Module 7
The Future of Metabolomics

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Informatics and Statistics for Metabolomics
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Metabolomics Is Growing
Pubmed: Metabolomics OR Metabonomics OR Metabonome

# Publications

Year

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But Where Is It Going?

Key Bottlenecks in Metabolomics

- Lack of automation
- Incomplete metabolome coverage
- Expensive/large equipment
- Lack of quantification
- Inability to translate findings to the clinic
- Making metabolomics matter to drug companies
Key Trends in Metabolomics

- Automated metabolomics
- Expanding metabolome coverage
- Making metabolomics portable
- Quantify, quantify, quantify…
- Moving metabolomics from the lab to the clinic
- Moving metabolomics (back) into drug development and discovery

Automated Metabolomics

- Bruker – Automated NMR
- Biocrates – Automated MS
Bayesil (Automated NMR)

- Uses probabilistic graphical models (PGM) – similar to HMMs
- Fits shift & peak intensity similar to the way humans perform fitting and pattern finding
- Requires prior knowledge of probable biofluid composition
- Fully automated phasing, referencing, water removal, baseline correction, peak convolution, identification and quantification
- Free web server

http://bayesil.ca

GC-AutoFit (Automated GC-MS)

- Requires 3 spectra (sample, blank, alkane standards)
- Performs auto-alignment, peak ID, peak integration and concentration calculation
- Accepts NetCDF or mzXML files
- 60 sec per spectrum
- 45-70 cmpds ID’ed and quantified, 96% accuracy
- Optimized for blood, urine, saliva and CSF
- Still requires careful sample preparation & derivatization

http://gcms.wishartlab.com
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Technology & Sensitivity

<table>
<thead>
<tr>
<th>Technology</th>
<th>Sensitivity or LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC-MS or DI-MS</td>
<td>fM</td>
</tr>
<tr>
<td>GC-MS Quad</td>
<td>nM</td>
</tr>
<tr>
<td>GC-MS TOF</td>
<td>pM</td>
</tr>
<tr>
<td>NMR</td>
<td>μM</td>
</tr>
<tr>
<td>Known unknowns</td>
<td></td>
</tr>
<tr>
<td>Unknown unknowns</td>
<td></td>
</tr>
</tbody>
</table>

# Metabolites detected (Log_{10})

0 1 2 3 4
What Are The Unknown Unknowns?

Metabolites of Metabolites

The Food Metabolome

Systematic Spectral Collection

- 100,000+ Compounds
- 800,000+ NMR, MS/MS Spectra

Systematic Spectral Prediction

- Predicts MS/MS spectra from known compounds via advanced machine learning techniques
- 50% more accurate than other systems
- Matches predicted MS/MS spectra (from HMDB, KEGG or user choice) to input MS/MS spectra
- Permits rapid compound ID from MS/MS spectra

http://cfmid.wishartlab.com

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Personalized Medical Monitoring Devices

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Democratizing Metabolomics

$10 million instrument, $200/test  $1000 instrument, $2/test

Not As Absurd As You Think

Qualcomm
TRICORDER XPRIZE
Miniaturization via Microfluidics & Nanotech

CE on a chip

HPLC on a chip

GC on a chip

E-Nose for Volatile Metabolites

E-Nose uses 32 tiny sensors, which together are about the size of the nose on your face. They are connected to a small computer that takes the information from the sensors and figures out just what the smell is, similar to how your brain, through experience, learns to identify what your nose is smelling.
Protein and Aptamer-Mediated Metabolite Sensing

“Open” form + Metabolite = “Closed” form

“Open” form + Metabolite With GNP = “Closed” form

Working Prototype: Impedance-Based Metabolite Sensor

Developed by Dr. Jie Chen, University of Alberta
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Quantification & Metabolomics

• >90% of published metabolomics studies are semi-quantitative (relative peak areas, intensities)
• <10% of published metabolomics studies use absolute quantification
• The field MUST become more quantitative if findings are to be translated to practical applications
Quantitative Metabolomics (Commercial)

Bruker – Automated NMR

Chenomx – Automated NMR

Biocrates – Automated MS

Quantitative Metabolomics (Academic)

Bayesil

Batman

GC-Autofit

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Some Impressive Results…

Human Biofluid Omics “Records” for Absolute Quantification

<table>
<thead>
<tr>
<th></th>
<th>Metabolomics</th>
<th>Proteomics</th>
<th>Genomics (Transcripts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum/Plasma</td>
<td>288 Identified &amp; Quantified</td>
<td>73 Identified &amp; Quantified</td>
<td>0</td>
</tr>
<tr>
<td>CSF</td>
<td>172 Identified &amp; Quantified</td>
<td>130 Identified &amp; Quantified</td>
<td>0</td>
</tr>
<tr>
<td>Urine</td>
<td>378 Identified &amp; Quantified</td>
<td>63 Identified &amp; Quantified</td>
<td>0</td>
</tr>
</tbody>
</table>

4. MRM Proteomics Inc. (Victoria BC) reported in 2014
5. Percy AJ. et al. (2014) J. Proteome Res. (ePub Jun 9)

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Some Grim Statistics

• Since 1970 > 700,000 biomarker papers published in PubMed
• Since 1970 <250 biomarkers have been approved for clinical use
• No markers approved (yet) using proteomics methods (lots use ELISA)
• 5 biomarker tests approved using transcriptomics or gene chips

But Did You Know… Almost Everyone <25 Has Had A Metabolomic Test?

Newborn Screening
“Omics” Testing

- Number of “approved” tests arising from Metabolomics/Clinical Chem. – 195
- Number of “approved” tests arising from or using Genomics – 100-110
- Number of “approved” single Protein tests (ELISA) – 60
- Number of “approved” tests arising from or using Transcriptomics – 5
- Number of “approved” tests arising from or using Proteomics - 0

How Does Metabolomics Do? (Prediction & Diagnosis)
Predicting Diseases

- Early Preeclampsia
  First trimester maternal serum
  AUC = 0.99 (2 metabolites)
- Late Preeclampsia
  First trimester maternal serum
  AUC = 0.96 (8 metabolites)
- Congenital Heart Defects (CHD)
  Maternal Serum
  AUC = 0.98 (3 metabolites)
- Trisomy 18
  First trimester maternal serum
  AUC = 0.91 (7 metabolites)
- Trisomy 21
  First trimester maternal serum
  AUC = 0.90 (3 metabolites + Age)
- Cancer Cachexia
  Adult Urine samples
  AUC = 0.82 (4 metabolites)

Diagnosing Diseases

- Adult kidney transplant rejection
  Adult Serum samples
  AUC = 0.96 (9 metabolites)
- Pediatric kidney transplant rejection
  Pediatric Urine samples
  AUC = 0.91 (4 metabolites)
- Systolic Heart Failure vs. Diastolic HF
  Adult Serum samples
  AUC = 0.98 (4 metabolites)
- Chronic Fatigue Syndrome
  Adult Serum samples
  AUC = 0.91 (8 metabolites)
- Eosinophilic Esophagitis (EoE)
  Pediatric Urine samples
  AUC = 0.95 (3 metabolites)
- Colonic Polyps
  Adult Urine Samples
  AUC = 0.78 (12 metabolites)
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Metabolomics & The Drug Industry

$280  $60  $90  $250  $120 million
3.5 yrs  1 yr  2 yrs  3 yrs  2.5 yrs
Discovery Phase I Phase II Phase III FDA Approval

Drug Development Pipeline

[Diagram showing the drug development pipeline with stages including Chemistry, Genomics, Proteomics, and Metabolomics]
Metabolomics in Drug Development

- Lead
- IND
- Synthesis
- Efficacy/HTS
- Efficacy/In Vivo
- TOX
- P1
- P2
- P3

Applications in Patient Compliance (P2/P3 Trials)

- Day 1
- Day 2
- Day 3
- Day 4
- Day 5

Ethanol!!
Applications in Drug Monitoring/Customization

Slow metabolizer

Day 5

Day 4

Day 3

Day 2

Day 1

Fast metabolizer

Day 5

Day 4

Day 3

Day 2

Day 1

Drug Metabolite!

Traditional Drug Discovery

1:5 success $2-10 million, 2-4 yrs

1:2 success

1:2 success

0.001% Success Rate, 20+ years, >$1 billion

1:2 success

1:500 success, $1 billion, 15 yrs

1:5 success, 1-5 yrs

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Metabolite-Based Drug Discovery

1:2 Success, $200K, 1 yr

1-2 days

1-2 days

15% Success Rate, 1+ years, <$250,000

1:2 Success, $200/yr

1-2 weeks (cmpds/diet)
5-10 yrs (enzymes, MAbs)

1:2 Success, 1-2 hours

Metabolomics, CVD & Therapy

Dietary target

Drug target

Drug target

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Summary – The Future of Metabolomics

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