## Why are you here?

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<th></th>
<th>Structure</th>
<th>Complexity</th>
<th>Scale</th>
<th>Design</th>
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<td><strong>Foundations</strong></td>
<td>Murray/</td>
<td>Parrilo</td>
<td>Bahmieh</td>
<td>Dahleh</td>
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<tr>
<td><strong>Physics</strong></td>
<td>Carlson</td>
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<td><strong>Information</strong></td>
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<td>Savageau</td>
<td>Mitra</td>
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<td>(Moderators)</td>
<td>Kitano</td>
<td>Tsao</td>
<td>Jacobs</td>
<td>Glover</td>
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### Matchmaking
Little change?

Technology has enabled better vigilance

Controls will make homeostasis under anesthesia more controlled

BUT….that’s the easy problem!
Genomic revolution has bypassed clinical anesthesiology?
Anesthesiology has avoided the genomic revolution?
Intuitive, hand-crafted assumptions allow pretty reasonable sedation algorithms
Controls will help here

(Dialing up and down is Distracting)

...but yet to be seen if will help here

All our cues are indirect: We don’t act on real mechanisms
GREAT PHYSICIANS ACT ON THIS
NONE OF THIS IS IN A TEXTBOOK (of Medicine)

Instead scattered around medical and biology journals

Combination of clinical gut/eye/taste
…and basic science

The basic science is physiology (education crisis)
 - completely controlled by feedback

Enormous clues exist in biology but the literature and language are not in contact with biologists
/translation="MMSSYKRATLDEEDLVDSLSEGDVYPNLQVNFRSPRSQGRCWA
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GLTSNQLFFLGFAQVWCSVRTPESSHEGLIDPHSPSRFRVIGSLNSKEFSEHFRCP
LGSPMNPRHKCEWV"
Elements of theories of complexity

- Modeling
- Simulation (NP)
- Analysis (coNP)
- Synthesis/design
- Hard limits/laws
Premature to jump here...
The biochemical basis of oxygen-mediated phenotypic changes?
So fundamental

- Medicine (Anesthesiology) obviously makes oxygen availability/management a priority
- Anesthesia A,B,C (Airway, Breathing, Circulation)
- But the elegant biological context of oxygen regulation is not part of medical dialogue
O2 regulated by feedback

- LOW O2: REGULATES COMPLEX DEVELOPMENT
- Breath more (hypoxic ventilatory drive)
- Use less energy (glycolytic pathways)
- Dilate the blood supply (NO, CO)
- Grow new blood vessels (VEGF)
- Make more red cells to carry oxygen (EPO)
- QUIETLY GOES ON IN ALL CELLS IN ALL CONDITIONS, ALL OF THE TIME
Normoxia

polyubiquitination

Degradation

pVHL

bHLH  PAS  P402  K532  P564  TAD  TAD

ODD

Transcriptional activation

Lee et al, 2004
Growth factors

receptor tyrosine kinase

PI3K       Ras

Akt (PKB)

MAPK

MEK

HIF-1α synthesis

Nucleus

β

α

HRE

Lee et al. 2004
VHL

2% O2

20% O2
O2 vs. ROS (reactive O2 species)

• HIF-1 expression modulated by ROS
• HIF-1 expression modulated by NO
• Hypoxic ventilatory drive is driven by SNO (S-nitrosothiols) rather than O2
• Glucose regulation of HIF-1
• Redox regulation of transcription independent of HIF-1
HIF as fundamental

- Cloned in 1996 (by a clinician)
- Recent visit to Mayo clinic: The prettiest story in biology
- (Complexity in medicine/biology is invisible—except for pain)

- Most defects in HIF process are EARLY embryonic lethal
- Lessons for early human development?
Is HIF-1 (and its regulation)

A protocol?
A module?
A law?

IMPORTANT:
-Facilitates, optimizes complex development
-Retained to facilitate plasticity (altitude, exercise, disease)…Robustness
-Its retention as a highly tuned system promotes cancer, chemotherapy resistance and metastases
-VHL…Fragility
WHY ARE YOU HERE?

Physics/Computer science/Biology/Economics
…don’t talk

Biology and Medicine have a huge wall between them
→ language (and style)
→ most complexity in both is feedback
→ the most glaring communication gap between sciences
→ mathematics is necessary to bridge the gap

Do Steven’s models of the internet inform HIF-1?
Do Hana’s bacterial heat shock models inform miscues in the HIF response that are oncogenic?
A CELEBRATION TO MARK JOHN DOYLE’S 50th JULY 15-16, 2004

Connections
Foundations and Edges

CONNECTING THEORY AND APPLICATIONS ACROSS COMPLEX SYSTEMS

A CELEBRATION TO MARK JOHN DOYLE’S 50th JULY 15-16, 2004