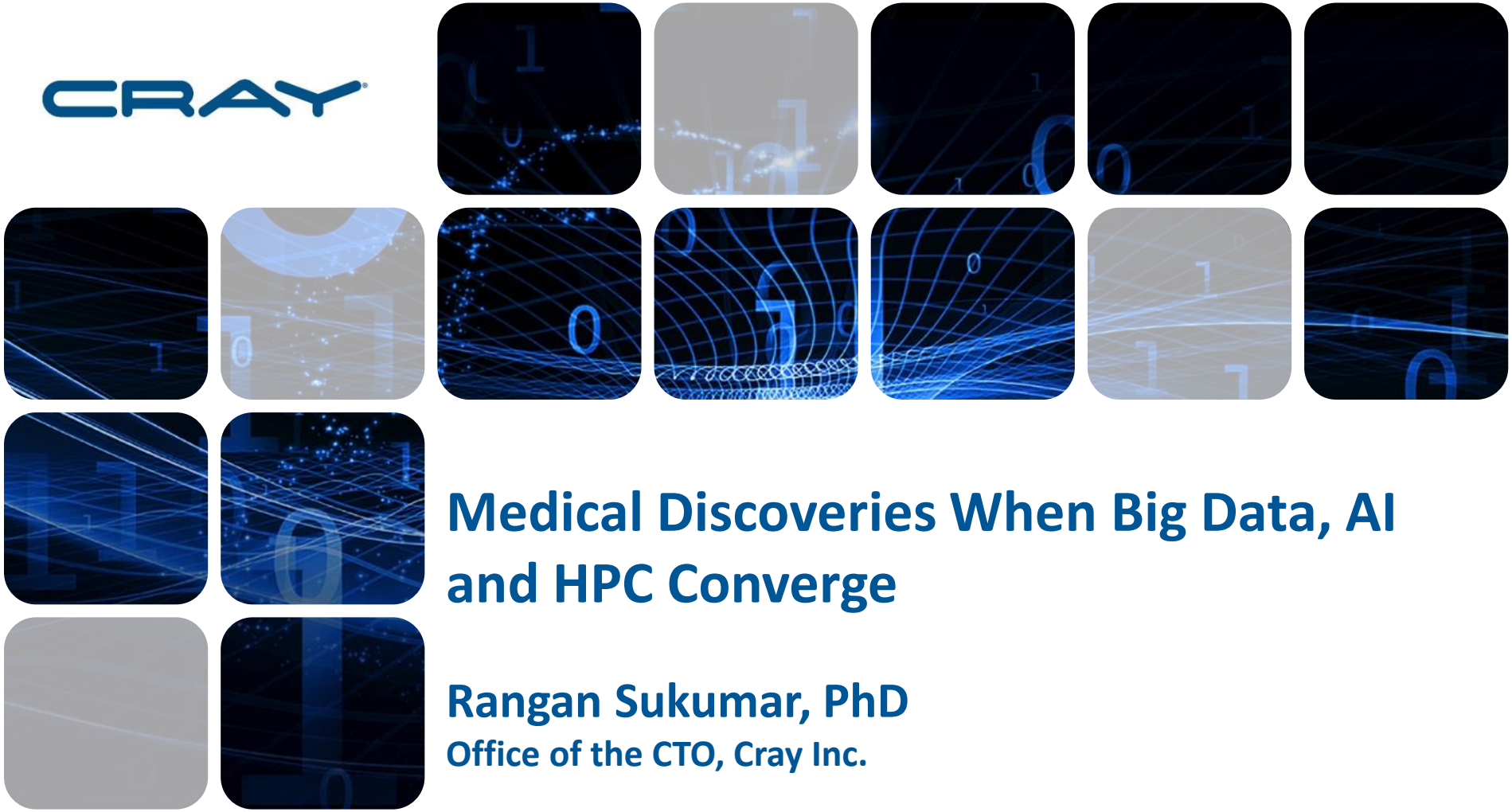
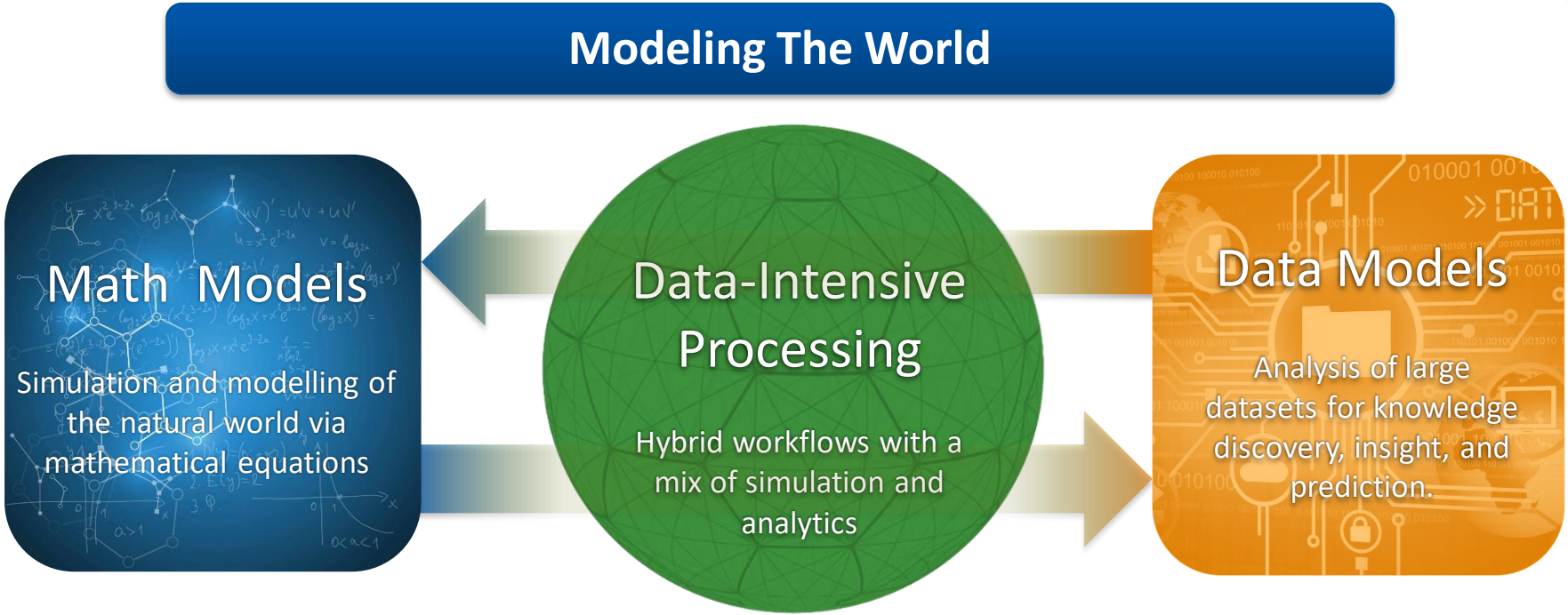


Medical Discoveries When Big Data, AI and HPC Converge

Rangan Sukumar, PhD

Office of the CTO, Cray Inc.

The Convergence of Big Data, AI and HPC



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The Convergence of Big Data, AI and HPC

CRAY URIKA-GX → CS-STORM 500NX → CS-STORM 500GT → CRAY XC SERIES → CRAY URIKA-XC

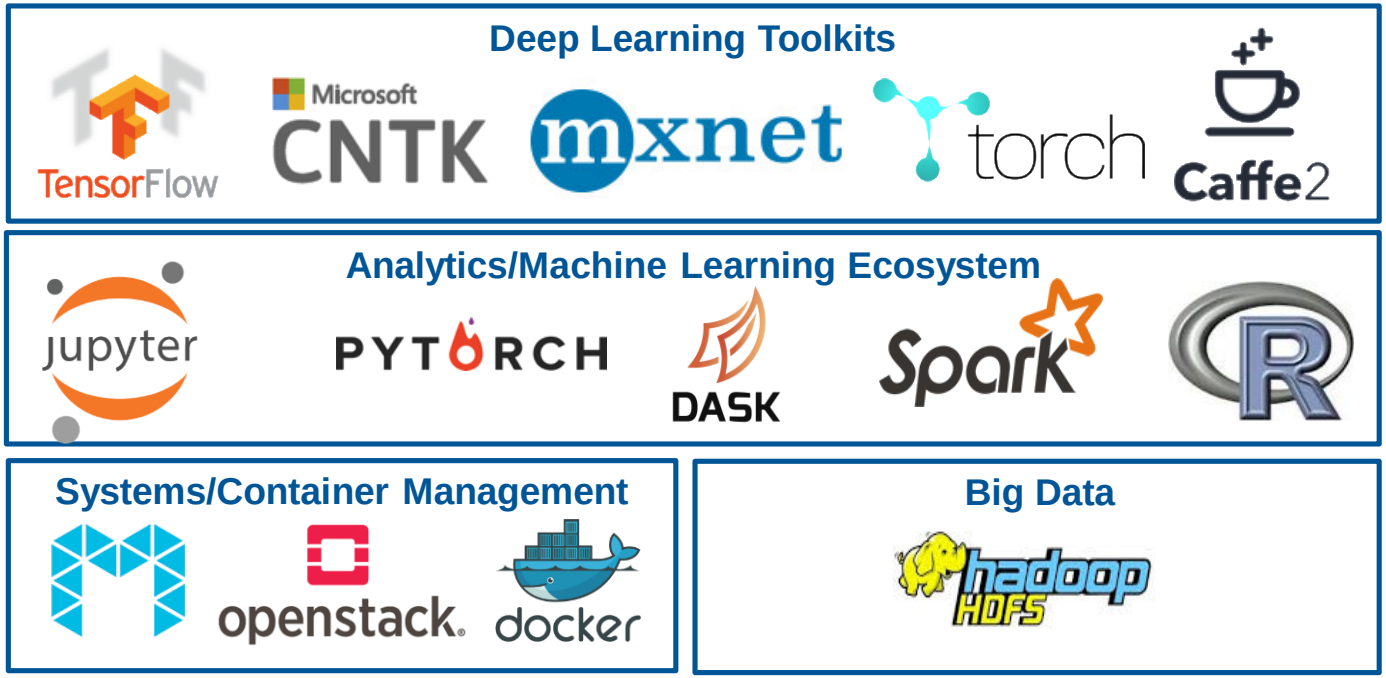
Integrated Analytics and AI platform for Data Preparation and Machine Learning

Dense GPU systems with broad support for NVIDIA® Tesla® Accelerators and FPGAs

Scalable high performance supercomputers with Analytics and AI/DL

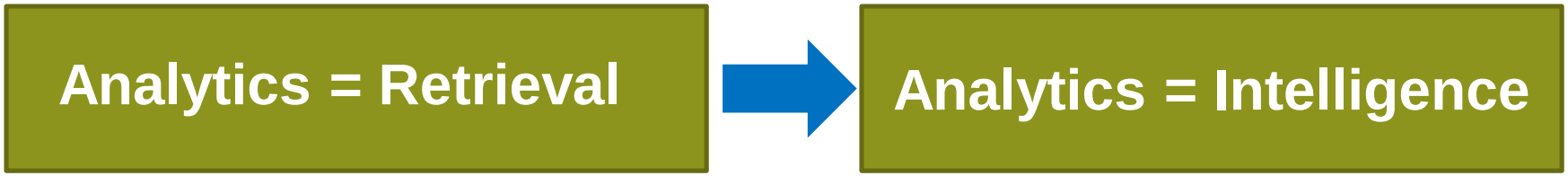
The Convergence of Big Data, AI and HPC

Today: Running software built for the cloud on HPC hardware



Benefit: Convergence of productivity and performance

Opportunity: HPC Contributions to Analytics and AI

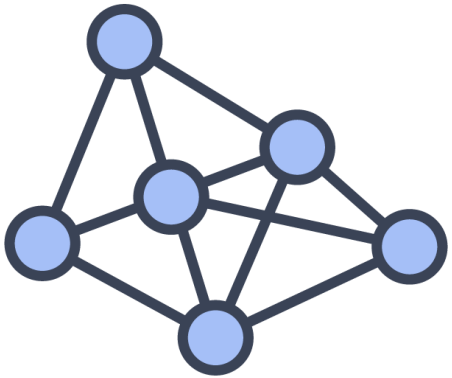


HPC Best Practices:

- Application fine-tuning / Performance optimization
- High-performance interconnect
- Algorithmic cleverness to trade compute and i/o
- Overlap compute and i/o with programming model

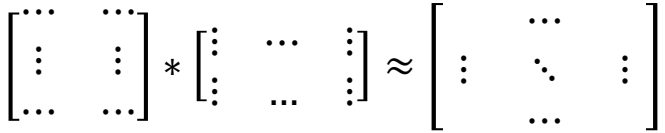
The Convergence of Big Data, AI and HPC

Graph Analytics



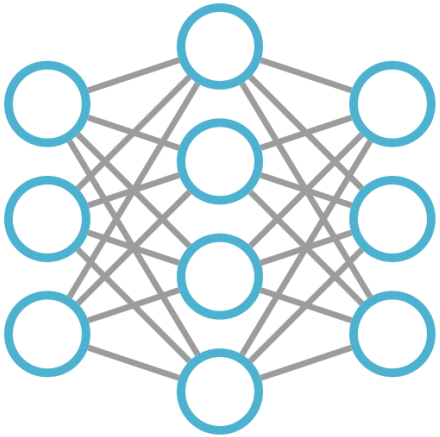
Handle 1000x bigger datasets with a 100x better speed-up with queries

Matrix Methods



Get 2-26x over Big Data Frameworks like Hadoop, Spark

Deep Learning



95%+ scalability efficiency that can reduce training time from days to hours

Observation: HPC has a lot more to offer to Big Data and AI

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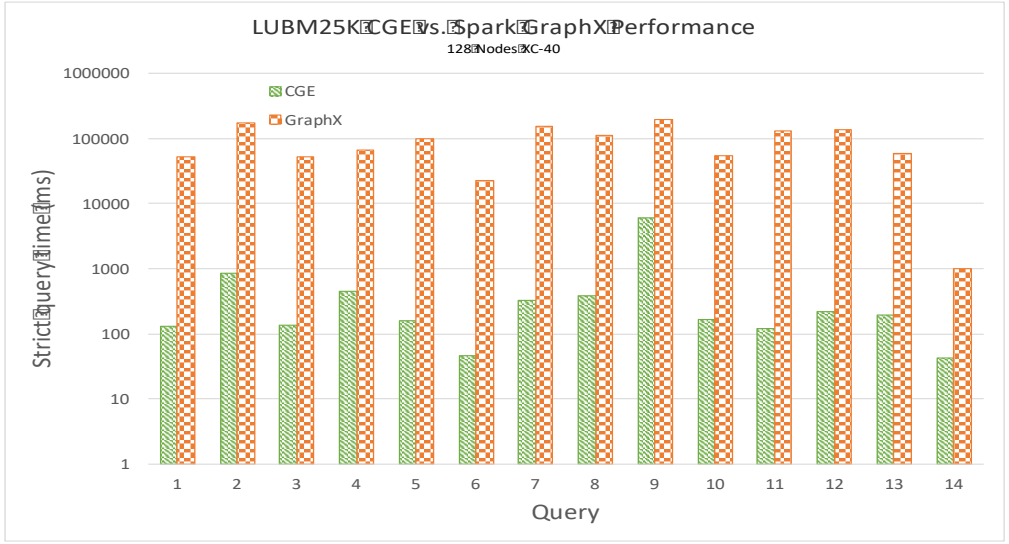
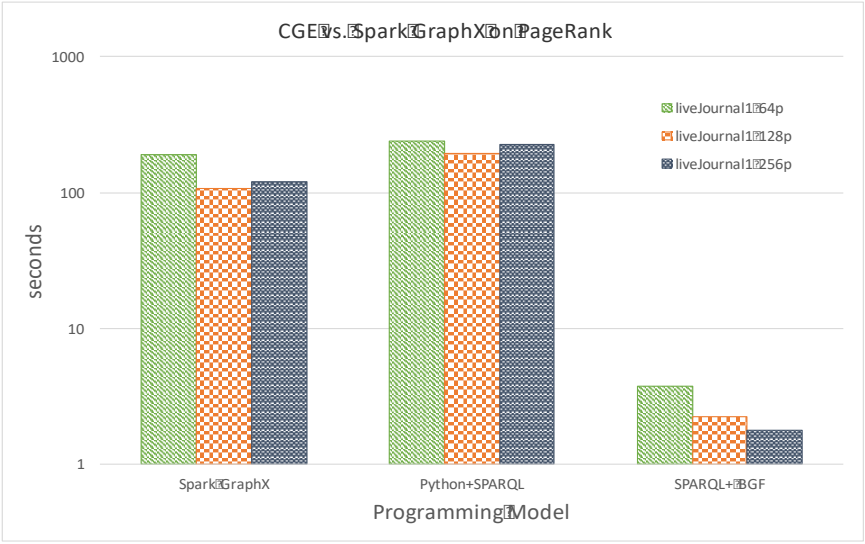
Benefits of Convergence: Graph Analytics

- Comparison to Spark+GraphX

Graph Pattern Search



Graph-Theoretic Algorithms



Nearly a 100x performance speed-up over GraphX....

Maschhoff, K., et al., Quantifying Performance of CGE: A Unified Scalable Pattern Mining and Search System, *in the Proc. Of the Cray User Group Conference*, 2017.

Benefits of Convergence: Matrix Methods

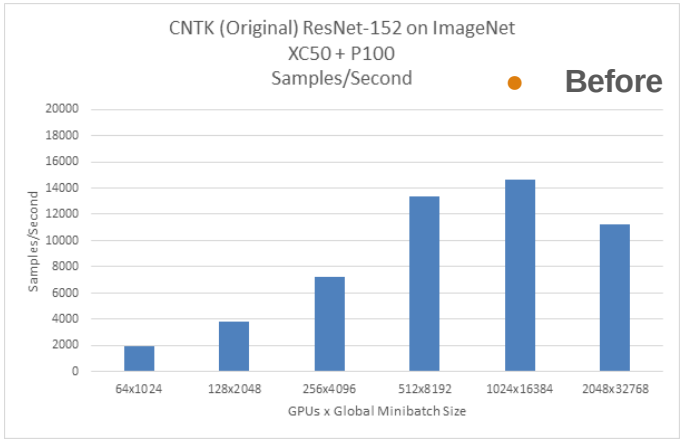
- **Experimental Setup**
  - Cori @ NERSC
  - 1630 compute nodes
  - Memory: 128 GB/node,
  - 32 2.3GHz Haswell cores/node

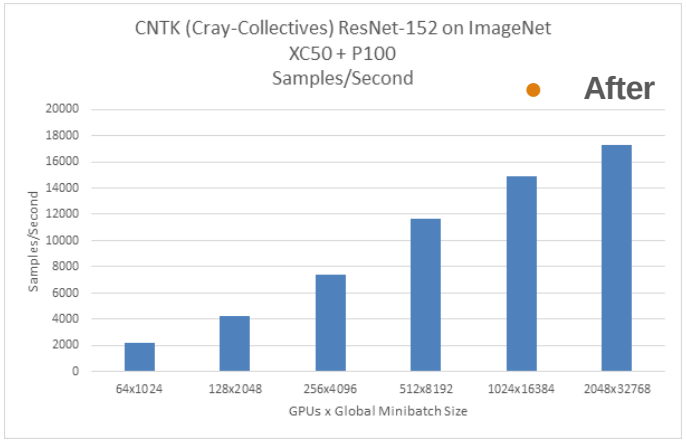
Science Area	Format/Files	Dimensions	Size
MSI	Parquet/2880	$8,258,911 \times 131,048$	1.1TB
Daya Bay	HDF5/1	$1,099,413,914 \times 192$	1.6TB
Ocean	HDF5/1	$6,349,676 \times 46,715$	2.2TB
Atmosphere	HDF5/1	$26,542,080 \times 81,600$	16TB

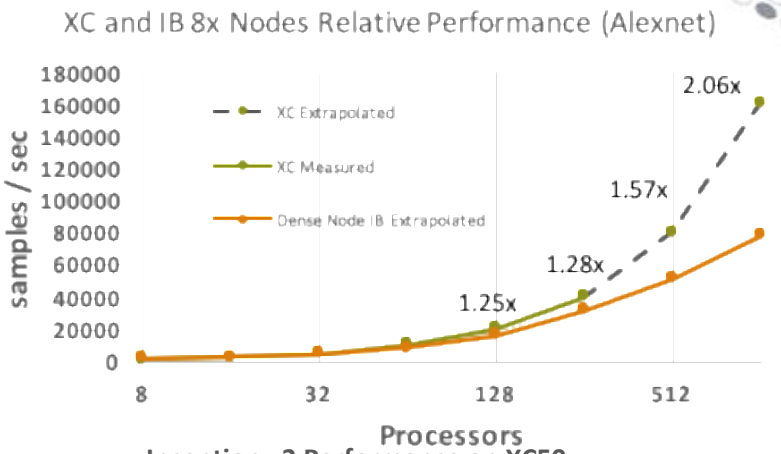
	Nodes / cores	MPI Time	Spark Time	Gap
NMF	50 / 1,600	1 min 6 s	4 min 38 s	4.2x
	100 / 3,200	45 s	3 min 27 s	4.6x
	300 / 9,600	30 s	70 s	2.3x
PCA (2.2TB)	100 / 3,200	1 min 34 s	15 min 34 s	9.9x
	300 / 9,600	1 min	13 min 47 s	13.8x
	500 / 16,000	56 s	19 min 20 s	20.7x
PCA (16TB)	MPI: 1,600 / 51,200 Spark: 1,522 / 48,704	2 min 40 s	69 min 35 s	26x

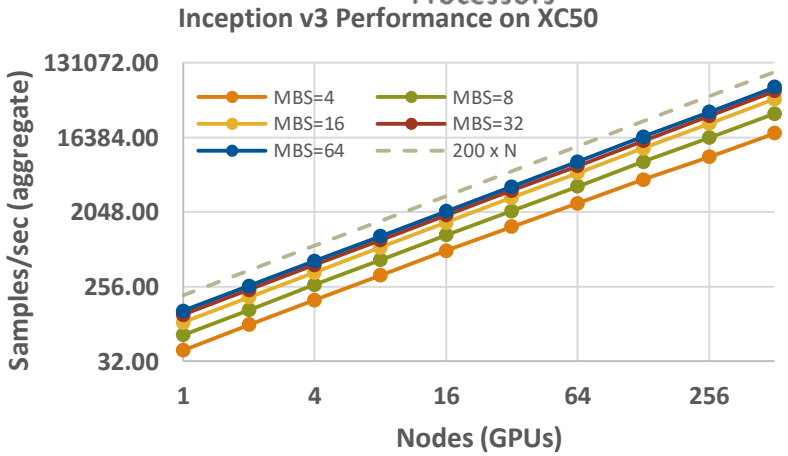
Gittens, Alex, et al. "Matrix factorizations at scale: A comparison of scientific data analytics in spark and C+ MPI using three case studies.", *IEEE International Conference on Big Data*.2016.

Benefits of Convergence: Deep Learning









S.R. Sukumar et al., in the Proceedings of the NIPS Workshop on Deep Learning at Supercomputing scale, 2017

How does convergence help answer questions like…

- How does “scorpion venom” work as a “tumor marker” ?
- Has the association between BUB1B, PLK4 and Cancer control already discovered?
- A patient is unable to stand on his toes, has high levels of Creatine Kinase, showing signs of muscle weakness (particularly in the calf), is walking awkwardly because of that. What rare disease could the patient be suffering from? What gene-mutations should we be looking to target for therapy?
- List all chemicals/small molecules – that interacts with protein P – is known to have associations with Gene X – that causes the symptoms S1,S2,…?
- We know the Molecule X and its properties so well ? Given its mechanism in humans, how can this be repurposed?

Big Data : The National Library of Medicine

Data source: Pubmed + Pubmed Central

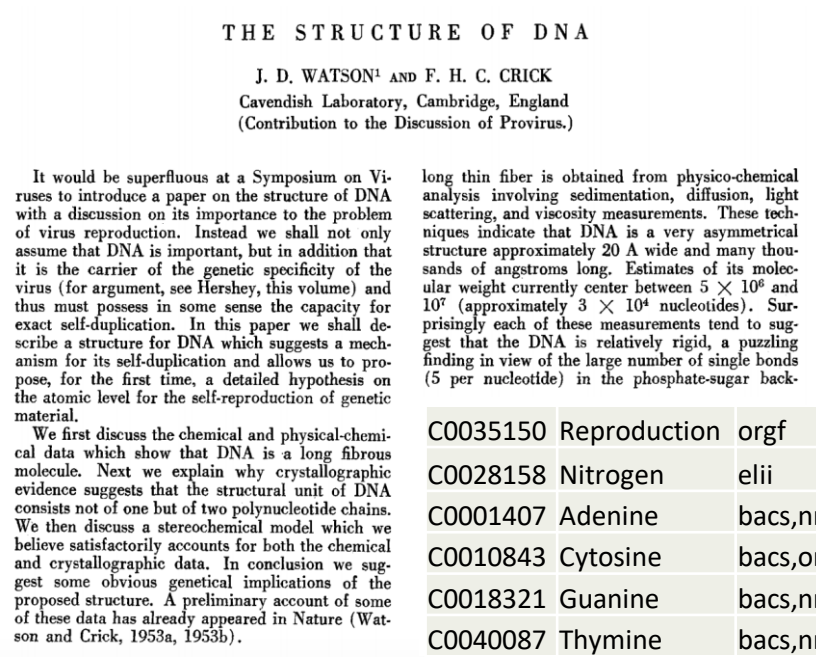
- Number of papers processed : ~27 million
- Number of predications : ~91 million
- Number of distinct terms : ~ 2 million
- Number of "node-types" : 133
- Number of "relationships" : 69

Other open-data sources:

- PubChem, Uniprot, ClinVar, ClinGen, KEGG, DrugBank, OrangeBook, Go, SNOMED, MedDRA , SNOMED,…..

Work conducted at Oak Ridge National Lab…

Matrix Methods for Knowledge Graph Extraction



THE STRUCTURE OF DNA

J. D. WATSON[1] AND F. H. C. CRICK
Cavendish Laboratory, Cambridge, England
(Contribution to the Discussion of Provirus.)

It would be superfluous at a Symposium on Viruses to introduce a paper on the structure of DNA with a discussion on its importance to the problem of virus reproduction. Instead we shall not only assume that DNA is important, but in addition that it is the carrier of the genetic specificity of the virus (for argument, see Hershey, this volume) and thus must possess in some sense the capacity for exact self-duplication. In this paper we shall describe a structure for DNA which suggests a mechanism for its self-duplication and allows us to propose, for the first time, a detailed hypothesis on the atomic level for the self-reproduction of genetic material.

We first discuss the chemical and physical-chemical data which show that DNA is a long fibrous molecule. Next we explain why crystallographic evidence suggests that the structural unit of DNA consists not of one but of two polynucleotide chains. We then discuss a stereochemical model which we believe satisfactorily accounts for both the chemical and crystallographic data. In conclusion we suggest some obvious genetical implications of the proposed structure. A preliminary account of some of these data has already appeared in Nature (Watson and Crick, 1953a, 1953b).

long thin fiber is obtained from physico-chemical analysis involving sedimentation, diffusion, light scattering, and viscosity measurements. These techniques indicate that DNA is a very asymmetrical structure approximately 20 A wide and many thousands of angstroms long. Estimates of its molecular weight currently center between 5×10^6 and 10^7 (approximately 3×10^4 nucleotides). Surprisingly each of these measurements tend to suggest that the DNA is relatively rigid, a puzzling finding in view of the large number of single bonds (5 per nucleotide) in the phosphate-sugar back-

Process

- **Term to concept mapping (UMLS)**
- **Entity resolution (Meta-Thesaurus)**
- **Relationship extraction using NLP.**

C0035150	Reproduction	orgf	orgf	*Process of*	C0042776	Virus	virs	virs
C0028158	Nitrogen	elii	elii	*Coexists with*	C0012854	DNA	bacs,nnon	bacs
C0001407	Adenine	bacs,nnon	bacs	*Is a*	C0034140	Purines	orch	orch
C0010843	Cytosine	bacs,orch	bacs	*Is a*	C0034289	Pyrimidines	orch	orch
C0018321	Guanine	bacs,nnon	bacs	*Is a*	C0034140	Purines	orch	orch
C0040087	Thymine	bacs,nnon	bacs	*Is a*	C0034289	Pyrimidines	orch	orch
C0029235	Organism	orgm	orgm	*location of*	C0010843	Cytosine	bacs,orch	orch
C0039202	T-Phages	virs	virs	*location of*	C0010843	Cytosine	bacs,orch	bacs
C0931513	Right helix	bpoc	bpoc	*part of*	C0018563	Hand	bpoc	bpoc

Natural language to machine-understandable language…

Deep Learning for Natural Language Understanding

Nexium						Heartburn

Filling in the blanks….and then ranking it for significance…

Nexium	‘Is a’	Esomeprazole	*‘Reverse(Is a)’*	Proton Pump Inhibitors	*‘Disrupts’*	Heartburn

Eksp Klin Gastroenterol. 2009;(4):86-92.

[Omeprazol and ezomeprazol pharmacokinetics, duration of antisecretory effect, and reasons for their probable changes in duodenal ulcer].

[Article in Russian]

Serebrova SIu, Starodubtsev AK, Pisarev VV, Kondratenko SN, Vasilenko GF, Dobrovol'skiĭ OV.

Abstract

There were authentic distinctions between the groups of healthy volunteers and patients with a peptic ulcer disease in Cmax, Tmax, AUC(0-t), AUC (0-infinity), Clt, Vd of omeprazole and Cmax of esomeprazole (Nexium, AstraZeneca). When the pharmacokinetics of omeprazole and ezomeprazole were compared in both groups, there were authentic distinctions in Cmax, AU(0-t), AUC(0-infinity), Clt, T1/2. The patients who had taken omeprazole the time of hypoacide condition was much shorter than in other groups. Disintegration test modeling pHmax for pH oscillation with large amplitude, that is typical for ulcer disease, demonstrated a possibility of early partial release of omeprazole, its acid-depended degradation and reduction of its bioavailability.

Aliment Pharmacol Ther. 2006 Sep 1;24(5):743-50.

Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs.

Edwards SJ[1], Lind T, Lundell L.

⊕ **Author information**

Abstract

BACKGROUND: No randomized controlled trial has compared all the licensed standard dose proton pump inhibitors in the healing of reflux oesophagitis.

AIM: To compare the effectiveness of esomeprazole with licensed standard dose proton pump inhibitors for healing of reflux oesophagitis (i.e. lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg).

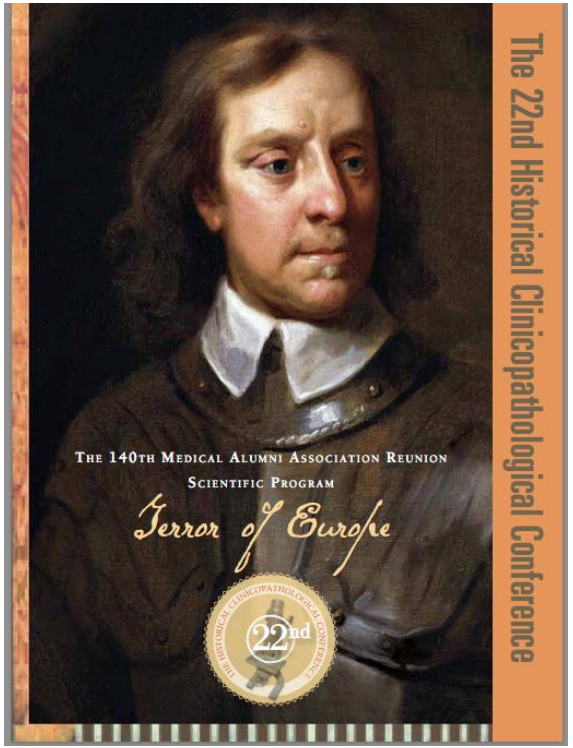
METHODS: Systematic review of CENTRAL, BIOSIS, EMBASE and MEDLINE for randomized controlled trials in patients with reflux oesophagitis. Searching was completed in February 2005. Data on endoscopic healing rates at 4 and 8 weeks were extracted and re-analysed if not analysed by intention-to-treat. Meta-analysis was conducted using a fixed effects model.

RESULTS: Of 133 papers identified in the literature search, six were of sufficient quality to be included in the analysis. No studies were identified comparing rabeprazole with esomeprazole. A meta-analysis of healing rates of esomeprazole 40 mg compared with standard dose proton pump inhibitors gave the following results: at 4 weeks [relative risk (RR) 0.92; 95% CI: 0.90, 0.94; P < 0.00001], and 8 weeks (RR 0.95; 95% CI: 0.94, 0.97; P < 0.00001). Publication bias did not have a significant impact on the results. The results were robust to changes in the inclusion/exclusion criteria and using a random effects model.

CONCLUSION: Esomeprazole consistently demonstrates higher healing rates when compared with standard dose proton pump inhibitors.

Applications/ Success Stories

The Historical Clinicopathological Conference



2015

2016

Use-case: Hypothesis Generation for Mystery Illness

2015

2016

Use-case: Hypothesis Generation for Mystery Illness

This patient, like the artist who made her famous, was a “cripple and an outsider,” though she was not always so. She began life as a small, blond-haired girl with a “silver giggle,” who seemed no different from other children. However, by the time she reached the age of three, she was walking on the outside of her feet with an odd gait. Even so, she was a bright, fiercely determined child, who stomped around ignoring her disability as it gradually increased in severity. By the time she was 13, she stumbled and fell frequently, though with a mind so “bright, curious and hungry,” her teacher had hopes that she too would one day be a teacher. The patient, if not beautiful at age 19, was slim and handsome enough to attract a suitor, who claimed that during their brief courtship, she could do anything–“row a boat, climb a tree, harness a horse, and drive a carriage.” Her letters at that time, however, told a different story, one involving a series of “bad falls.” Her one and only suitor vanished from her life as suddenly as he had appeared. The patient’s balance soon worsened to the point that it was unsafe for her to look up without having a firm grip on something for steadiness. Although she was still able to walk, her crablike gait forced her to use the entire width of the road when ambulating. Her mother made her kneepads to wear under her skirt as protection against her many falls. Her hands, as yet unaffected, were capable of the intricate work of a talented seamstress. By the time she reached 26, the patient could walk only three or four steps without assistance, and her hands had become so misshaped and unsteady she had to use her wrists, elbows, and knees to do those things formerly done with her hands. Offers of help were gently but firmly refused. By the end of her fifth decade, she had lost the ability to stand and resorted to crawling to get where she wanted to go. Her mind continued to be as sharp as ever. No neurological disorders are known to have affected other members of the patient’s family. Her father was a Swedish sailor with a disabling arthritis, who died at age 72 of unknown cause. Her mother developed kidney disease in her 40s and died edematous at age 68 of either renal failure or congestive heart failure. There were three brothers, one who died in his 80s of metastatic bone cancer. The medical histories of the other two are unknown. The patient was evaluated medically just once, when she was 26, at the Boston City Hospital. After a week of observation and tests failed to produce a diagnosis, she was told “to just go on living as [she] had always done. When the patient was 56, she developed a severe illness thought to have been pneumonia. One evening, while recuperating, she sat with one leg stretched out beneath a stove and fell asleep. When she awoke, the heat from the fire had seared the flesh from her withered leg. The third-degree burn healed slowly in response to repeated application of cod liver oil. At age 74, the patient finally consented to the use of a wheelchair and died shortly thereafter.

Use-case: Hypothesis Generation for Mystery Illness

This patient, like the artist who made her famous, was a "cripple and an outsider," though she was not always so. She began life as a small, blond-haired girl with a "silver giggle," who seemed no different from other children. However, by the time she reached the age of three, she was walking on the outside of her feet with an odd gait. Even so, she was a bright, fiercely determined child, who stomped around ignoring her disability as it gradually increased in severity. By the time she was 13, she stumbled and fell frequently, though with a mind so "bright, curious and hungry," her teacher had hopes that she too would one day be a teacher. The patient, if not beautiful at age 19, was slim and handsome enough to attract a suitor, who claimed that during their brief courtship, she could do anything—"row a boat, climb a tree, harness a horse, and drive a carriage." Her letters at that time, however, told a different story, one involving a series of "bad falls." Her one and only suitor vanished from her life as suddenly as he had appeared. The patient's balance soon worsened to the point that it was unsafe for her to look up without having a firm grip on something for steadiness. Although she was still able to walk, her crablike gait forced her to use the entire width of the road when ambulating. Her mother made her kneepads to wear under her skirt as protection against her many falls. Her hands, as yet unaffected, were capable of the intricate work of a talented seamstress. By the time she reached 26, the patient could walk only three or four steps without assistance, and her hands had become so misshaped and unsteady she had to use her wrists, elbows, and knees to do those things formerly done with her hands. Offers of help were gently but firmly refused. By the end of her fifth decade, she had lost the ability to stand and resorted to crawling to get where she wanted to go. Her mind continued to be as sharp as ever. No neurological disorders are known to have affected other members of the patient's family. Her father was a Swedish sailor with a disabling arthritis, who died at age 72 of unknown cause. Her mother developed kidney disease in her 40s and died edematous at age 68 of either renal failure or congestive heart failure. There were three brothers, one who died in his 80s of metastatic bone cancer. The medical histories of the other two are unknown. The patient was evaluated medically just once, when she was 26, at the Boston City Hospital. After a week of observation and tests failed to produce a diagnosis, she was told "to just go on living as [she] had always done." When the patient was 56, she developed a severe illness thought to have been pneumonia. One evening, while recuperating, she sat with one leg stretched out beneath a stove and fell asleep. When she awoke, the heat from the fire had seared the flesh from her withered leg. The third-degree burn healed slowly in response to repeated application of cod liver oil. At age 74, the patient finally consented to the use of a wheelchair and died shortly thereafter.

Use-case: Hypothesis Generation for Mystery Illness

2015	2016
Malaria	**Charcot Marie Tooth Disease**
Lichen disease	**Welander Distal Myopathy**
Urinary tract infection	Fasciitis Plantar
Coccidiosis	Talocalcaneal coalition
Bacteremia	**Cerebellar atrophy**
Encephalomyelitis Western Equine	Friedreich Ataxia
Poisoning syndrome	Hypolipoproteinemia
Adult Still's Disease	Multi infarct state
MRSA (Staph Infection)	Neuroleptic Induced Parkinson
Septecemia	Quadriplegic spastic cerebral palsy

Use-case: Hypothesis Generation for Mystery Illness

Hypothesis	Probability
Hereditary Motor and Sensory Neuropathies	0.035417
Charcot Marie Tooth Disease	0.035417
Welander Distal Myopathy	0.022746
Fasciitis Plantar	0.02125
Talocalcaneal coalition	0.02125
Cerebellar atrophy	0.003833
Friedreich Ataxia	0.002471
Hypolipoproteinemia	0.002471
Multi infarct state	0.002471
Neuroleptic Induced Parkinson	0.002471
Quadriplegic spastic cerebral palsy	0.002471
Subcortical vascular encephalopathy	0.002471

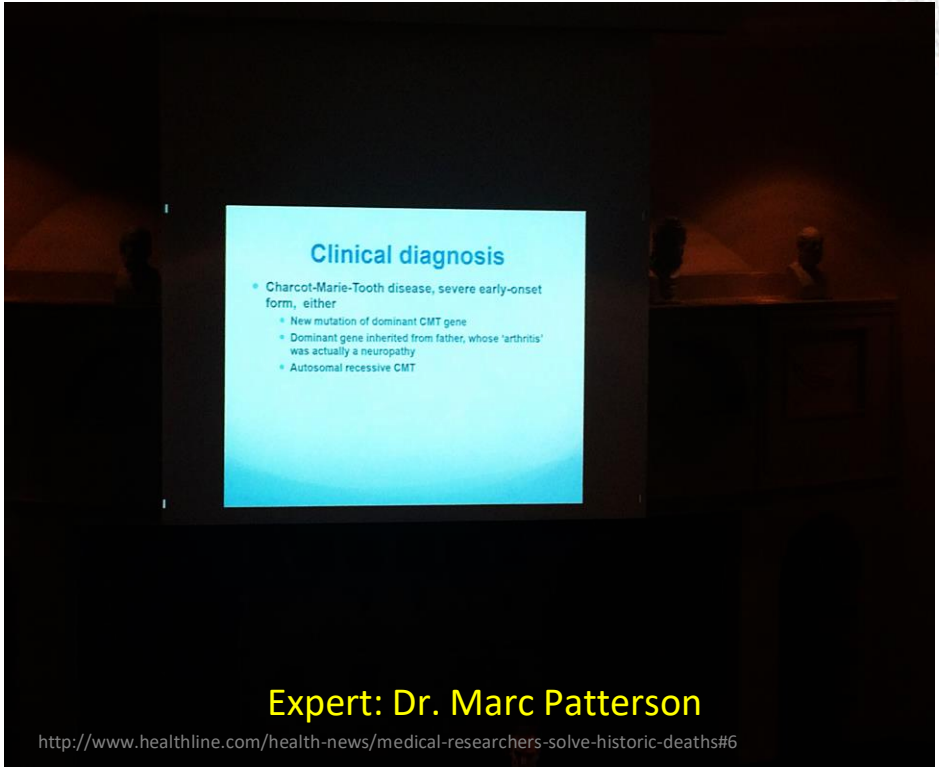
Base probability for random disease : 1e-6

Use-case: Hypothesis Generation

2015

Expert: Dr. Sanjay Saint + House staff

2016



Expert: Dr. Marc Patterson

http://www.healthline.com/health-news/medical-researchers-solve-historic-deaths#6

ORIGAMI now has answers for 23 previous mysteries….

Use-case: Hypothesis Generation

Blonde hair	CAUSES (Rev)	Tyrosinase related protein 1	COEXISTS WITH	PER2 protein mammalian	COEXISTS WITH (Rev)	MTMR2	ASSOCIATED WITH	Charcot Marie Tooth Disease

SCANDINAVIAN	PART OF (Rev)	9p21	PART OF	11q22	CAUSES	Charcot Marie Tooth Disease

- https://www.ncbi.nlm.nih.gov/pubmed/12659723
  - https://www.ncbi.nlm.nih.gov/pubmed/11951580
    - https://www.ncbi.nlm.nih.gov/pubmed/18728766
      - https://www.ncbi.nlm.nih.gov/pubmed/24575447

Charcot-Marie-Tooth dis
chromosome 17p11.2.

Holmberg BH[1], Holmgren G, Nel

⊕ **Author information**

Abstract

Sixty-seven patients in 29 families with the diagnosis of Charcot-Marie-Tooth disease o
Sweden were examined by pedigree and DNA analysis for the CMT1a duplication within
families with Charcot-Marie-Tooth type 1 and autosomal dominant inheritance and in all
families with Charcot-Marie-Tooth type 1 the pedigrees strongly suggested autosomal re
informative but in the others no duplication was shown. There were also 11 "sporadic" p
type 1, but there was no duplication shown although in four patients DNA analysis was
type 2 from five families and in 13 unaffected relatives of Charcot-Marie-Tooth patients

PMID: 8071969 [PubMed - indexed for MEDLINE] PMCID: PMC1049919 Free PMC Article

PID	SID	PNUMBER	PMID	predicate	s_cui	s_name	s_type	s_novel	o_cui	o_name	o_type	o_novel
689663	40006674	1	8071969	USES	C0030705	Patients	podg	0	C0441730	Type 2	clas	1
727938	40006674	1	8071969	PROCESS_OF	C0007959	Charcot-Marie-Tooth Disease	dsyn	1	C0030705	Patients	humn	0
2659744	40006253	1	8071969	USES	C0015576	Family	famg	1	C0441729	Type 1	clas	1
2659744	40006388	1	8071969	USES	C0015576	Family	famg	1	C0441729	Type 1	clas	1
4921272	40005656	1	8071969	LOCATION_OF	C0008662	Chromosomes, Human, Pair 2	celc	1	C0007959	Charcot-Marie-Tooth Disease	dsyn	1
4921301	40005862	1	8071969	DIAGNOSES	C0200898	DNA analysis	lbpr	1	C0007959	Charcot-Marie-Tooth Disease	dsyn	1
4921324	40005862	1	8071969	DIAGNOSES	C0200898	DNA analysis	lbpr	1	C0027888	Hereditary Motor and Sensory Neuropathies	dsyn	1

Search is not only about results but also the evidence….

Use-case: Knowledge + Data = Discovery

Sample Measurements | **Images** | **Text**

Patient ID	Pregnant	Race	OD Condition	Age	HgbA1c	Cholest.
19	N	African	NPDR Severe + CSME	37	Null	185
43	N	Caucasian	No diabetic retinopathy	64	11.7	161
58	Y	Unknown	Null	33	10.2	220
104	N	Hispanic	Other	53	9.7	Null
135	N	African	NPDR Mild/Minimal - CSME	62	8.2	148

Comments
Poor quality images but adequate for diagnosis
Vascular tortuosity (congenital). No retinopathy
Mild ischemia (cotton woll spots) No hemorrhages or edema
possible mild drusen No DR evident
rare microaneurysms only f/u 12 months

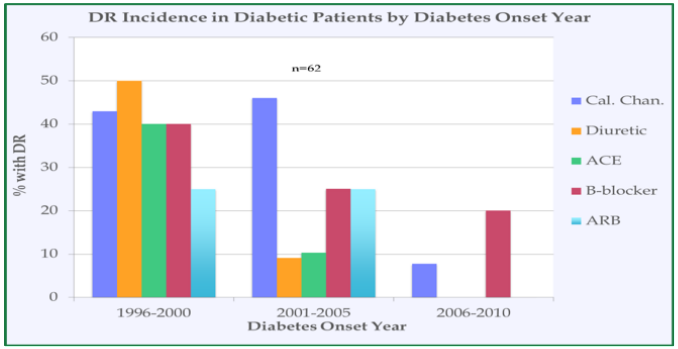
Dataset: 7600 patients, 31 clinical lab measurements, at least 1 image and report per patient, about a 100 meta-data variables over 3 year period.

Use-case: Beta-Blockers and Retinopathy

Existing Knowledge + New Data = New Knowledge

Attributes common with patients without DR (> 80% support)

DM Status: Normal routine history
DM Problem: Hypertension
DM Drug: Lisinopril



Attributes common patients with DR (> 80% support)

DM Medication : "INSULIN + PILL"
Condition EE : "NPDR Mild/Minimal + CSME"
DM Drug : "Glyburide"

Diabetic Retinopathy (DR) and Beta Blockers (BB) in Cross-Sectional Data: Hypothesis Testing

Incidence of DR by Population Characteristic

Characteristic	Incidence of DR (%)	Total (n)	With DR (n)
BB	46.5	88	41
No BB	28.6	412	118
No BB + hypertension (HTN)	29.0	338	98
Diabetes mellitus (DM) onsett > 5 years	39.1	233	91
DM onsett ≤ 5 yr.	7.8	115	9
DM onsett > 5 yr. + BB	54.0	50	27
DM onsett ≤ 5 yr. + BB	14.3	14	2
DM onsett > 5 yr. no BB	35.7	207	74
DM onsett ≤ 5 yr. no BB	6.9	101	7

Incidence of DR: 2 × 2 Fisher's Exact Tests

BB vs. No BB

	DR	*No DR*
BB	41	47
No BB	118	294

p = 0.0010 (extremely statistically significant)

K. Senter, *S. R. Sukumar*, R.M. Patton and E. Chaum, "Using Clinical Data, Hypothesis Generation Tools and PubMed Trends to Discover the Association between Diabetic Retinopathy and Antihypertensive Drugs", in the Proc. of the Workshop on Mining Big Data to Improve Clinical Effectiveness in conjunction with the IEEE Conference on Big Data, pp. 2366-2370, 2015.

Success Stories…Bringing Transformation

The Washington Post

Calling in big brains

To solve the riddle of Cromwell's death, Mackowiak invited a new kind of sleuth to weigh in. While Saint hit his books, computer specialists from the U.S. Department of Energy's Oak Ridge National Laboratory in Tennessee fed details of Cromwell's medical history into a network of supercomputers. A software program designed by Oak Ridge engineers churned through 27 million medical articles and texts, analyzing 70 million data associations relevant to Cromwell's case.

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"Who would I rather have making a diagnosis? It would be hands-down Dr. Saint," Siegel said. On the ot hand, "if you told me there was a mystery disease and no one had any ideas about it and we needed some new insight . . . I like the computer."

Oak Ridge engineers are preparing to reopen several of the cases pondered by Mackowiak and his collea through the years. The results may upend some of the conclusions so painstakingly drawn — and deeper medical mysteries thought to be solved.

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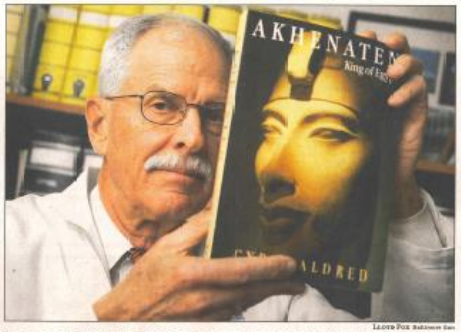
LATIMES.COM Los Angeles Times ★ SATURDAY, JANUARY 23, 2016 A7

Taking on postmortem puzzles



Lloyd Fox Baltimore Sun

THE HISTORICAL Clinicopathological Conference, launched by Dr. Philip A. Mackowiak, has examined the deaths of Herod the Great, Pericles and Egyptian Pharaoh Akhenaten.

[Mysteries, from A1]
ure's cause of death is a puzzle that combines their diagnostic skill and medical intuition with biographical research, archival excavation, epidemiological sleuthing and a dash of guesswork.

"It is the ultimate whodunit," said Dr. Sanjay Saint, who, after weeks of research and deliberation, concluded that Cromwell had died of malaria — which was endemic to the British Isles at the time — combined with a salmonella infection that gave him typhoid fever.

"The reason we go into medicine is to help patients," said Saint, the associate chief of medicine at the Veterans Affairs Healthcare System in Ann Arbor, Mich. But that's not all.

"There's also that part of playing detective, of being curious about a mystery and wanting to figure it out."

Dr. Jay Hirschmann, a staff physician at the VA Puget Sound Health Care System in Seattle, caught the medical detective bug nearly 20 years ago, and has been at it off and on ever since.

On a lark in the late 1990s, a musician and medical colleague of Hirschmann's invited him to lecture on the death of Wolfgang Amadeus Mozart in 1791, just shy of his 36th birthday. Hirschmann, an [illegible] expert and [illegible]ader with a penchant [illegible]-solving, knew next to [illegible]at Mozart's life or the [illegible]es of his demise. But [illegible]p sounded like fun, [illegible]dived into every [illegible]ding and find.

[illegible]nd suffered from a [illegible]int pain as a child. [illegible]doctors have [illegible]ute rheumatic fever. [illegible]s caused to chronic [illegible]cations, many as[illegible]strian composer [illegible]t failure.

[illegible]e historian suggested [illegible]been poisoned by his [illegible]lian composer Anto[illegible]Other candidates for [illegible]th included kidney [illegible]nfective endocarditis. [illegible]ose diagnoses acded [illegible]een thought. Mo[illegible] letters said he was "in [illegible]th" before he was [illegible]ertaken by fever and a skin rash.

These symptoms — along with physicians' notes and diary entries from the time — pointed to some sort of outbreak. "The only one that matched Mozart's symptoms was trichinosis, a parasitic disease caused by eating undercooked meat, usually pork. But Hirschmann had one big problem: He didn't know what Mozart ate.

As he sat in the hospital library waiting to give his lecture, Hirschmann leafed through a book one last time. That's when he came across a letter that stopped him cold.

Mozart was writing to his wife, Constanze, when he was interrupted by a servant bringing dinner. He wrote:

"And what do [illegible]? ... Pork cutlets! *Che gusto* I eat to your health."

The letter was dated Oct. 7, 1791. Mozart fell sick 4 days later — about the time it typically takes for trichinosis symptoms to appear after infection.

Triumphant, Hirschmann presented his findings to a fascinated audience. He published them in the Archives of Internal Medicine in 2001.

"I call it the smoking — or not-so-smoking — pork chop," he said.

The diagnosis produced what Hirschmann laughingly calls the two "scenes" of his career: a spot in the grocery store tabloid the Star and a mention in Jay Leno's "Tonight Show" monologue.

"That got me my 15 minutes of fame," he said.

It also got him noticed by Dr. Philip A. Mackowiak, the University of Maryland physician and epidemiologist who launched the medical school's annual Historical Clinicopathological Conference in 1995.

Mackowiak asked Hirschmann to investigate the death of Herod the Great in 4 B.C., when the Judean ruler was 69. (Hirschmann's diagnosis: kidney disease, complicated by Fournier's gangrene.)

Over the last 20 years, Mackowiak's medical sleuthing has reached as far back in history as ancient Greece (the statesman Pericles probably succumbed to typhus fever in what was called "the plague of Athens") and as close to home as Baltimore (the writer Edgar Allan Poe most likely died of rabies).

"Physicians are hungry for liberal arts outlets," said Mackowiak, who has published two books on historical medical mysteries. At the same time, students of the liberal arts "crave a way into an arcane field like medicine." Conducting postmortems on historical figures "seemed like the perfect opportunity" to enrich the lives of both communities, he said.

In 2007, for instance, physicians, historians and mystery enthusiasts considered how Abraham Lincoln's gunshot wound to the head might have been treated in a modern neurosurgical unit, and whether he would have lived. Their conclusion: Though Lincoln certainly would have been disabled, survival would be "a very reasonable expectation."

Conference attendees have also learned that after death, the blood vessels in Vladimir Lenin's brain were so calcified they "sounded like stone" when tapped with tweezers, that the Egyptian Pharaoh Akhenaten probably inherited a hormone disorder that made him look like a woman, and that Beethoven's deafness was probably a consequence of syphilis passed down from his father.

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Maria L. La Ganga, a former Times staff writer based in Seattle, and special correspondent Melissa Pandika in Los Angeles contributed to this report.

Thank you…

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