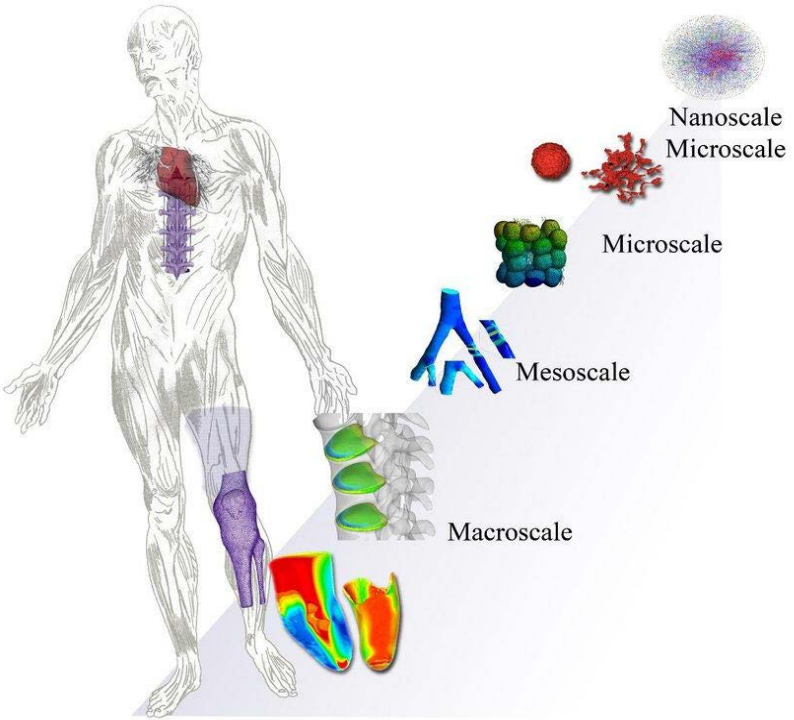
Challenge #1 – Next Generation Multiscale Models that Integrate Between Different Scientific Fields and Predict Integrated Functions

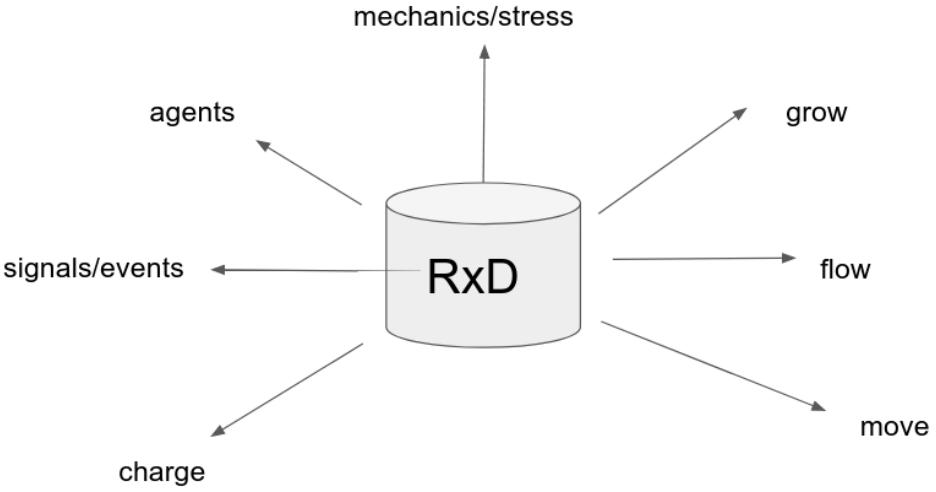
Multiphysics, Multialgorithmic, Multiscale



quantum mechanics/spectroscopic
radiological
molecular dynamics
genomic/transcription factors
stochastic particle "free flight"
stochastic Gillespie
chemical reactions
proteomic/interactomic/metabolomic
rule based reaction modeling
Boolean reaction modeling
Event-based models
Fick's deterministic diffusion
Electromagnetic (Maxwell) fields
(Hidden) Markov Models
Electric circuit models
Flow models
Growth and tissue tectonics
Biomechanical models
Tissue compliance

Integration via innovative methods like AI/ML

Reaction-diffusion (RxD) as a tissue commonality?



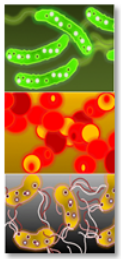
add-ins

Doesn’t work for all areas, some rely on chemistry, quantum mechanics, etc. Can machine learning/AI bridge the divide? Can it replace conventional modeling in cases where we have data but no idea about how to build a model?

Life on a gradient: Predictive multiscale model

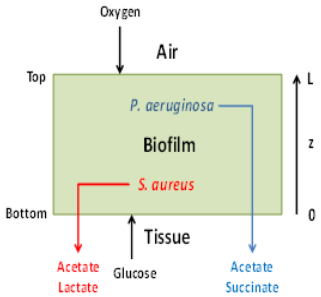
genes→enzymes→metabolites→cellular phenotype(z,t)→consortia phenotype(z,t)

size scales: <1 um to > 300 um time scales: ~1 s to ~weeks



1. Genome-scale metabolic reconstructions of species

2. Dynamic, spatial community modeling



Rates determined from genome scale models

Spatiotemporal modeling

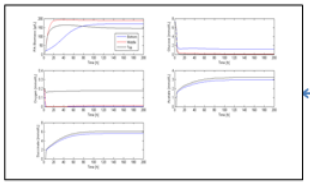
$$\frac{\partial X_i}{\partial t} = \mu_i X_i \left(1 - \frac{Z}{Z_{max}}\right) - \mu_{ij} X_i + D_i \frac{\partial^2 X_i}{\partial z^2}$$

$$\frac{\partial M_j}{\partial t} = \sum_{i=1}^{N} v_{ij} X_i + D_j \frac{\partial^2 M_j}{\partial z^2}$$

Spatial discretization

DFBAlab: MATLAB code for dynamic flux balance analysis

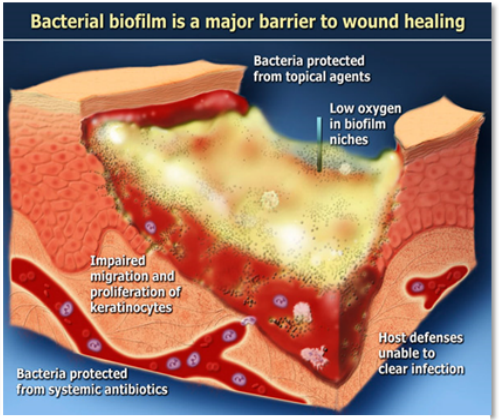
Dynamic simulation



Major methods:
1. ODEs and reaction-diffusion (cellular interactions, spatial and temporal changes)
2. Linear programming (identifying cellular metabolism and rates as a function of local environment)

Chronic wounds

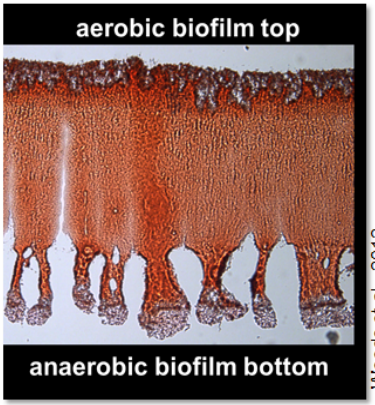
- Non-healing wound (3+ months)
- Often associated with venous disease, diabetes and obesity
- Cost $25+ billion per year to treat
- Colonized by biofilm consortia (ave. 5-6 species)
- Tolerant to many treatments
- Complex spatial and temporal dynamics



Center for Biofilm Engineering

Multiscale Consortia Biofilms :

1) Construct and evaluate multiscale modeling framework for multispecies consortia biofilms
2) Develop and implement analytical techniques for measuring spatially-resolved monoculture and consortia biofilm physiologies
3) Predict and test metabolic responses of biofilm consortia to perturbations



Woods et al., 2012

Accomplishments to Date

methodologies developed: bridging scales, addressing sparse data, simulating across scales, addressing uncertainty quantification

Multi-Scale Models for:

Topic Clusters *- ongoing projects & where additional synergy could be realized*

- **Diseases**
- **Tissue Functions**
- **Neural Systems**
- **Tissue Repair and Regeneration**

Accomplishments to Date

methodologies developed: bridging scales, addressing sparse data, simulating across scales, addressing uncertainty quantification

Multi-Scale Models for:

Diseases

Muscular Dystrophy - link muscle inflammation and regeneration related to disease progression in Duchene muscular dystrophy – muscle degeneration, regeneration, locomotion [Blemker, Peirce-Cottler]

Breast Cancer - in vivo imaging with muscle models of tumor growth, mechanics, response of breast tumors to therapy, predicting tumor growth and morphology, pharmacokinetic, pharmacodynamics models [Yankeelov, Quaranta]

Tuberculosis – pharmacology approaches to therapy using antibiotics to treat granulomas in lung tissue, comparing drug efficiencies, assessing drug resistance, role of pro- and anti-inflammatory cytokines on granuloma function [Dartois, Flynn, Kirschner, Linderman]

Cancer and Cytoskeletal Systems – systems biology, physics and molecular cancer biology related to tumor migration and proliferation [Zaman, Kamm]

Accomplishments to Date

methodologies developed: bridging scales, addressing sparse data, simulating across scales, addressing uncertainty quantification

Multi-Scale Models for:

Tissue Functions

Coronary Blood Flow - simulate coronary vascular physiology – from cell to whole organ cardiac systems, perfusion, cell metabolic demands, smooth muscle physiology, cardiac mechanics [Beard, Kassab]

Cardiac Tissues – mitochondria functions related to bioenergetics, calcium transport [Lederer, Jafri, Mannella]

Trauma – cardiovascular hemodynamics, immunology and hematology, clotting regulation during trauma, mechanobiology of shear effects [Diamond]

Neuronal, Heart – vagal outflow to link cardiovascular control and neuronal adaptation in the brainstem to maintain cardiovascular homeostasis after injury [Schwaber, Vadigepalli]

Cerebral Blood Flow – cardiovascular and neuroscience links, microvascular networks - to spatially and temporally resolve tissue regions and link neural activation, blood flow and oxygen in brain cortex [Secomb]

Lymphatics – lymph flow in lymph nodes, mass transport of chemokines, origin and effects of pressure related to lymphedema, mechanical properties of lymphatic vessels [Zawieja, Moore]

Gas Transport – gas permeation through protein channels in cell membranes [Boron, Tajkhorshid, Somersalo]

Accomplishments to Date

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Multi-Scale Models for:

Neural Systems

Neuronal Systems – bioelectric responses by neuronal tissue to electrical stimulation [Lazzi, Berger]

Neuronal Systems – connectivity of neocortex linked via chemophysiology and electrophysiology, using network circuity from optogenetic data for neocortical network models [Lytton]

Neuronal Systems – spinal cord, neurophysiological single unit recordings and circuit knowledge with behavior and biomechanics – electromyographic recordings to predict spinal motor behavior from model neural data [Danger Giszter]

Accomplishments to Date

methodologies developed: bridging scales, addressing sparse data, simulating across scales, addressing uncertainty quantification

Multi-Scale Models for:

Tissue Repair and Regeneration

ACL Reconstruction – mechanics of human knee, surgical planning, joint mechanics, motor control, neuromuscular training – connecting tissue biology with tissue mechanics [Dhaher, Thelen]

Biomaterials - role of molecular weight, domain sizes and distributions, impact of hydrophobic/hydrophilic partitioning on protein polymer assembly and mechanical properties of biomaterials [Kaplan, Buehler]; connecting modeling, synthesis and characterization

Wound Healing – molecular, supramolecular, cellular and tissue scales of complexity - signaling pathways related to wound healing, actin/myosin dynamics, morphodynamic cell models, cell migration, macrophage migration during inflammatory phase [Haugh]

Biofilms - chronic wounds to link microbial consortia physiology on temporal and spatial basis with microbial stress responses and consortia functions [Carlson, Henson, Hanley, Fields]

Impact of Methods on Each Field

changed questions or approaches, new theories resulting from the work to improve understanding of problems in the field

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New Tools – microscopy and image processing (muscle responses to injury)

Biomaterials - new way to design for structure-function, including predictions of material mechanics, response to environmental changes (e.g., shape change), in vivo degradation time

Disease – new approach to predicting progression of disease, physiological impact

Tissue repair/regeneration – new approaches to predict outcomes

Inflammation – impact on tissue repair, regeneration, tissue function

New Challenges - What Needs to Be Done

methods from other fields, connections to address unmet needs, questions for the MSM Consortium

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Scientific topics

- Better integration of engineering and modeling with fundamental biology
- Incorporation of the diversity of cell stimuli (effect cell fate, tissue function…)
- Consideration of Heterogeneity in tissues – cells, matrices, gradients (challenges, refinement)
- Link between models and experimental work from a more mechanistic (vs. phenomenological) approach – to promote cell interventions (e.g., treatments)
- Links between top down phenomenological models of behavior with bottom up models of basic physiology
- Further integration of immune science into modeling efforts

New Challenges - What Needs to Be Done

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Modeling topics

Improved annotation, data structures and data comparisons for complex, multi-clinician medical interventions (e.g., surgery, resuscitation therapy, anesthesiology)

Standardized strategies for multiscale models, methods and approaches

Broader community impact

Leadership role as peer reviewers for multiscale modeling papers

Tutorials to communicate findings and approaches

Summer school

Freely accessible training resources with illustrative applications

Conclusions

- **Significant opportunities exist in leading the next generation multiscale models at IMAG, but need new mechanisms to do the work**
- **Those must bridge disparate scales and disciplines: Need innovative ways to fund research and activities**
- **Often, the divide between different areas is significant (e.g. model types/methods and their maturity vary a lot)**
- **There exists a need for data sharing and archiving – ML and AI can be transformative to build new types of models!**
- **New experimental validation is needed, and expand the use of proxy model to connect exp and sim**