not(u.#title string-islike "%H.sapien%")} as H
where
    c.#chrom_num = "22" &
    g.#object_id = c.#locus_id &
    not (H = { });
```

Optimising Disease Treatments

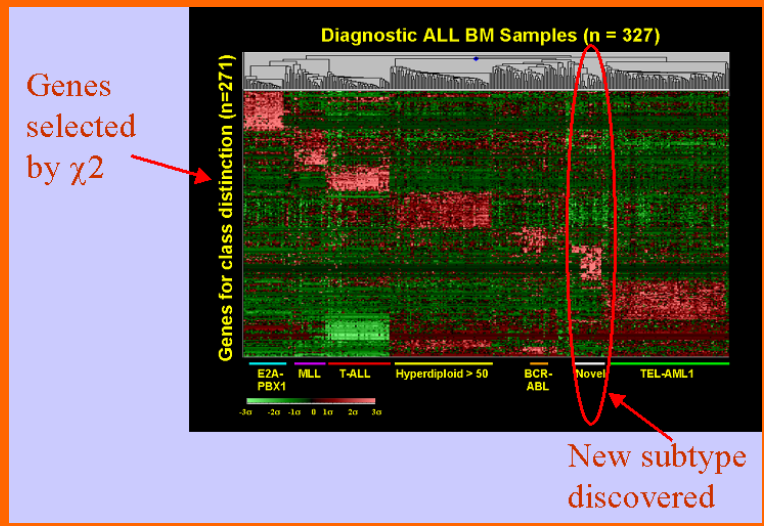


Image credit: Yeoh et al, 2002

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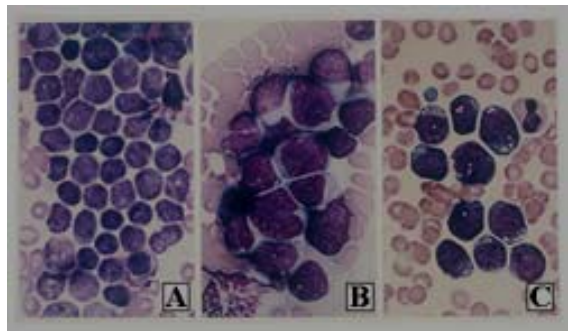
Childhood ALL

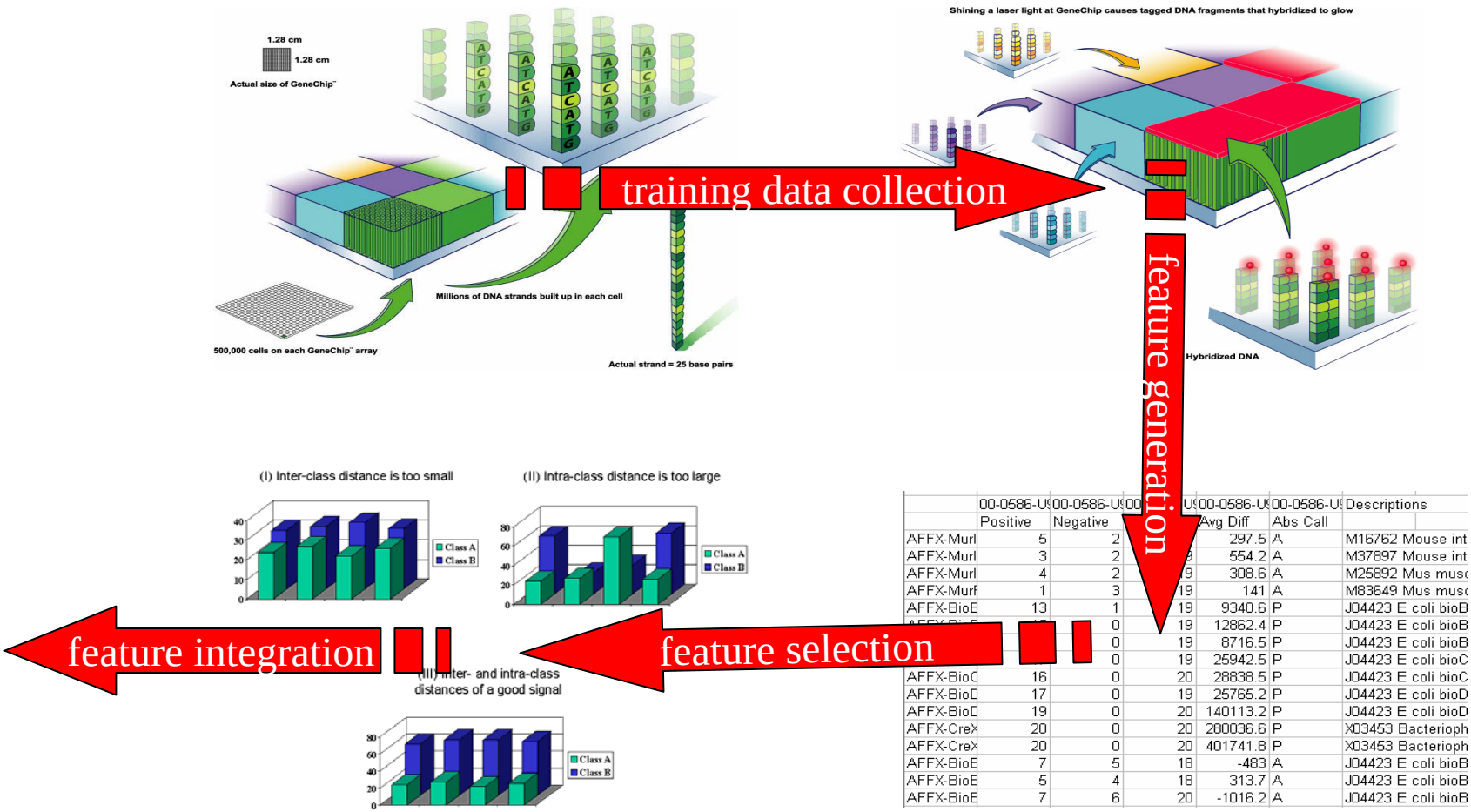
- **Major subtypes: T-ALL, E2A-PBX, TEL-AML, BCR-ABL, MLL genome rearrangements, Hyperdiploid>50,**
- **Diff subtypes respond differently to same Tx**
- **Over-intensive Tx**
  - Development of secondary cancers
  - Reduction of IQ
- **Under-intensiveTx**
  - Relapse

- **The subtypes look similar**



- **Conventional diagnosis**
  - Immunophenotyping
  - Cytogenetics
  - Molecular diagnostics
- **Unavailable in most ASEAN countries**

Single-Test Platform of Microarray & Knowledge Discovery



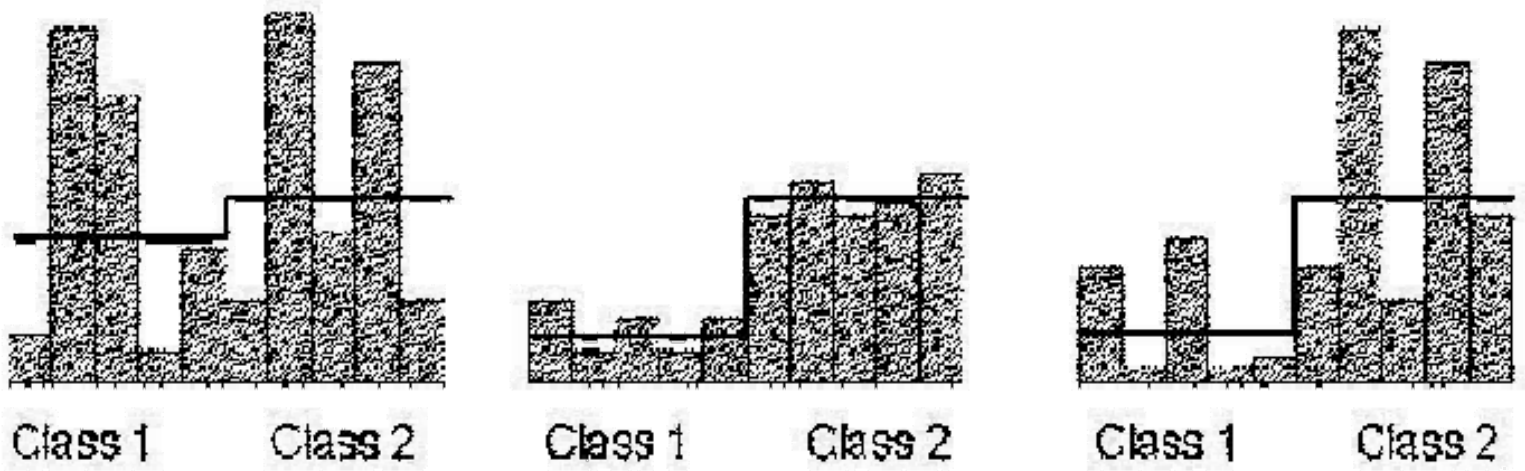
	00-0586-U	00-0586-U	00-0586-U	00-0586-U	Descriptions
	Positive	Negative	Avg Diff	Abs Call	
AFFX-MurI	5	2	297.5	A	M16762 Mouse int
AFFX-MurI	3	2	554.2	A	M37897 Mouse int
AFFX-MurI	4	2	308.6	A	M25892 Mus musc
AFFX-MurF	1	3	141	A	M83649 Mus musc
AFFX-BioB	13	1	9340.6	P	J04423 E coli bioB
		0	12862.4	P	J04423 E coli bioB
		0	8716.5	P	J04423 E coli bioB
		0	25942.5	P	J04423 E coli bioC
AFFX-BioC	16	0	28838.5	P	J04423 E coli bioC
AFFX-BioD	17	0	25765.2	P	J04423 E coli bioD
AFFX-BioD	19	0	140113.2	P	J04423 E coli bioD
AFFX-CreX	20	0	280036.6	P	X03453 Bacterioph
AFFX-CreX	20	0	401741.8	P	X03453 Bacterioph
AFFX-BioB	7	5	-483	A	J04423 E coli bioB
AFFX-BioB	5	4	313.7	A	J04423 E coli bioB
AFFX-BioB	7	6	-1016.2	A	J04423 E coli bioB

Image credit: Affymetrix

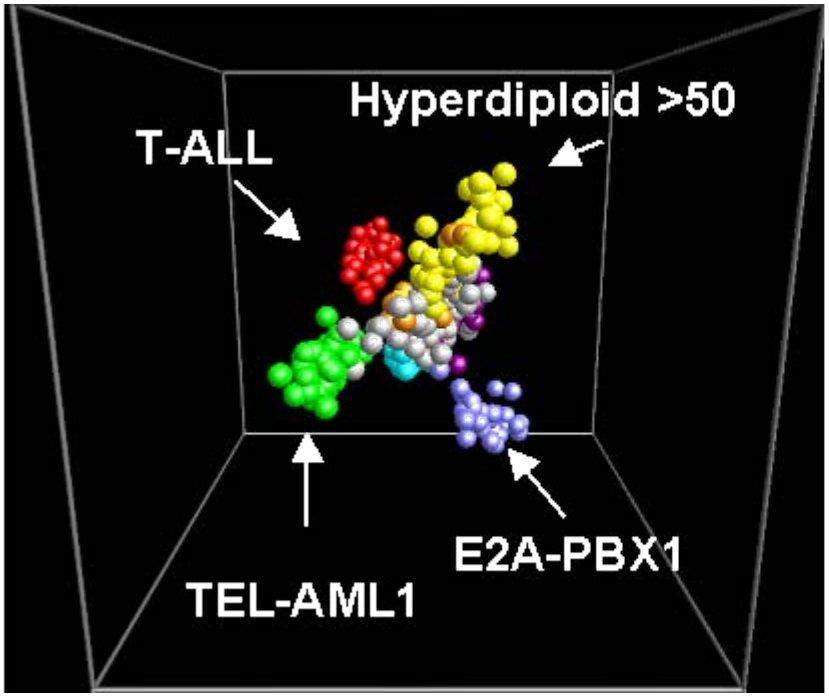
Signal Selection Basic Idea

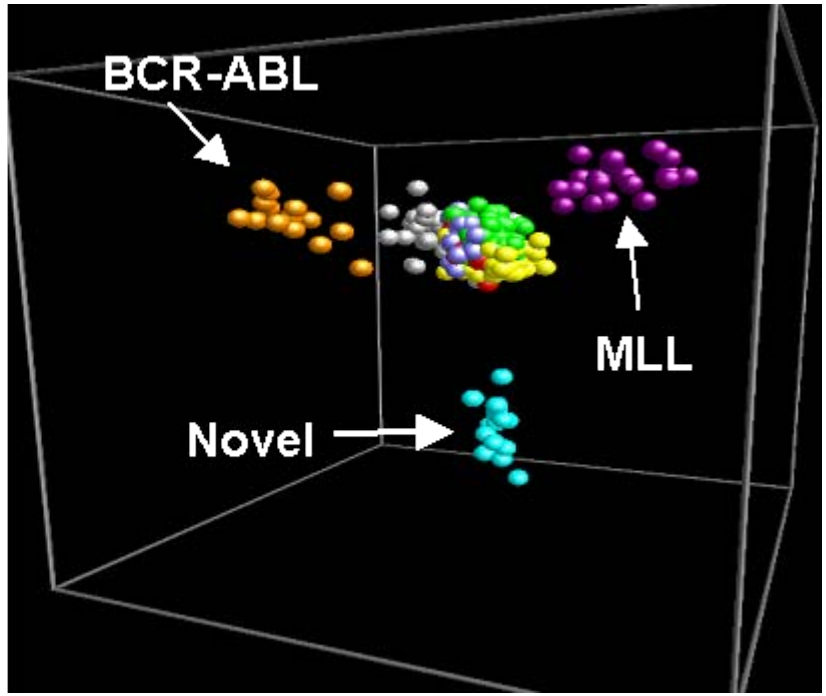
- **Choose a signal w/ low intra-class distance**
- **Choose a signal w/ high inter-class distance**

$\Rightarrow$ **An invariant of a disease subtype!**



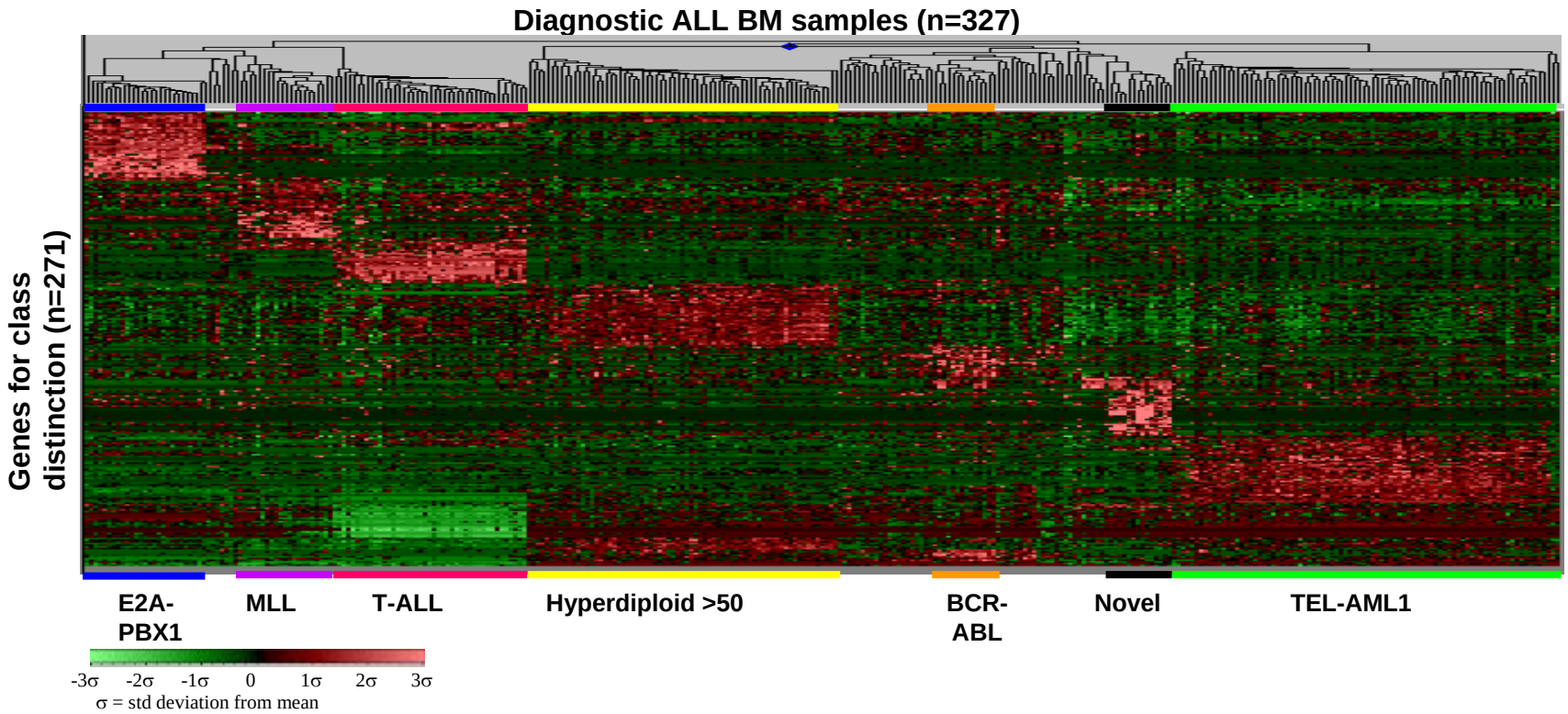
Multidimensional Scaling Plot for ALL Subtype Diagnosis



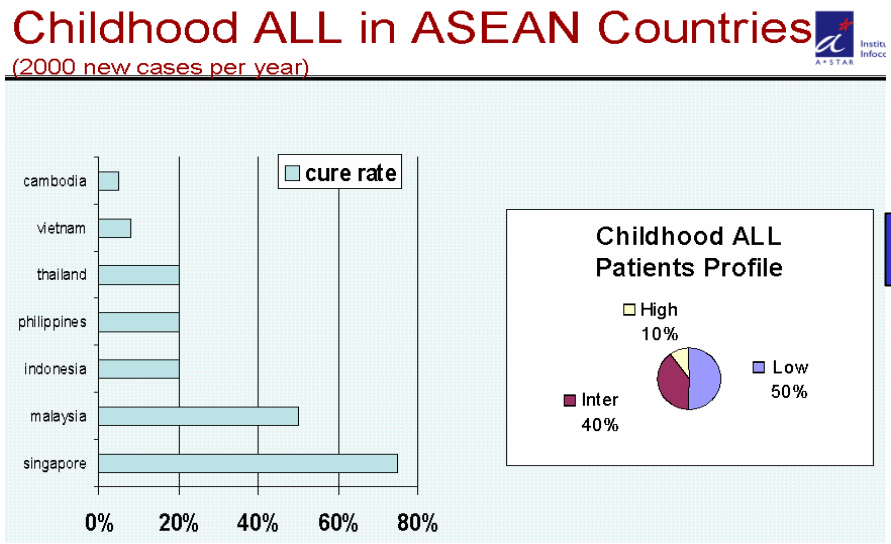


Obtained by performing PCA on the 20 genes chosen for each level

Gene Expression Profiles for ALL Subtype Diagnosis



Impact



Conventional Tx:
- intermediate intensity to all

⇒ 10% suffers relapse

⇒ 50% suffers side effects

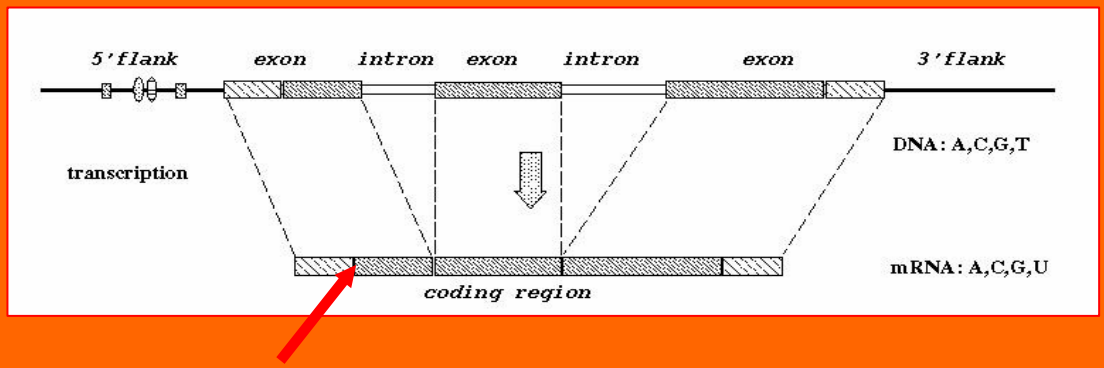
⇒ costs US$150m/yr

Our optimized Tx:
- high intensity to 10%
- intermediate intensity to 40%
- low intensity to 50%
- costs US$100m/yr

•High cure rate of 80%
• Less relapse
• Less side effects
• Save US$51.6m/yr

Yeoh et al, *CANCER CELL*, 2002

Recognizing DNA Feature Sites



A Sample cDNA

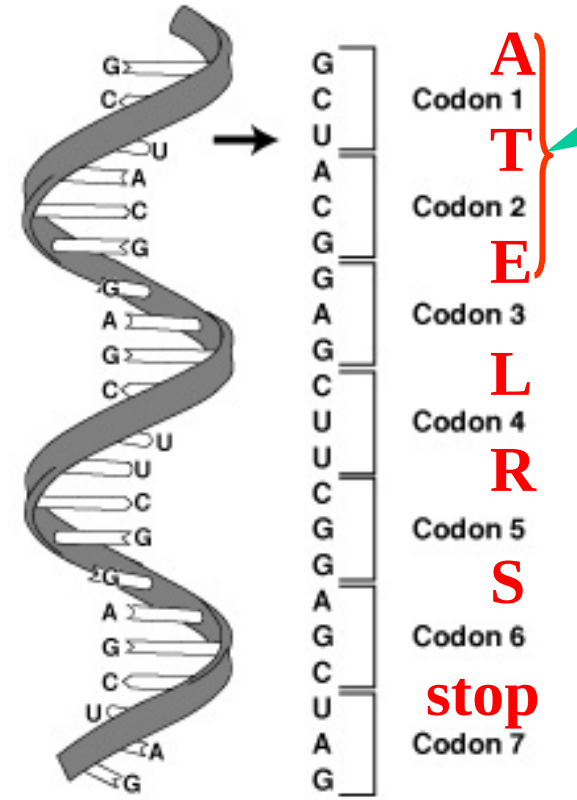
```
 299 HSU27655.1 CAT U27655 Homo sapiens
CGTGTGTGCAGCAGCCTGCAGCTGCCCCAAGCCATGGCTGAACACTGACTCCCAGCTGTG      80
CCCAGGGCTTCAAAGACTTCTCAGCTTCGAGCATGGCTTTTGGCTGTCAGGGCAGCTGTA     160
GGAGGCAGATGAGAAGAGGGAGATGGCCTTGGAGGAAGGGAAGGGGCCTGGTGCCGAGGA     240
CCTCTCCTGGCCAGGAGCTTCCTCCAGGACAAGACCTTCCACCCAACAAGGACTCCCCT
.................................................................  80
.............................iEEEEEEEEEEEEEEEEEEEEEEEEE     160
EEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEE     240
EEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEEE
```

- **What makes the second ATG the TIS?**

Approach

- **Training data gathering**
- **Signal generation**
  - k-grams, distance, domain know-how, ...
- **Signal selection**
  - Entropy, $\chi 2$, CFS, t-test, domain know-how...
- **Signal integration**
  - SVM, ANN, PCL, CART, C4.5, kNN, ...

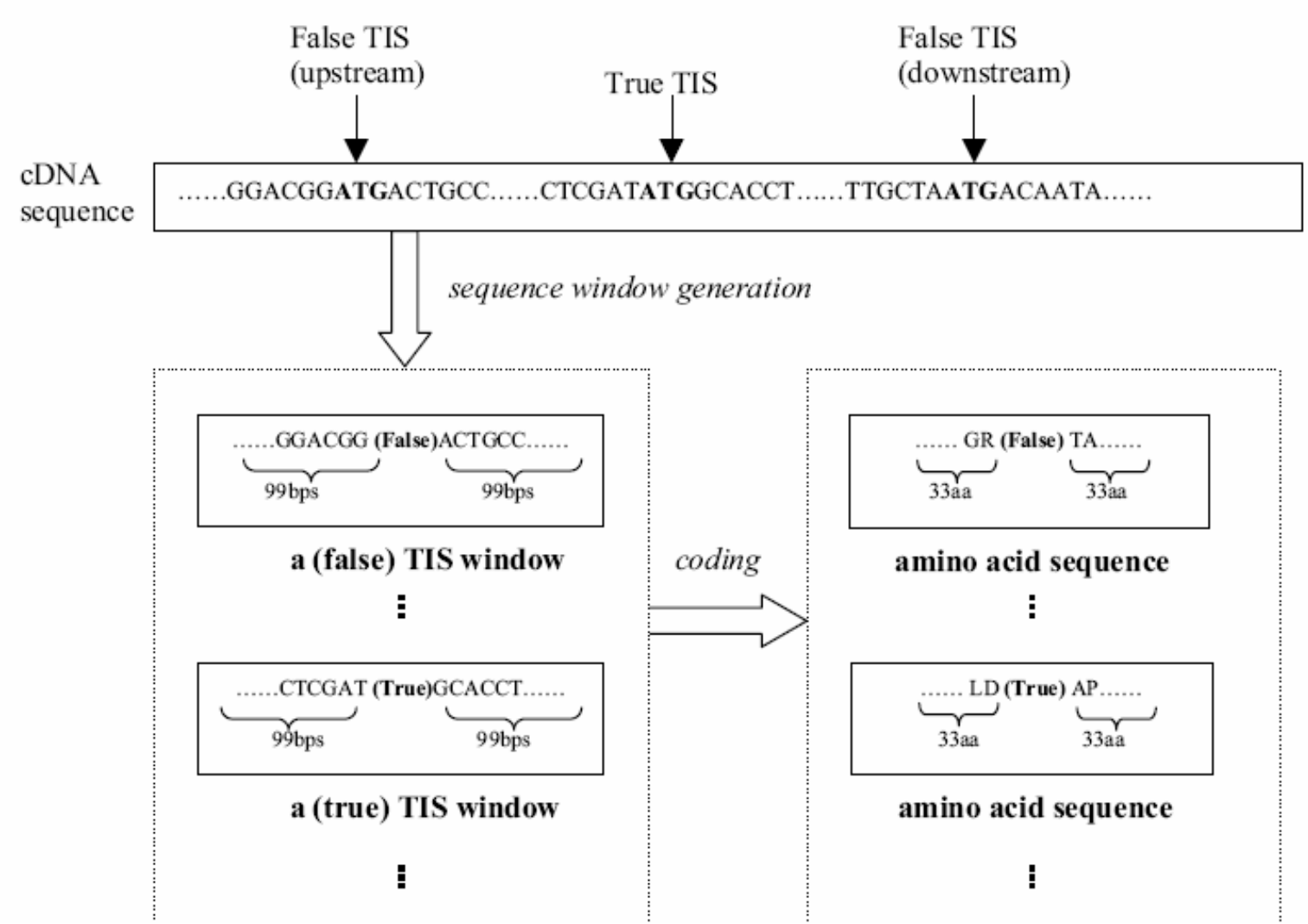
mRNA→protein



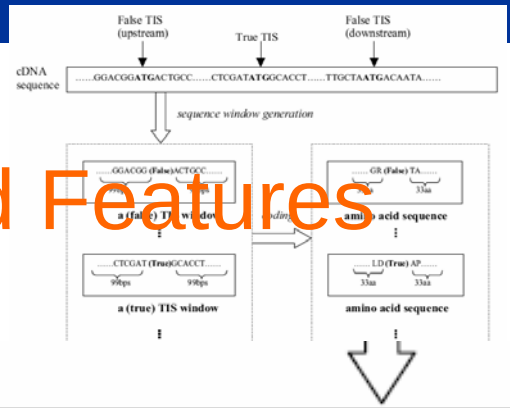
How about using k-grams from the translation?

First	U	C	A	G	Last
U	Phe F	Ser S	Tyr Y	Cys C	U
	Phe	Ser	Tyr	Cys	C
	Leu L	Ser	**Stop** (Ochre)	**Stop** (Umber)	A
	Leu	Ser	**Stop** (Amber)	Trp W	G
C	Leu	Pro P	His H	Arg R	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln Q	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile I	Thr T	Asn N	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys K	Arg	A
	Met M	Thr	Lys	Arg	G
G	Val V	Ala A	Asp D	Gly G	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu E	Gly	A
	Val	Ala	Glu	Gly	G

Amino-Acid Features

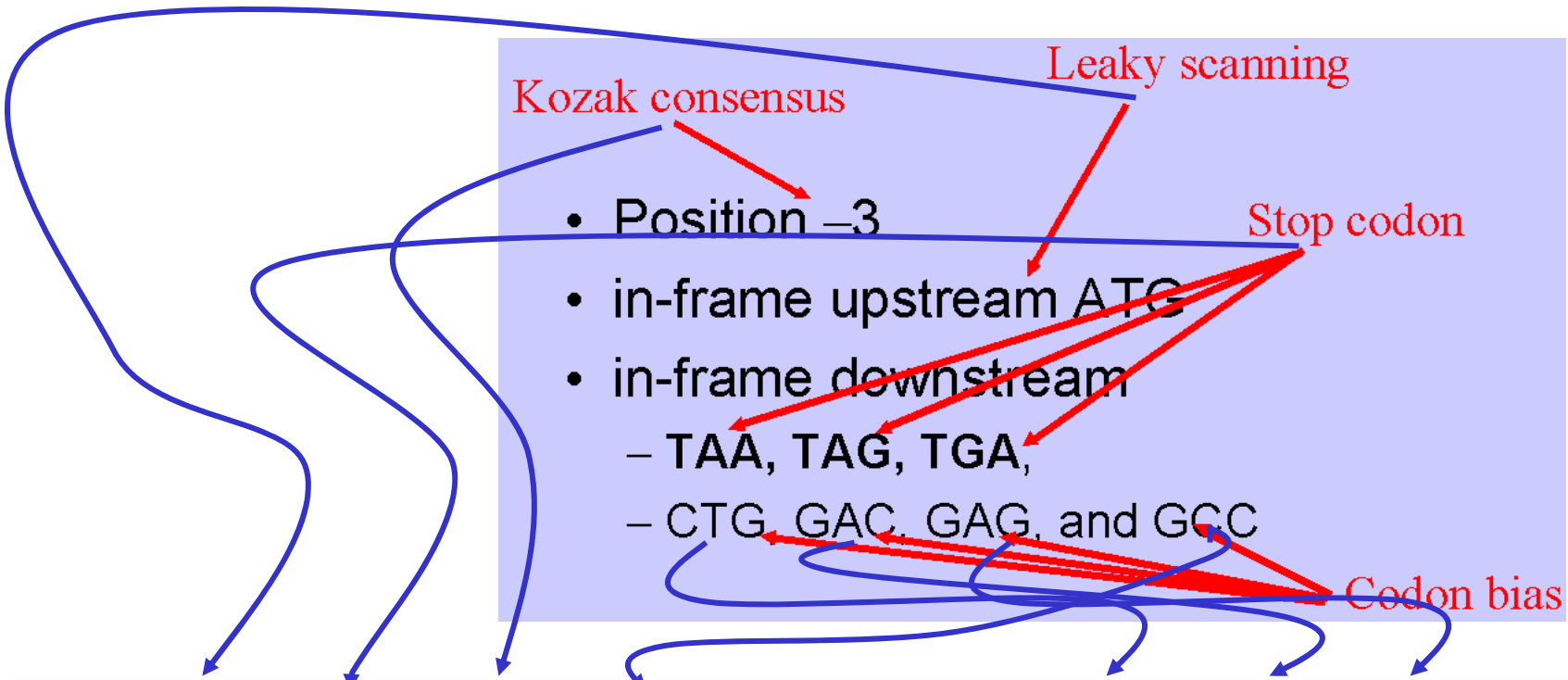


Amino-Acid Features



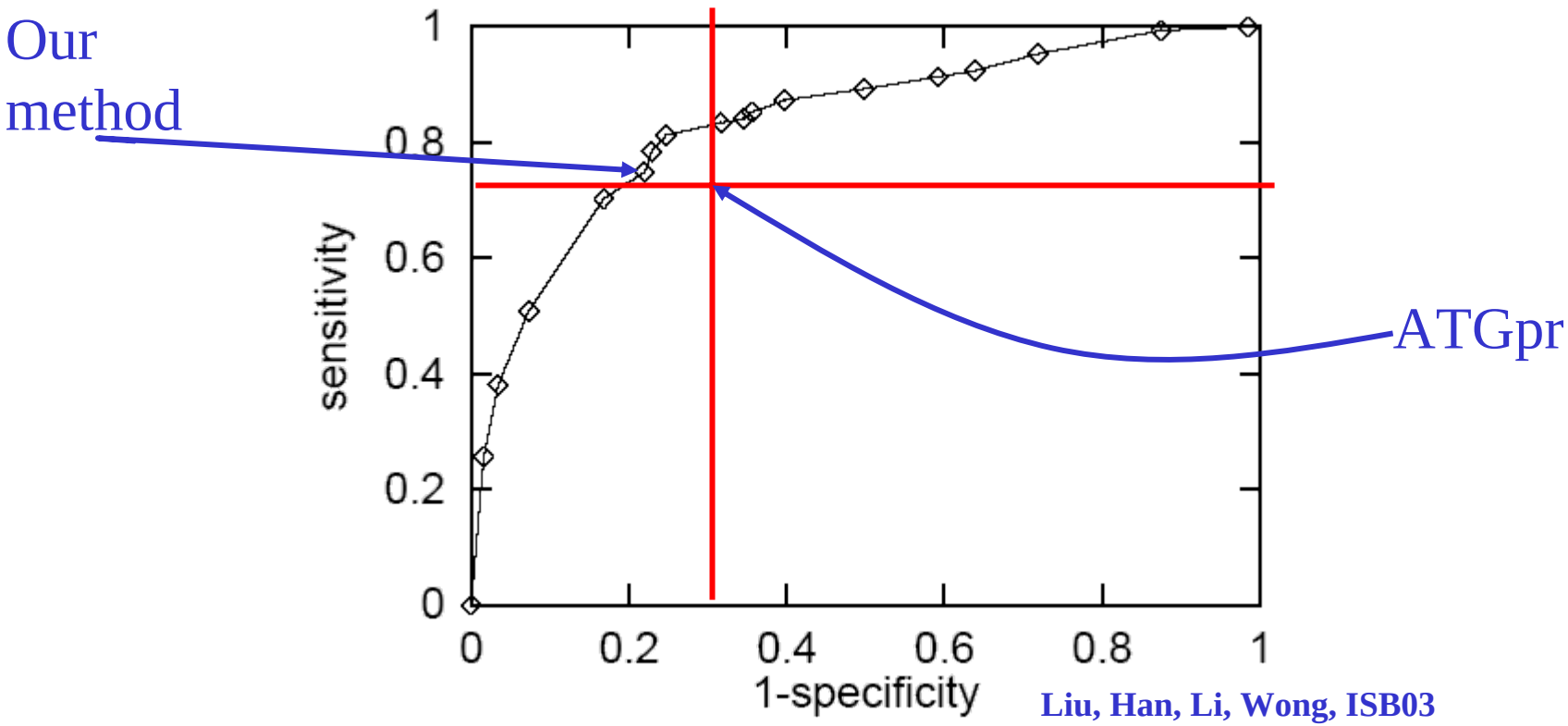
New feature space (total of 927 features + class label)			
42 1-gram amino acid patterns	882 2-gram amino acid patterns	3 bio-know-ledge patterns	class label
UP-A, UP-R, ….,UP-N, DOWN-A, DOWN-R, …., DOWN-N (numeric type)	UP-AA, UP-AR, …., UP-NN, DOWN-AA, DOWN-AR , …, DOWN-NN (numeric type)	DOWN4-G UP3-AorG, UP-ATG (boolean type, Y or N)	True, False
Frequency as values			
1, 3, 5, 0, 4, …	6, 2, 7, 0, 5, …	N, N, N,	False
6, 5, 7, 9, 0, …	2, 0, 3, 10, 0, …	Y, Y, Y,	True

Amino Acid K-grams Discovered By Entropy



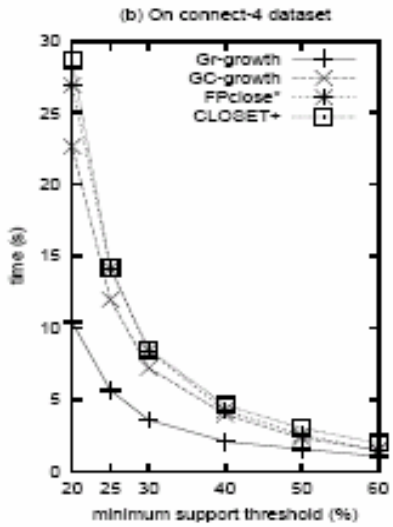
Fold	UP-ATG	DOWN-STOP	UP3-AorG	DOWN-A	DOWN-V	UP-A	DOWN-L	DOWN-D	DOWN-E	UP-G
1	1	2	4	3	6	5	8	9	7	10
2	1	2	3	4	5	6	7	8	9	10
3	1	2	3	4	5	6	8	9	7	10

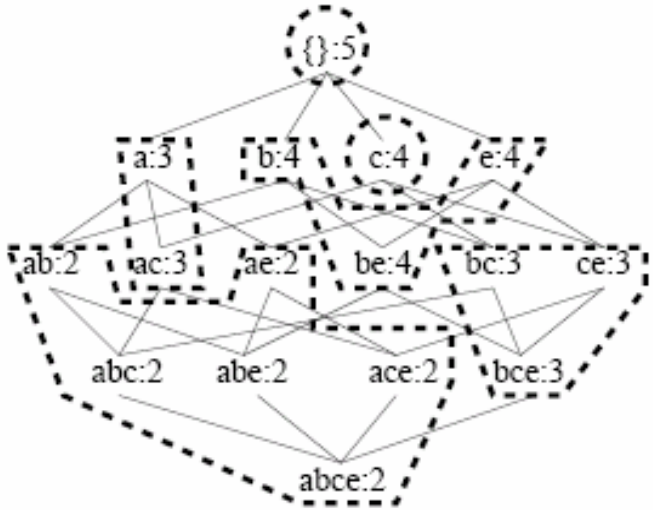
Validation Results on Chr X and Chr 21



- **Using top 100 features selected by entropy and trained on Pedersen & Nielsen's**

Discovering Reliable Patterns





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Discovering Invariants

- **Conservative extension property**
- **Bounded degree property**
- **Logical layer of self-describing exchange formats**

Insights of an expert

- **Diagnosis patterns of ALL subtypes**
- **Signals for protein translation initiation**

Identified using existing machine learning methods

- **Next Goal: Improve capability of machines to discover useful invariants**

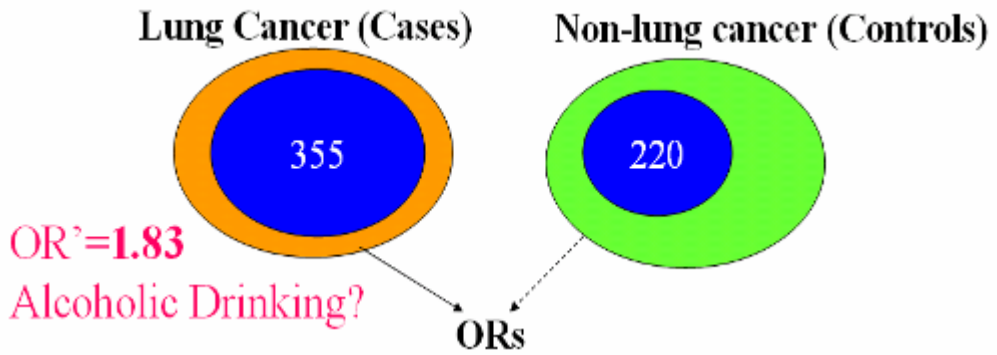
Going Beyond Frequent Patterns: Marrying Statisticians and Data Miners

- **Statisticians use a battery of "interestingness" measures to decide if a feature/factor is relevant**

- **Examples:**
  - Odds ratio
  - Relative risk
  - Gini index
  - Yule's Q & Y
  - etc

- **Odds ratio**

$$OR(P,D) = \frac{\frac{P_{D,ed}}{P_{D,-d}}}{\frac{P_{D,e-}}{P_{D.--}}}$$



Smoking and lung cancer in US hospitals [Stellman etc 2001]

	Cases	Controls
Total	371	373
Smokers	355	220
Non-smokers	16	153
Odds	22.18	1.44

OR = 22.18 / 1.44 = 14.56

Going Beyond Frequent Patterns: Experimenting With Tipping Events

- **Given a data set, such as those related to human health, it is interesting to determine impt cohorts and impt factors causing transition betw cohorts**

⇒ **Tipping events**

⇒ **Tipping factors are "action items" for causing transitions**

- **"Tipping event" is two or more population cohorts that are significantly different from each other**
- **"Tipping factors" (TF) are small patterns whose presence or absence causes significant difference in population cohorts**
- **"Tipping base" (TB) is the pattern shared by the cohorts in a tipping event**
- **"Tipping point" (TP) is the combination of TB and a TF**

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