Perspectives on High Throughput Experimentation ("HTE")

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Tioga Research Pursues R&D of Formulations for Application to Skin
High throughput experimentation ("HTE")

Approach to directed discovery & development that is engineered to provide multiple-fold efficiencies over conventional methods

Drivers:
- Directed towards specific objective
- Face vast compositional landscape
- Have broad space of processing options
- Multiple criteria determine ‘performance’
- Optimum(optima) not predictable
Ce-rich oxygen evolution catalysts

• 5456 Ni/Fe/Co/Ce oxide compositions by inkjet printing

• Catalytic performance by three-electrode scanning drop electrochemical cell (4s per sample)

• \( \text{Ni}_{0.2}\text{Co}_{0.3}\text{Ce}_{0.5}\text{O}_{x} \) provides 10 mA cm\(^{-2}\) \( \text{O}_2 \) evolution current at 310 mV overpotential

Computational Screening of AQDS Derivatives for Low Cost Flow Batteries

- 9,10-anthraquinone-2,7-disulphonic acid (AQDS) in sulphuric acid (-ve side) and Br$_2$ in HBr (+ve side) pumped through flowcell
- Reduction potential & solubility computed for library of AQDS derivatives
- Addition of 2 –OH groups increases open circuit potential by 11%

Simulation and Experiment – Some Complementary Strengths

**Experiment**
Difficult to make simple

Constrained to real (accessible) surface

**Simulation**
Difficult to make complex

Free to roam (with attendant pitfalls)
Sampling materials that are inaccessible experimentally

- Model Al placement at each of 12 T-sites in MFI-framework (of zeolite ZSM-5)
- 12 (TPA+) or 48 (H+) configurations optimized with cff91_czeo force field
- Compute role of Al-placement on geometry & properties

How small is big enough?
High-resolution dose–response screening

• Concentration gradients segmented into picoliter microdrop reactors
• >10k data points yield precise (±2.40% at 95% confidence) & reproducible (CV=2.45%, n=16) IC50
• Novel inhibitors (eg sodium cefsulodine) found in 704 compounds screened against protein tyrosine phosphatase 1B

Sampling a Processing Space for Improved Control of Protein PEGylation

- PEGylation extends useful protein lifetime
- Lysozyme presents 6 lysine residues as PEGylation sites
- HTE samples role of (i) protein:PEG ratio, (ii) buffer pH, and (iii) reaction time on PEGamers, isoforms & enzymatic activity


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Fluid Formulation Opportunities

- Mixing & working viscous materials
- Time-sequenced additions of multiple fluids into arrays of vessels
- Sampling libraries of processing geometries

Formulation Controls Delivery

Various excipients (all at <5 wt%) added to a base 50/50 water/ethanol chassis (leftmost bar is flux from chassis + API only)

• Translation from one active to another is rare

Text mining: to define formulation compositional fields of interest

Chemical synonyms dictionary

Patent Texts Database

Search, weight, analyze proximity

1-hydroxyethane, 100c.npa, 121182-78-3, 200 proof, 64-17-5, 8000-16-6, 8024-45-1, absolute ethanol, aethanol, aethanol [german], aethylalkohol, aethylalkohol [german], ahd 2000, a13-01706, alcarn hand degermer, alcool ethylique, alcool ethylique [french], alcool etilico, alcool etilico [italian], algrain, alkohol, alkohol [german], alkoholu etylowego, alkoholu etylowego [polish], anhydrol, anhydrol pm 4085, anhydrous ethanol, anhydrous ethanol (jp15), avagard, bmse000297, c00069, c0038, c2h5oh, c2h6o, caswell no. 426, caswell no. 430, ccris 945, cda 19, cda 19-200, chebi:16236, cologne spirit, cologne spirits, d00068, d04732, db00898, dehydrated ethanol, dehydrated ethanol (tn), denatured ethanol, desinfektol el, distilled spirits, duplicating fluid 100c.npa, einecs 200-578-6, epa pesticide chemical code 001501, esumiru wk 88, eta, etanol, etanolo, etanolo [italian], eth, ethanol, ethanol (9ci), ethanol 200 proof, ethanol absolute, ethanol anhydrous, ethanol extra pure, ethanol solution, ethanol [jan], ethanol, undenatured, ethicap, ethyl alc, ethyl hydrate, ethyl hydroxide, ethylol, etoh, ethylol alkohol, etylowy alkohol [polish], fema no. 2419, fema number 2419, hinetoless, hsdb 531, hsdb 82, hydroxyethane, ims 99, infinity pure, irits of wine, jaysol, jaysol s, ls-1539, ls-187821, lux, methylcarbinol, mixture name, nci-c03134, nsc 85228, nsc85228, sd alchol 23-hydrogen, sda 3a, sda 40-2, sdm no. 37, sekundasprit, spirit, spirits of wine, spiritus vini, spirt, sy fresh m, synasol, tecsol, tecsol c, thanol, unii-3k9958v90m, usar ek-1597

Permeation into & through Skin

- Barrier function provided mainly by dead cells
- Real skin preferred as substrate

HTE aims:
- $10^{-10^2}$ throughput gain
- Reduced variance
- Optimized use of data
- Alert to simulation opportunities

INSIGHT™: Screening Skin Permeabilization

- Concept from UC Santa Barbara (S. Mitragotri)
- Impedance change as proxy of skin barrier permeabilization
- >3,000 measurements day⁻¹ [conventional ~30]

(INSIGHT™ = IN vitro Skin Impedance Guided High Throughput Screening)

Permeation Enhancer Cocktails

Skin permeabilization (vertical) as \( f(A:B, [A+B]) \) in fixed chassis (\( A,B= \) selected pairs of MPE™️s)

- **MMPE™️S:** excipient cocktails providing step-out performance
- **Basis for composition of matter patent claims**
- **Performance depends also on Active and Chassis**

\[
\# \text{MPE™️} = \text{Molecular skin Permeation Enhancer} \\
\text{MMPE™️} = \text{Multiplexed MPE™️}
\]

TORNADO™ - Diffusion Cell Arrays

Development illustrates some typical HTE implementation issues:

• In depth knowledge of problem area
• Parallelization presents special engineering challenges
  – Control of temperature & well stirring
  – Well access mechanics
  – Well integrity & cross talk
  – Skin sourcing & preparation
• Measurement coupled closely with library preparation, analysis
• Informatics underpinning
• Throughput gain (~10x) provides acceptable investment return
• Careful design of each experiment
• Maintain as trade secret

TORNADO™ = high ThrOughput skin peRmeatioN And Dermal uptake Observation
Nuvo’s Pennsaid® 2%

**Target Product Profile:**

- Osteoarthritis indication
- Gel format
- Twice-a-day dosing
- Improved esthetics
- ≥ 2 yr shelf life
- Limited composition change from Pennsaid®
- Patentable

**Graph:**

- Accumulated Dose (µg/cm²)
- Time (hrs)

- Pennsaid®
- Pennsaid® 2%

**Nutritional Information:**

- Sodium 0g
- Fat 0g
- Carbohydrate 0g

**Product:**

- For external use only
- Read ingredients carefully
- Do not use if sensitive to any ingredient

**Legal:**

- Mallinckrodt to Launch PENNSAID 2% in the U.S. in Q1 2014

Kisak ET, Singh J: Diclofenac Gel. US 8,252,838; 2012
Discovery to Deployment Gap

Multi-Year Timeline has Negative Consequences:

- Reduced value of research advance
- Compromised efficiency from discontinuities
- Diminished investment appeal

Materials Genome Initiative for Global Competitiveness (June 2011)
(US National Science And Technology Council)
http://www.whitehouse.gov/sites/default/files/microsites/ostp/materials_genome_initiative-final.pdf
Concluding Remarks

• HTE ‘mind set’ appears well-established
• Unifying principles do span breadth of applications
• Experiment & simulation are healthily complementary
• Chance will continue to favor the prepared mind
• Major new developments are expected

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