Matrix Computation in Precision Health and Wellness

Joel Dudley, PhD
Director of Biomedical Informatics &
Assistant Professor of Genetics and Genomic Sciences,
Icahn School of Medicine at Mount Sinai
Mount Sinai Health System

7 Member hospital campuses

>3,500 Hospital beds

>6,000 Physicians

>3,100,000 Patient visits
There are rarely smoking guns in human health
There are rarely smoking guns in human health
No such thing as a “simple” disease

Lungs and sinuses
Infection, inflammation and obstruction

Sweat gland
Elevated sweat chloride concentration

Liver
Cirrhosis

Pancreas
Exocrine dysfunction, diabetes and pancreatitis

Intestine
Neonatal obstruction (meconium ileus) and distal intestinal obstruction

Male reproductive tract
Obstructive male infertility

Airway obstruction
TGFβ1, MBL2, EHF, AP1, Chr20q13.2, SLC9A3 and SLC6A14

Infection with P. aeruginosa
MBL2, DCTN4 and SLC6A14

Exocrine insufficiency

Risk and age at onset of diabetes
TCF7L2, CDKAL1, CDKN2A/B, IGF2BP2 and SLC26A9

Risk of intestinal obstruction
MSRA, SLC6A14, SLC26A9 and SLC9A3

BMI
Chr1p36.1 and Chr5q14

CFTR genotype
Genetic modifiers
Environmental and stochastic factors

Cutting GR. Nature Reviews Genetics. (2014) doi:10.1038/nrg3849
We must embrace complexity to fully understand patient physiology and disease.
We must embrace complexity to fully understand patient physiology and disease.

A complex adaptive system has three characteristics. The first is that the system consists of a number of heterogeneous agents, and each of those agents makes decisions about how to behave. The most important dimension here is that those decisions will evolve over time. The second characteristic is that the agents interact with one another. That interaction leads to the third—something that scientists call emergence: In a very real way, the whole becomes greater than the sum of the parts. The key issue is that you can’t really understand the whole system by simply looking at its individual parts.”

- Michael J. Mauboussin (investment banker)
Although our ability to embrace complexity will bump up against our want to tell stories.

Zeus, the sky god; when he is angry he throws lightning bolts out of the sky.

The earth is flat.

Ptolemaic astronomy: the earth is the center of the universe.

Biological processes are driven by simple linearly ordered pathways (e.g. TGF-beta signaling).
Who wants to hear actors talk?
– H.M. Warner
Warner Brothers, 1927

Anyone who thinks the ANC is going to run South Africa is living in cloud-cuckoo-land
– Margaret Thatcher
British Prime Minister, 1987

There is no reason anyone would want a computer in their home
– Ken Olsen
Founder and president of Digital Equipment Corp., 1977

I think there is a world market for maybe five computers
– Thomas Watson
Chairman of IBM, 1943

There will never be a bigger plane built
– A Boeing engineer after first flight of the 247, a 10-seater

Biological processes are organized into simple pathways
– Life and Biomedical Sciences
The biggest challenge for matrix computation

“When you have a hammer, everything looks like a nail”
We can measure more than we know
Exploring the transcriptional landscape of human disease

~300 Diseases and Conditions

Blue: gene goes down in disease

Yellow: gene goes up in disease

20k+ Genes

Redefining disease with data
Data Driven Approach to Connect Drugs and Disease Using Molecular Profiles

Topiramate Reduces IBD Severity in a TNBS Rodent Model of IBD

- TNBS chemically induced rat model of IBD
- Animals treated with 80mg/kg topiramate oral after sensitization
- Prednisolone positive control (approved for IBD in humans)

Approved compound for non-cancer indication prevents formation of SCLC tumors in a genetic model of SCLC

**Control**

**Imipramine**

Mice dosed after tumor formation

p53/Rb/p130 triple knockout model of SCLC
Welcome to the era of the enabled discovery bioinformatician
No hospital needed: human tissues from commercial tissue banks
No wet lab needed: contract research organizations are cheap and abundant
No wet lab needed: contract research organizations are cheap and abundant
How do approved drugs modulate networks in immune cells?
Antifungal activates neutrophil migration

Antifungal activates neutrophil migration

Immunemod score predicts immune cell perturbations in patient populations

Understanding the multiscale complexity of patient populations
Capturing rich multi scale data on patients through the Mount Sinai Biobank

DNA

RNA

Microbiome

Immune

Diagnoses

Drugs

Labs

Procedures
**CACNA1E Variants Affect Beta Cell Function in Patients with Newly Diagnosed Type 2 Diabetes. The Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) 3**

Maddalena Trombetta, Sara Bonetti, MariaLinda Boselli, Fabiola Turrini, Giovanni Malerba, Elisabetta Trabetti, PierFranco Pignatti, Enzo Bonora, Riccardo C. Bonadonna

Department of Medicine, University of Verona, Verona, Italy, 2Azienda Ospedaliero Universitaria Integrata di Verona, Verona, Italy, 3Department of Life and Reproduction Sciences, University of Verona, Verona, Italy

*Diabetologia* December 2007, Volume 50, Issue 12, pp 2467-2475

Polymorphisms in the gene encoding the voltage-dependent Ca²⁺ channel Ca.2.3 (CACNA1E) are associated with type 2 diabetes and impaired insulin secretion

Type 2, Type 3, and Type 4 diabetes?
Subtype 1: More T2D Complication & Infection

- Other upper respiratory infections
- Immunizations and screening for infectious disease
- Diabetes mellitus with complications
- Other skin disorders
- E Codes: Place of occurrence
- Blindness and vision defects
- Other screening for suspected conds. (not mental disorders or infec. dise)
- Screening and history of mental health and substance abuse codes
- Other circulatory disease
- Acute and unspecified renal failure
- Pulmonary heart disease
- Deficiency and other anemia
- E Codes: Adverse effects of medical care

Odds Ratios with 95% Wald Confidence Limits

Li Li
Joel Dudley
Genetic Variants

Subtype 3:
- Cardiovascular system
- Mental neurologic system
- HIV related neurologic disorder
- Vitamin D
- Allergy
- Response to the drug of statin

Subtype 1:
- T2D complication
- Diabetic retinopathy/vision
- Diabetic nephropathy
- Vitamin D
- CBC panel
- Respiratory system
Network based precision medicine for Multiple Myeloma

Gene Expression Profile  
DNA Variants  
Biochemical / Pathology  
Clinical Traits  

Multiscale Multiple Myeloma Network

In collaboration with Dr. Samir Parekh & Dr. Sundar Jagganath
Network based precision medicine for Multiple Myeloma

In collaboration with Dr. Samir Parekh & Dr. Sundar Jagganath
Mapping and mining the universe of drugs and disease
Multi-scale drug profile

Perturbed transcriptional modules

Targets

DRD3  5HT1A  HRH1  ADRA1A
Chemo-genomic Network
Ceterizine chemogenomic neighborhood
# Side effects enriched in ceterizine neighborhood

<table>
<thead>
<tr>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>paralytic ileus</td>
<td>5.28E-11</td>
</tr>
<tr>
<td>extrapyramidal symptoms</td>
<td>9.85E-11</td>
</tr>
<tr>
<td>drowsiness</td>
<td>2.44E-10</td>
</tr>
<tr>
<td>ileus</td>
<td>3.61E-10</td>
</tr>
<tr>
<td>mydriasis</td>
<td>2.64E-08</td>
</tr>
<tr>
<td>parotid swelling</td>
<td>3.90E-08</td>
</tr>
<tr>
<td>dry mouth</td>
<td>1.64E-07</td>
</tr>
<tr>
<td>testicular swelling</td>
<td>2.25E-06</td>
</tr>
<tr>
<td>hyperpyrexia</td>
<td>3.15E-06</td>
</tr>
<tr>
<td>peculiar taste</td>
<td>1.40E-05</td>
</tr>
<tr>
<td>addiction</td>
<td>1.42E-05</td>
</tr>
<tr>
<td>neuroleptic malignant</td>
<td>1.64E-05</td>
</tr>
<tr>
<td>malignant syndrome</td>
<td>1.64E-05</td>
</tr>
<tr>
<td><strong>oculogyric crisis</strong></td>
<td><strong>1.67E-05</strong></td>
</tr>
</tbody>
</table>

Dryness of the mouth, nose and throat, drowsiness, urinary retention, blurred vision, nightmares and headaches are commonly reported side effects of this drug (in over 40% of the patients). Stomach aches are usually rare, but mostly present in patients with lactose intolerance.[15] Cetirizine does not block the action of the muscarinic acetylcholine receptors, even though these side effects can occur in some patients. Also, cetirizine does not have antidopaminergic properties. In 2012, the FDA added cetirizine in Drugs to Watch List for oculogyric crisis.
Mapping and mining the universe of drugs and disease

DrugGraph - Open Resource for Multiscale Drug Discovery and Repurposing
“The future is already here — it's just not very evenly distributed”.

- William Gibson
Data Feeds
5Gb Data/lap
300 Sensors
3,000 Variables/0.1 sec
>200Gb Data/day
<table>
<thead>
<tr>
<th>SIGN</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>1 min</th>
<th>5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>Less Than 100</td>
<td>Over 100</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory Effort</td>
<td>Absent</td>
<td>Slow, Irregular</td>
<td>Good Cry</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Limp</td>
<td>Some Flexion</td>
<td>Active Motion</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Reflex Irritability</td>
<td>No Response</td>
<td>Grimace</td>
<td>Cry</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Color</td>
<td>Pale</td>
<td>Body Pink, Extr. Blue</td>
<td>All Pink</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

6 10
We are on the crest of a tsunami in consumer sensor technologies.
Printable tattoo biosensor
one tiny drop changes everything.

At Theranos, we’re working to shape the future of lab testing. Now, for the first time, our high-complexity CLIA-certified laboratory can perform your tests quickly and accurately on samples as small as a single drop.
Get answers about your health without the hassle.

Feel better, have more energy & find out what’s going on inside your body - quickly and conveniently. Spend more time doing what you love, less time at the doctor.

Create FREE Account  Compare all packages
Consumer health tools as a driver of data-driven healthcare

Where will most of the health data be in 5-10 years?

Apple's iWatch Project Is Starting To Sound Incredible: They're Hiring Experts In Blood Monitoring

Google to make smart contact lenses

Google is developing smart contact lenses that will measure diabetics' blood glucose levels.
Now everybody can do their part to advance medical research.

Medical researchers are doing some of the most important work in the world, and they’re committed to making life-changing discoveries that benefit us all. To help, we’ve created ResearchKit, an open source software framework that makes it easy for researchers and developers to create apps that could revolutionize medical studies, potentially transforming medicine forever.

Watch the film ⚪
Helping asthma sufferers breathe more easily.

Mount Sinai, Weill Cornell Medical College, and LifeMap developed their Asthma Health app to gain greater insight into triggers for the disease. It helps participants self-manage their asthma by avoiding areas where air quality could worsen symptoms. And since the study tracks symptom patterns in individuals, researchers hope to discover new ways to personalize treatment.

Data from the GPS in your iPhone is combined with information about the air quality in your city to help you avoid areas where symptoms could be triggered.
A Learning Digital Health Platform for Chronic Lung Disease

- Environmental/Geospatial data
- Inhaler
- Activity/Vitals
- Spirometry

Real-time learning on patient population data

Actionable insights delivered to EMR at point-of-care
It’s all about context
It’s all about context

- eQTL
  - What?
  - Where?
  - When?
It’s all about context
The emergence of science- and data-driven wellness

Harris Center for Precision Wellness
Advancing health and vitality through science and technology

info@precisionwellness.org
The emergence of science- and data-driven wellness

Digital Health

Data Science

Molecular Profiling

Clinical Medicine

The Harris Center for Precision Wellness

info@precisionwellness.org

www.precisionwellness.org
The emergence of science- and data-driven wellness

AN EXAMINED LIFE
A nine-month study will collect data at daily and three-month intervals, and allow personalized interventions — such as changes in diet — as the study proceeds.

**BRAIN**
- **What’s measured:** Sleep patterns
- **Frequency:** Daily
- **Method:** Wrist sensor

**HEART**
- **Pulse, physical-activity level**
- **Daily**
- **Wrist sensor**

**COLON**
- **Microbiome ecology**
- **Every three months**
- **Stool sample**

**LIVER, LUNGS, BRAIN & HEART**
- **100 proteins to track organ health**
- **Every three months**
- **Blood sample**

**LYMPHATIC SYSTEM**
- **Immune-cell activity**
- **Every three months**
- **Blood sample**

**INSULIN SENSITIVITY**
- **Blood glucose**
- **Every three months**
- **Blood sample**

**CHROMOSOMES**
- **Whole-genome sequence**
- **At enrollment**
- **Blood sensor**
In the future you will have coordinates instead of a diagnosis

Figure 1. Geographic Information System of a Human Being

Topol EJ. Individualized Medicine from Prewomb to Tomb Cell 157, March 27, 2014
Matrix computation on “long” data in Precision Wellness
Personalized multiscale networks to model dynamics of complex disease

DNA
Cell-specific RNA
Cytokines
Clinical labs
Mobile devices
Microbiome
Physiometrics
Positions available

- Postdocs
- Bioinformatics Programmers/Developers
Thank you for your attention

Email: joel.dudley@mssm.edu
Twitter: @jdudley
Web: dudleylab.org
      precisionwellness.org
Eat your own dog food
WHAT IF I TOLD YOU
NO ONE CARES.