Computer Simulation of Developmental Processes and Toxicities

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DISCLAIMER: The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.
Scope of the Problem

- **Problem**: Too many chemicals (~80K) in production and/or the environment to test each for DevTox by traditional animal-based methods (cost, time, 3Rs).

- **HTS profiling**: newer automated high-throughput screening (HTS) assays to efficiently profile chemical-biological interactions in vitro.

- **ToxCast**: Stemina’s DevTox QuickPredict human stem cell assay predicts 16-18% of the 1065 chemicals tested as positive for DevTox (~180 chemicals, 90% BA) [in preparation].

- **Challenge**: determinants of teratological outcomes are complex:
  1) nature of exposure
  2) dosimetry
  3) initiating mechanisms
  4) genetic susceptibility
  5) stage vulnerability.

  - Pregnant mother is the exposure unit
  - Placental metabolism & dynamics change during pregnancy
  - Chemicals interact with biological systems wired for change
  - Variation by species (e.g., thalidomide)
  - Embryogenesis is critically dependent on cellular dynamics
Embryogenesis is an orchestration of complex cell behaviors

<table>
<thead>
<tr>
<th>EMBRYONIC CELL BEHAVIORS</th>
<th>CONSEQUENCES OF DISRUPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>cell growth &amp; death</td>
<td>incorrect cell number</td>
</tr>
<tr>
<td>differentiation &amp; function</td>
<td>missing cell types</td>
</tr>
<tr>
<td>cell motility &amp; adhesion</td>
<td>disorganization</td>
</tr>
<tr>
<td>clocks &amp; organizers</td>
<td>chaos and ataxia</td>
</tr>
<tr>
<td>genetic signals &amp; responses</td>
<td>dysregulation</td>
</tr>
<tr>
<td>ECM synthesis &amp; remodeling</td>
<td>loss of mechanical properties</td>
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How can we model this complexity for developmental toxicity?
Using the new HTS data streams to model DevTox

▸ **Hypothesis**: computer models that recapitulate embryology can be used analytically (to understand) and theoretically (to predict) developmental hazards.

▸ **Approach**: design, development, and implementation of computational models that integrate toxicological data with knowledge of the embryo.

▸ **Application**: ‘Virtual Embryo’ - a novel way to predictively model the complexity of development for exposure-based hazard assessment.
Anatomical homeostasis in a self-regulating Virtual Embryo

Mouse Morula
SOURCE: Science Photo Library

Cellular Agent-Based Model
(angiogenesis)

- CompuCell3D modeling environment (Indiana University – J Glazier)
- steppables for distinct cell behaviors (growth, proliferation, apoptosis, differentiation, polarization, motility, ECM, signal secretion, ...)
- rules coded in Python for cellular ‘agents’ that have autonomy as individual models
- agents interact in shared microenvironment and self-organize into emergent phenotypes
- models run differently each time (stochastic) and each run reveals one possible solution
Virtual Genital Tubercle Development: urethral closure

Embryonic GT

Abstracted GT

Control Network (mouse)

ABM simulation for sexual dimorphism (mouse GD13.5 – 17.5)

androgen

SHH field

FGF10 field

no androgen

Sulik and Bream (2010)
Urethral Closure: complex process disrupted in ‘hypospadias’

- Driven by urethral endoderm (contact, fusion apoptosis) and androgen-dependent effects on preputial mesenchyme (proliferation, condensation, migration) via FGFR2-IIIb.

Leung et al. (2016) Reproductive Toxicology

<table>
<thead>
<tr>
<th>Androgenization (n = 10 sims)</th>
<th>Closure Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>0.80</td>
</tr>
<tr>
<td>67%</td>
<td>0.57</td>
</tr>
<tr>
<td>33%</td>
<td>0.13</td>
</tr>
<tr>
<td>0%</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Virtual Palate Development: medial edge fusion

Hutson et al. (2016) submitted
ABM for Fusion

Jin and Ding (2006) Development
Hacking the Control Network:

*in silico* knockouts → Cybermorphs

**Fusion Switch**

- TGFβ3 triggers apoptosis, epithelial-mesenchymal transition, and retraction to break down the midline seam.
- EGF has the opposite effect, maintaining epithelial proliferation and survival.
- ToxCast profiling for 63 cleft palate teratogens pointed to ~10 bioactivity clusters (eg, retinoid, glucocorticoid, GPCR, ...).
TGF-EGF circuit dynamics: modeling acute exposure to retinoic acid

tipping point >1.8x (n=24) (reversible)

tipping point ~1.5x (n=16) (non-reversible)
Toward a Virtual Embryo

- Vasculature
- Limb-bud
- Palate
- Genital Tubercle
- NVU/BBB
- Heart
- Neural Tube
- Liver / GI
- Testis / BTB
- Renal

Status:
- Underway
- Planned
- Future
Special Thanks

- Sid Hunter – NHEERL / ISTD
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- Shane Hutson – Vanderbilt U / STAR
- Kate Saili – NCCT
- Todd Zurlinden – NCCT
- Richard Judson – NCCT
- Imran Shah – NCCT
- RS Thomas – Director, NCCT
- Kevin Crofton – NCCT
- John Cowden – NCCT/CSS
- Tina Bahadori – CSS
- Jill Franzosa - CSS

Integrating biological activity and exposure in the U.S. EPA’s ToxCast Program. RS Thomas

S6: Innovations in the Human Health Risk Assessment of Uxmal 6 room, Mon 2:30-4:30
Virtual Tissues Laboratory System

**Virtuoso**
Web Services and Queries

**HPC**
Massively-parallel simulation

- Video or 3D Results
- Data Analysis

VTKB
- CC3D simulations
- ToxCastDB
- Bionetworks
- Literature mining
- Provenance

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