# Challenge 5

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- Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields (e.g. tissue engineering, regenerative medicine, drug and gene delivery, preventive interventions)

# Repeatability, Replicability, and Reproducibility

These terms have strongly overlapping normal parlance, and that we might do better figuring out another set of three terms that start with different letters, or alternatively, use a prefatory term.

1. Repetition variance (e.g., practicing pipetting → mean ±SD)
2. Translocation replicability
3. "Square 1" reproducibility = independent bottom up redevelopment

While the terms chosen are not particularly relevant, it seems important to use a common set of terms when trying to define standards. This is needed for archiving and classifying or grading what is archived.

# Challenge 5 – Survey questions

**Context of model development:**

**The computational model(s) developed as part of the project has/have been:**

- **Q0: Shared:**
- **Q1: Repeated:** Same team, same code. Researcher repeated their own computation
- **Q2: Replicated:** Different team, same code. Another researcher used the code and obtained similar results
- **Q3: Reproduced:** Different team, different code. Another researcher developed new, working code based on the model specification and equations
- **Q4: Reused:** Different scientific question, different team, starting from the same code or model specification and modified

# Challenge 5 – Survey questions

## Context of model development:

- Develop models of **cardiac** biophysics/biochemistry, mechanics and electrophysiology fro molecular to whole heart level.
- We are building multiscale models of the proliferative phase of **wound healing** …
- We use a multi-scale systems pharmacology approach with computational modeling to track drug distributions in **granulomas** and development of resistance.
- Our modeling platform and model are being developed in the context of the **innate immune response to respiratory fungal infections** …
- developing platform to **extend neural simulations** from electro- to chemophysiology
- Our model is being developed in the context of **liver regeneration and repair** response to injury …
- Our model is being developed in the context of **cardioprotection** …
- We will develop a sBone system to shift the paradigm of traditional **bone regeneration** approaches to a predictive multi-scale model …

# Challenge 5 – Five questions

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# Challenge 5 – Five questions

The computational model(s) developed as part of the project has/have been:

- **Q0 Shared: Publications, Supplements, Online database**

- All models, published or not, are shared open source. Over 400 models. Mostly cardiovascular and respiratory, with a good many biochemical and some pharmacokinetic.
- Deterministic models have been implemented in Virtual Cell and are publicly available. Code for the stochastic models have been included as supplementary material for the respective publications.
- Preliminary versions of component models have been shared via the publications Oremland et al., BMC Syst Biol (2016) and Brandon et al., BMC Syst Biol (2016)
- all code has been shared; platform (NEURON) is publically available
- Several publications…. An executable of our code and all the specs can be found at: http://malthus.micro.med.umich.edu/GranSim/
- Model specification and code shared via Anderson et al., Plos Comp Bio (2017), J Comp Neurosci (2015), and Makadia et al., Biophys J (2015). All model code is available online via ModelDB.
- Model specification and code shared via Cook et al., BMC Sys Bio (2015) and Verma et al., IEEE Trans Biomed Engg (2016) in the main text and in the supplemental material.
- Model specification and code shared via Tan et al., Oncotarget (2016) and Tan et al., npj Regenerative Medicine (2017) in the main text and in the supplemental material.

# Challenge 5 – Five questions

- **Q1: Repeated:** Same team, same code. Researcher repeated their own computation

- All of the JSim models have been repeated using different solvers, different time steps, and almost always different computing platforms (Windows, Linux, Macintosh)
- Deterministic models have been implemented in Virtual Cell and are publicly available. Code for the stochastic models have been included as supplementary material for the respective publications.
- Multiple users test under a variety of conditions; ODE sub-models: compare in-house and Matlab solutions; PDE sub-models: compare to COMSOL; implement multiple algorithms (FTCS, ADE, spectral methods) within code and compare; Tunable resolution: compare behavior of model versions with coarse/fine graining of particular pathways/mechanisms
- The model in publication 1 above has been implemented by us in a new modular software architecture, and both implementations are being compared side-by-side in order to test the new software design.
- yes, always do with diff random
- We repeated the computations using stiff and non-stiff ODE integrators within Matlab.
- We repeated the computations by perturbing parameters within Matlab.

# Challenge 5 – Five questions

- **Q2: Replicated:** Different team, same code. Another researcher used the code and obtained similar results

- Shipping the JSim code to another of our 4 institutions is not really a test since the software is machine independent. Uploading JSim to SBML or Cell ML is a test, possible only for ODEs, not for PDEs, Is a better test, relatively easy with automated JSim-> SBML conversion, and then allows round tripping of code, i.e. now downloading the SBML version to JSim. Can also be done with matlab, but with limitations.
- Our standard validation is to confirm that the results are not significantly altered by a modest change of the time or spatial step size.
- parts of it only.
- yes.
- A lab colleague that is not involved with the project utilized the model code and performed the simulations as specified in the manuscript, prior to submission for peer review.
- Our papers were cited, while we are not aware of the detail about how they used our codes.

# Challenge 5 – Five questions

- **Q3: Reproduced:** Different team, different code. Another researcher developed new, working code based on the model specification and equations

- Our model code (many models) for capillary-tissue exchange and intra-tissue reactions has been reproduced many times in other code.
- We are not aware of another team reproducing our models.
- yes, Two groups. (1) Ruth Bowness, and Mark Chaplain (paper coming out in 2018)and (2) Elebeoba E. May (Sershen et al., Front Cell Infect Microbiol 2016)
- Nothing yet to report.
- yes
- A lab colleague that is not involved with the project based on the model equations and parameter tables in the manuscript, prior to submission for peer review. We are not aware of another team reproducing our published models.
- Our paper (Oncotarget 2016) has been cited 3 times and paper (npj RM 2017) has been cited one time by other groups. They developed new, working code based on the model specifications and equations as proposed to adapt to their own biological questions.

# Challenge 5 – Five questions

- **Q4: Reused:** Different scientific question, different team, starting from the same code or model specification and modified

- These convection-diffusion reaction models have used, in many different variants, for many different solutes world wide. One of our implementation variants is a compartmental version that can be used as a finite-element PDE or be set at fewer axial compartments or reduced to a single compartment with the choice made at run time when analyzing data. This allows comparison between compartmental modeling and more physiologically realistic models. Beard's model of mitochondrial oxidative phosphorylation, updated by Dash, is seemingly the world's standard.
- We are not aware of another team reusing our models.
- Nothing yet to report.
- yes
- Our model from Cook et al., BMC Sys Bio (2015) has been re-used by Pedone et al., Cell Reports (2017) to investigate whether inclusion of bone marrow cell dynamics improves the model fit to experimental data on mouse liver regeneration. Pedone et al., utilized a subset of our model equations and parameters.
- Our model from Tan et al. (2017) has been re-used by Nath Das et al., Molecular Biosystems (2017) to investigate calcium homeostasis in diabetic cardiomyocytes.

# Challenge 5 – next steps

- Need for a single point resource to share and download models
  - Lessons from the success and wide acceptance of NCBI Gene Expression Omnibus resource

- Promoting best practices for repeating, replicating, reproducing and reusing models
  - Coordination with the Committee on Credible Practice of Modeling and Simulation in Healthcare