Development of a multiscale skin barrier model for de novo, in silico prediction

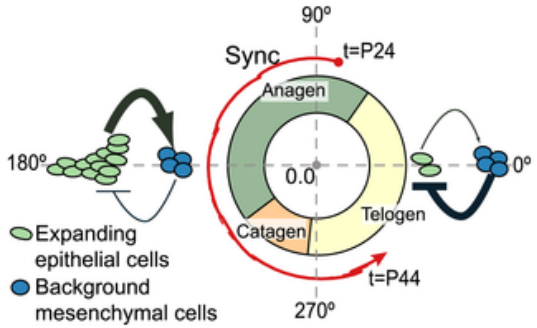
Rosa Webinar Series

20170913

Ryan Tasseff

Procter and Gamble

Life and Work…



Chem Plant Ops
Thu 8/1/02 - Sun 8/1/04

Molecular Dynamics
Mon 8/2/04 - Tue 8/1/06

Intracellular kinetic networks
Wed 8/2/06 - Tue 8/4/09

experimental cell biology
Sat 8/2/08 - Mon 8/1/11

NLD, biological oscillators
Wed 2/2/11 - Mon 8/4/14

clinical -omics
Fri 8/2/13 - Tue 8/4/15

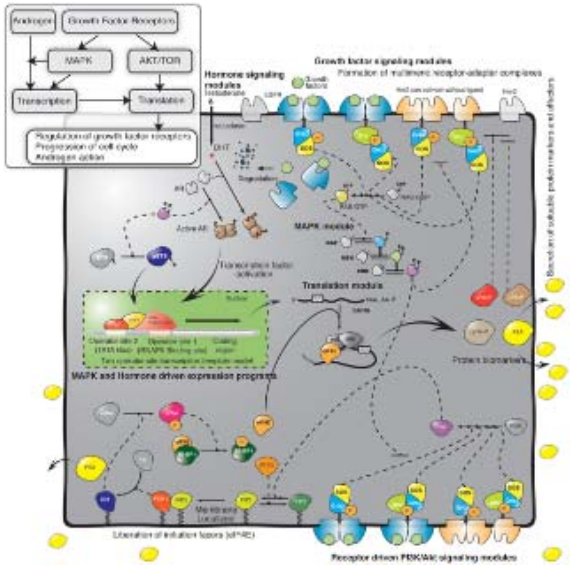
Data Scientist
Wed 8/5/15 - Thu 9/7/17

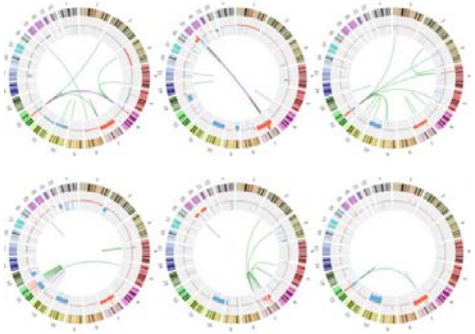
integrative/multiscale/multicellular modeling
Thu 8/2/12 - Wed 8/2/17

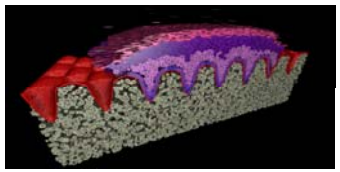
Skin Grant
Thu 8/2/12 - Sat

Microfluidic Design
Sun 1/26/14 - Sun

Product-Skin Interaction
Wed 8/5/15 - Thu 9/7/17



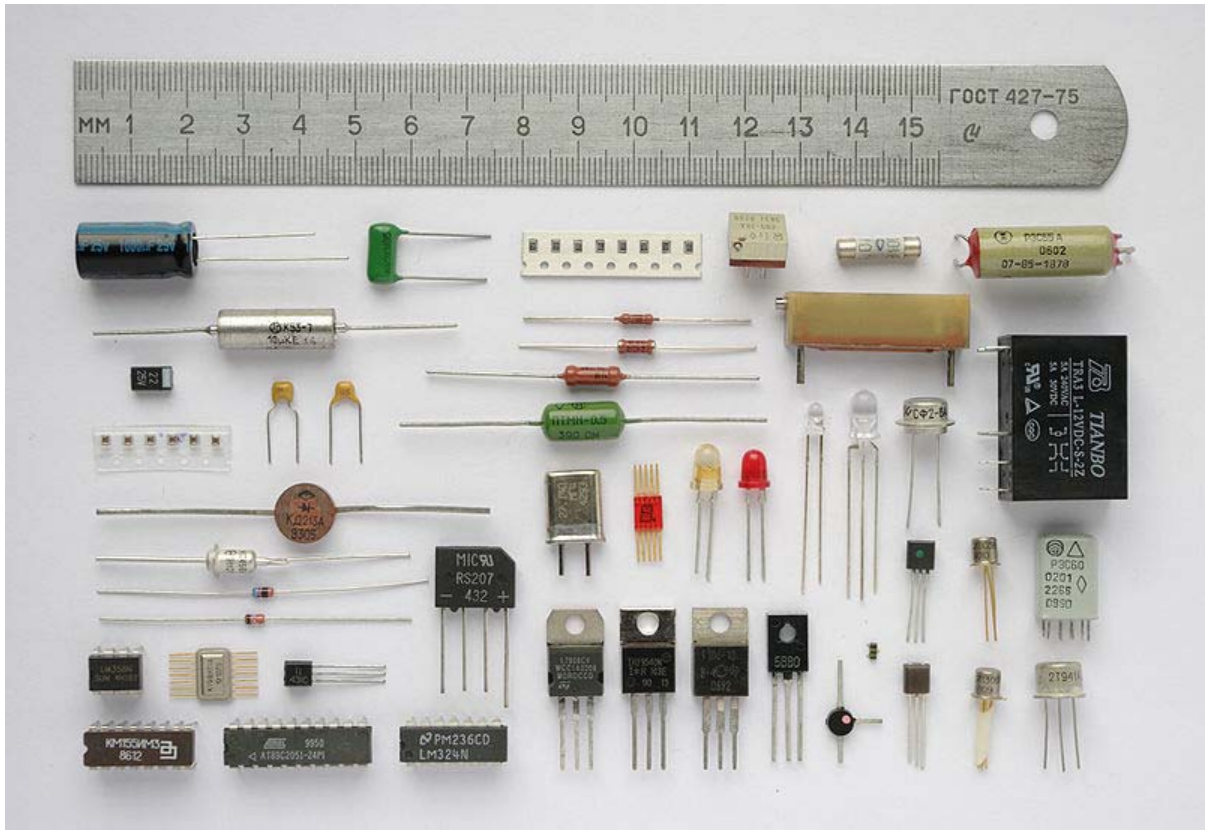




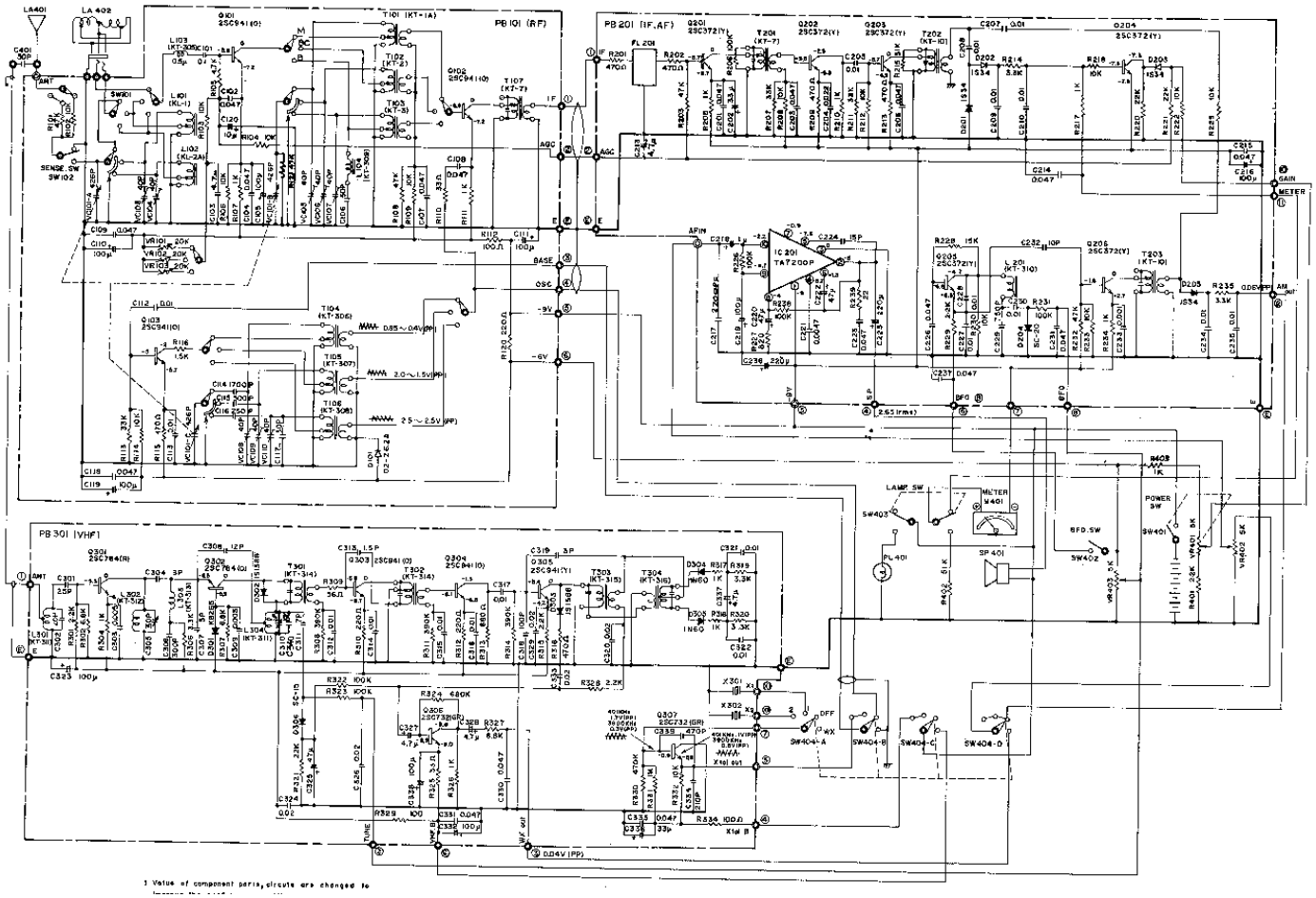
Three goals of *in silico modeling*

- Forecasting results with minimal resources
  - Optimal design of otherwise complex experiments (clinical studies)
  - Filter and focus screening results for priority
  - Suggest novel transformative materials
- Formalize understanding
  - Drives technical model development
  - More efficient interpretation of data, focuses exploratory investigations
- Communicating
  - Internally – Efficient archiving of institutional knowledge
  - Externally – The science behind how products work

Start with parts list…



Define the relationships objectively *in silico*.



Done well in physics, chemistry and engineering:

- Safety assessment alternatives
- Test manufacturing processes
- Facilitates rapid package design
- Chemical hit expansion
- Predict mechanical (like pressure points) product-body interactions

But capabilities underdeveloped in Biology.

We have the parts; still developing and formalizing the qualitative and quantitative relationships between the parts.

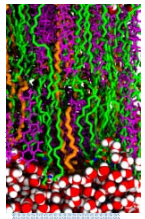
THOUGHTS

Nearly all P&G products interact with skin.

Procter&Gamble

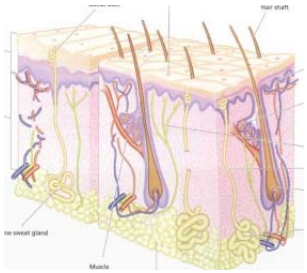
In Silico - skin modeling should be holistic.

Molecule



Cell

Tissue

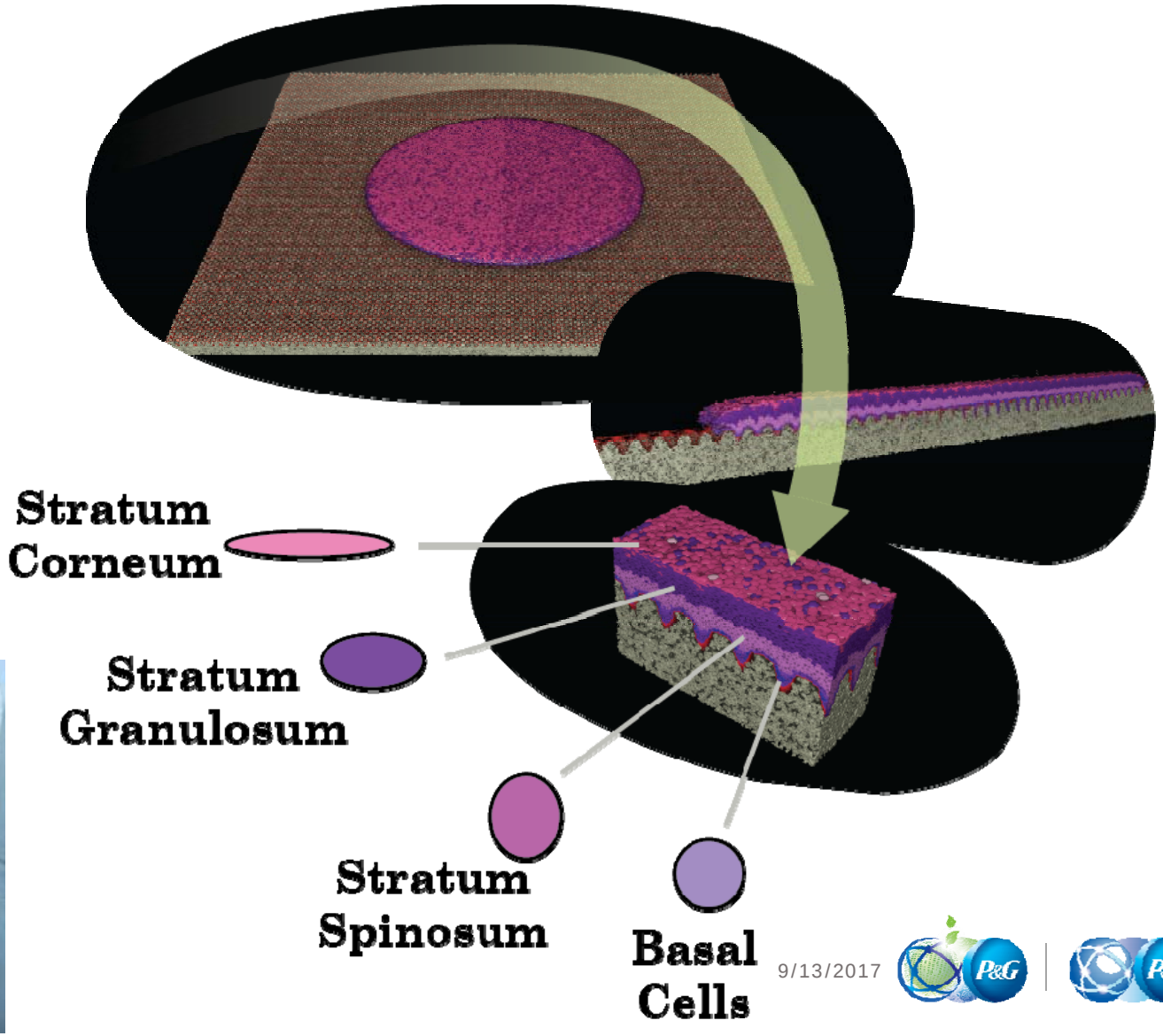


Individual

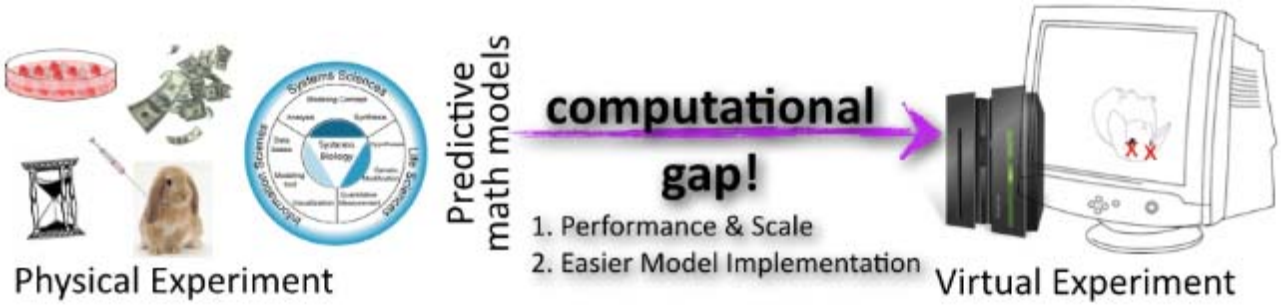
Populations

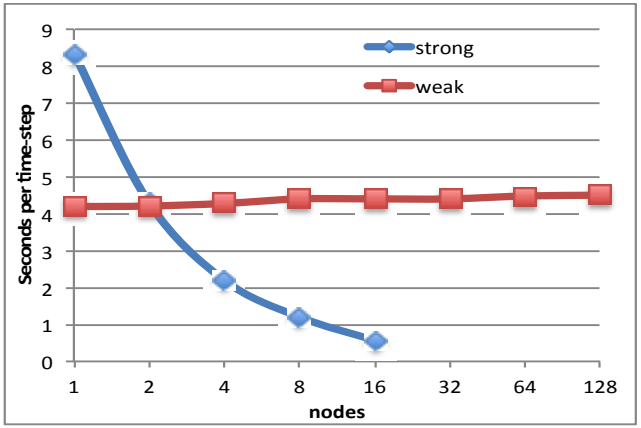
The Multi-Cell Skin Model:

Tissue scale.
Cell resolution.



biocellion





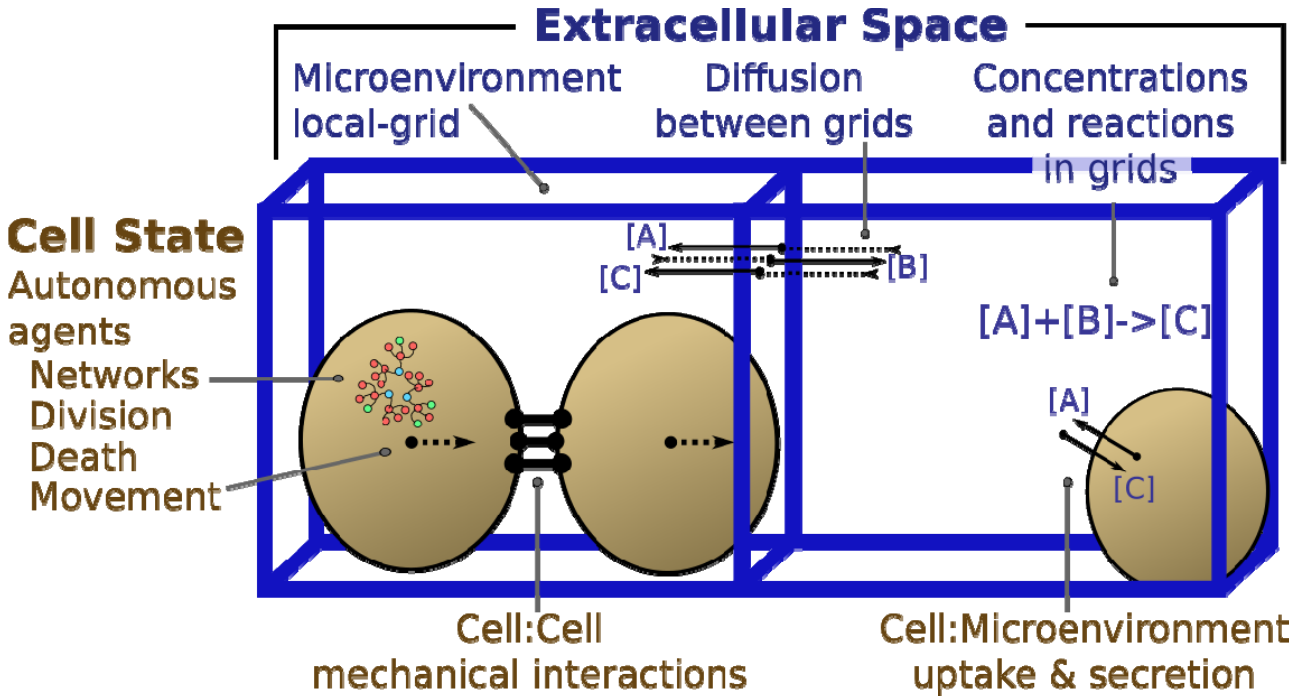
Biocelion (blue) strong scaling: time to sort 26.8 million cells; (red) weak scaling: time if simulating 13.4 million cells

- Spinout of Pacific Northwest National Lab
- Developed in association with the Institute for Systems Biology
- Special Purpose Corporation: reduce and eliminate animal testing via comp. modeling

info@biocellion.com

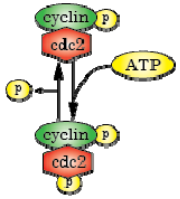
Foundation in Agent-Based Modeling...

- Cells as agents (spheres, ellipsoids, potentially multi point agents)
- Intracellular logic and ODE solver
- Paired and non-paired mechanical interactions
- extracellular space with PDE solvers for reaction diffusion systems

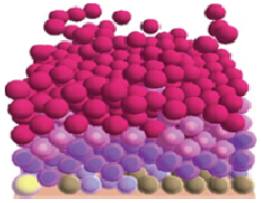


QUESTIONS ON PLATFORM DETAILS

Life Science Centered

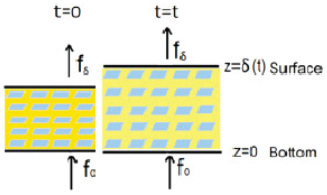


Kinetic Cell Cycle

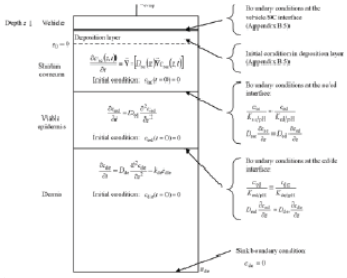


Tissue Morphology

Physics Centered



Water loss & Occlusion



Penetration & Transport

Single integrated, multiscale model on the Biocellion HPC platform

Strategy:

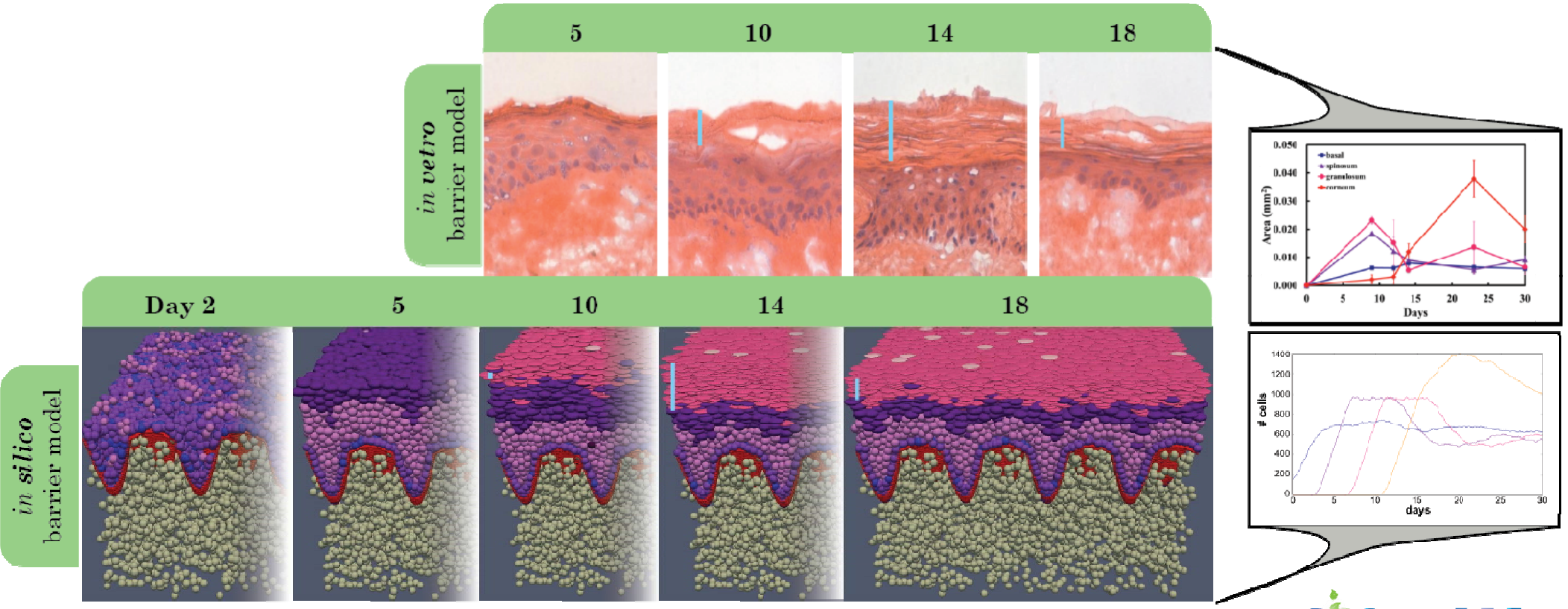
Model Integration

High Performance Computing

1. Dancik Y, et al. Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure. Advanced drug delivery reviews. 2
2. Li X et al. Dynamics of water transport and swelling in human stratum corneum. Chemical Engineering Science. 2015
3. Li X, et al. Skin stem cell hypotheses and long term clone survival–explored using agent-based modelling. Scientific reports. 2013
4. Tyson JJ. Modeling the cell division cycle: cdc2 and cyclin interactions. Proceedings of the National Academy of Sciences. 1991

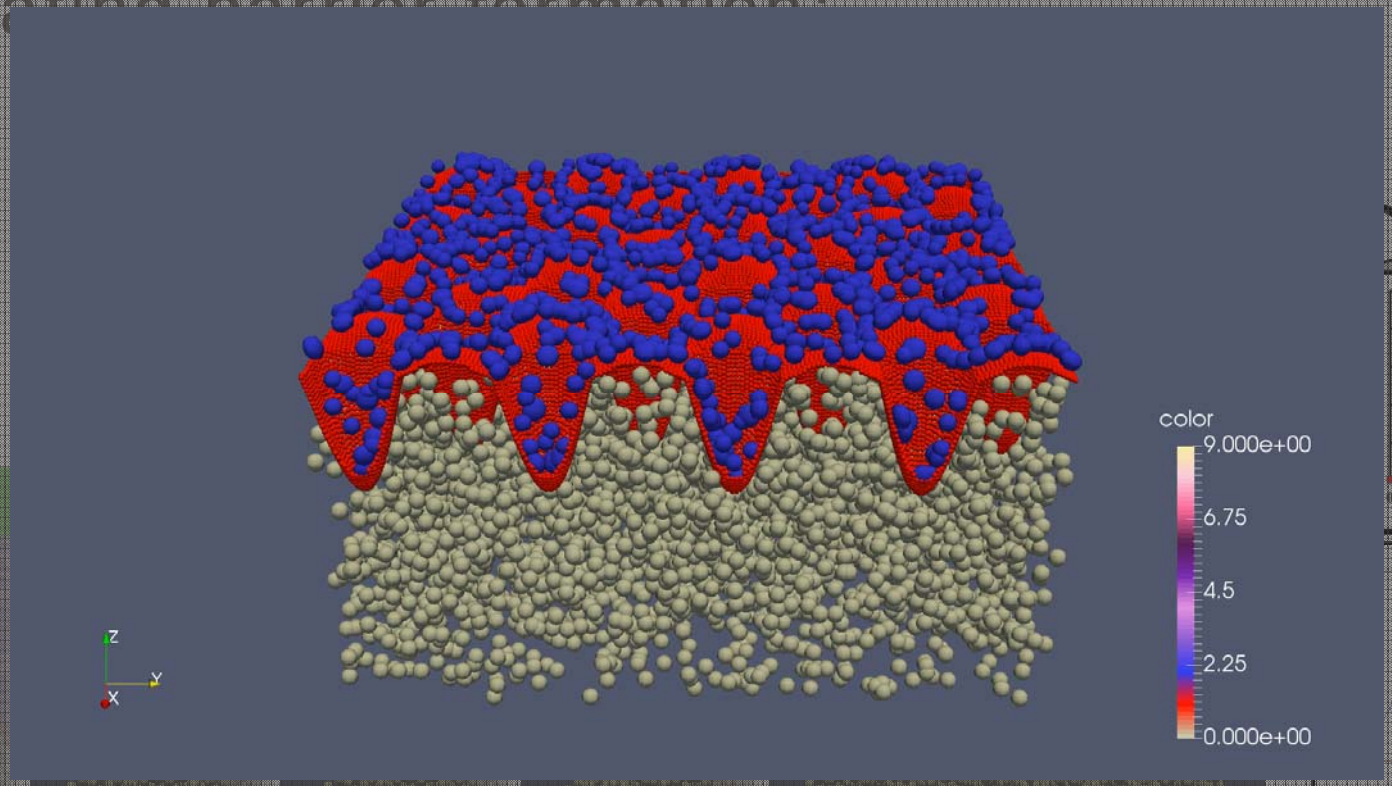
QUESTIONS ON MODEL DETAILS

Simulating barrier formation:

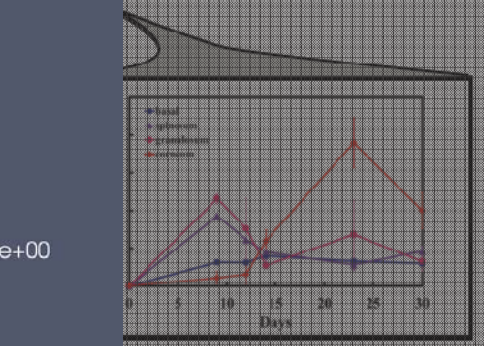


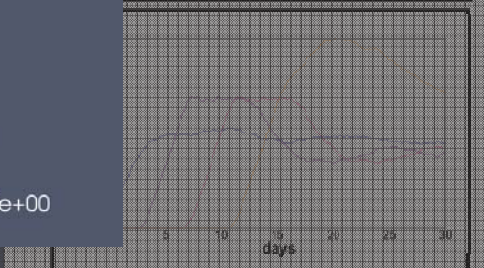
in vitro skin model - Bachelor, M, et al. Transcriptional profiling of epidermal barrier formation in vitro. Journal of dermatological science 2014

Simulating barrier formation:



in silico barrier model

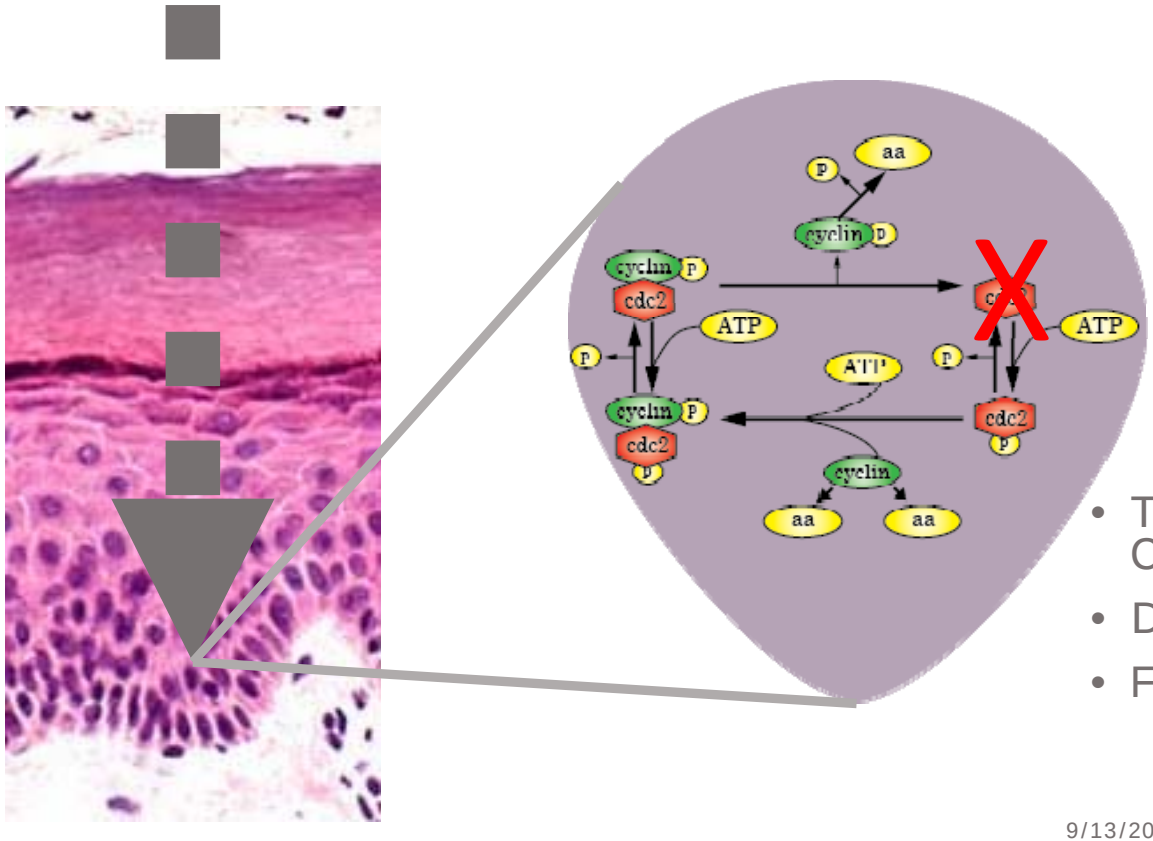




in vitro skin model - Bachelor, M, et al. Transcriptional profiling of epidermal barrier formation in vitro. Journal of dermatological science 2014

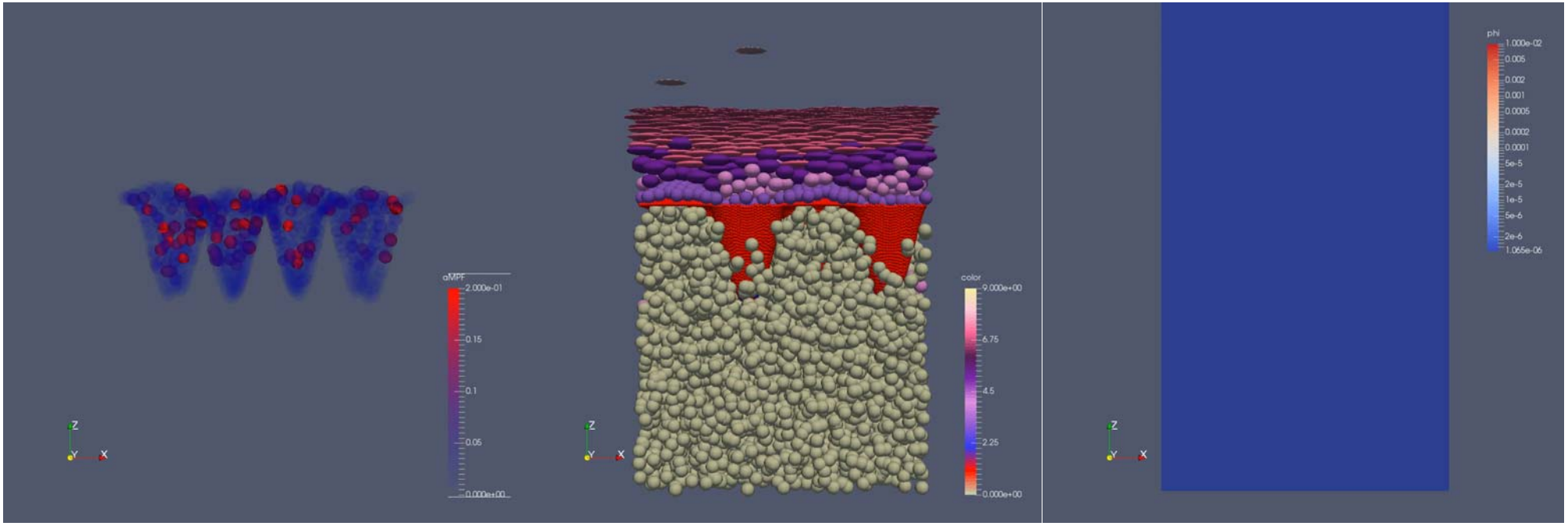
Proof of Concept – CDK1 CD22 inhibitor.

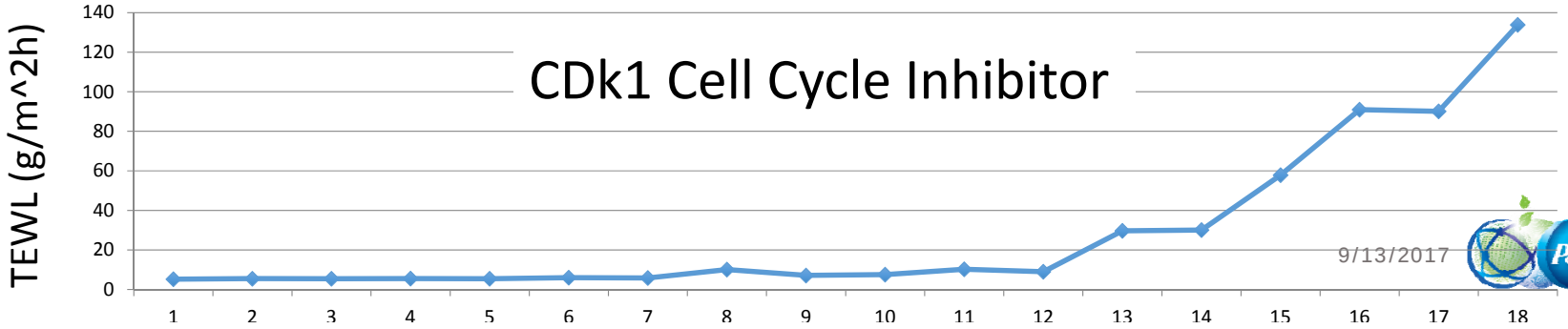
- Topical application
- Transport through skin
- Permeates basal cells



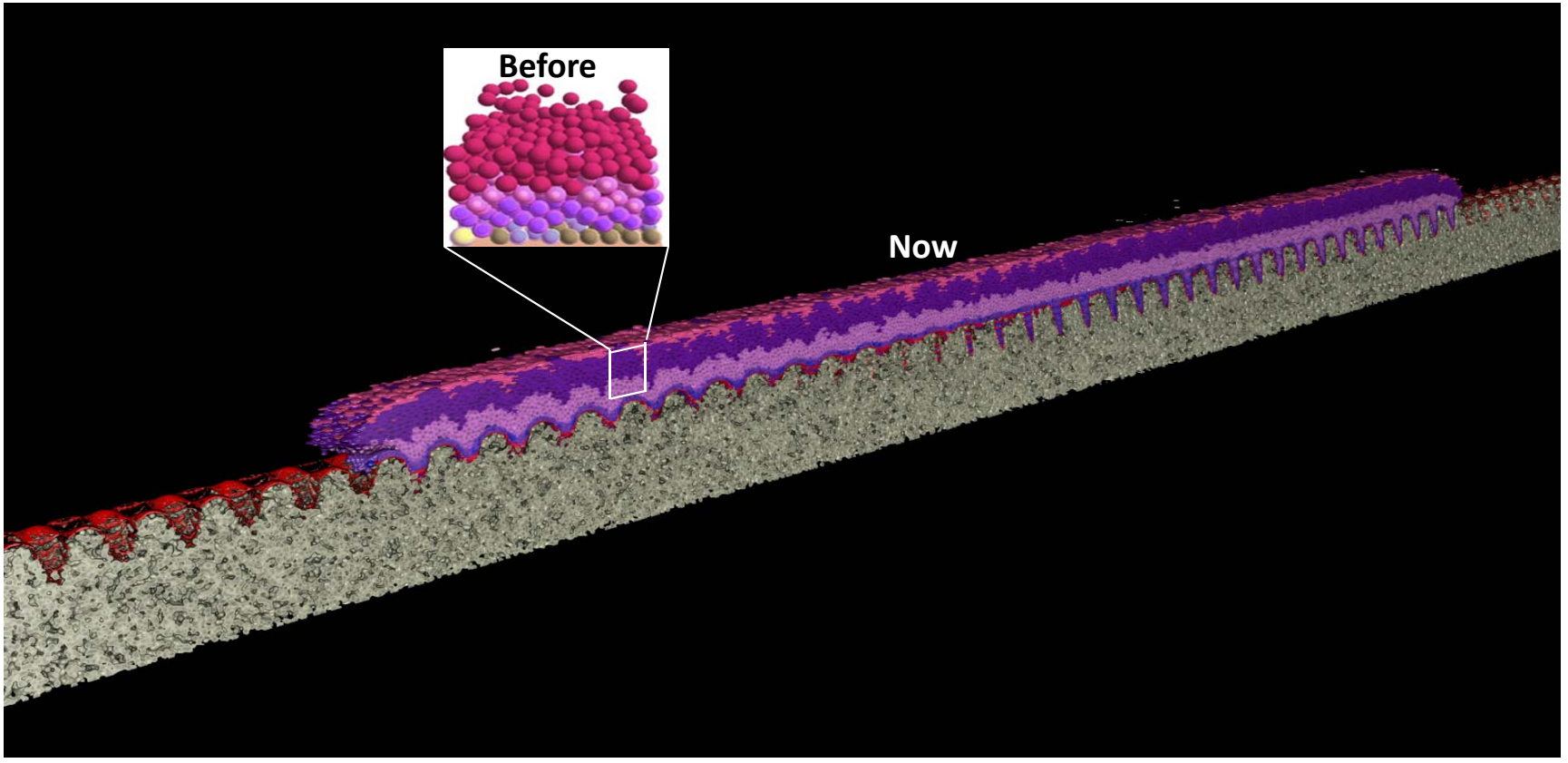
- Terminates Cell Cycle
- Disrupts Barrier
- Feedback

Model approximated material response – *de novo*.



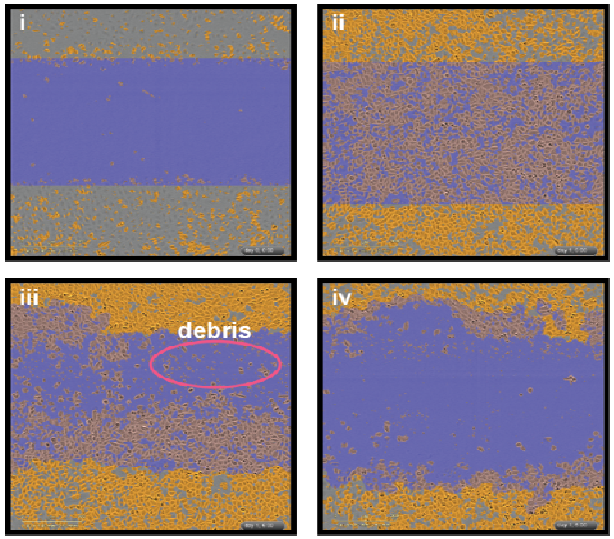


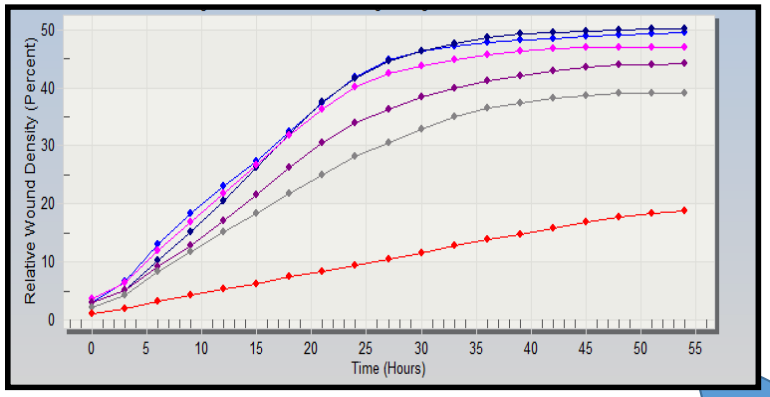
High-performance computing allows scalability.



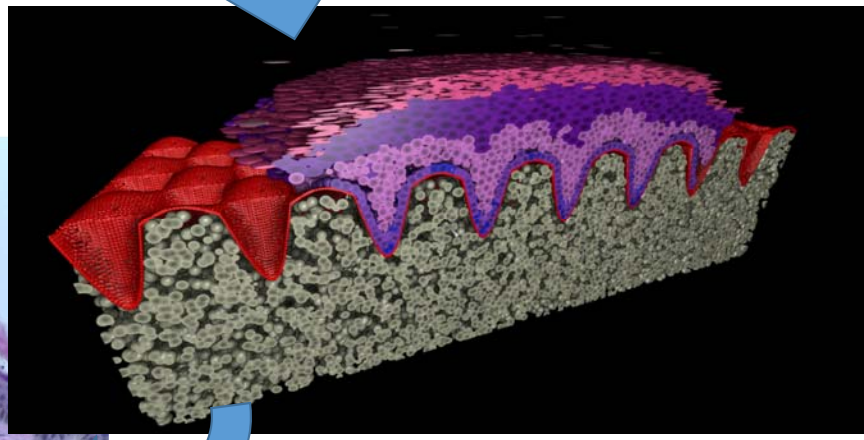
Into the Future, Image analysis…

Learn *in vitro*

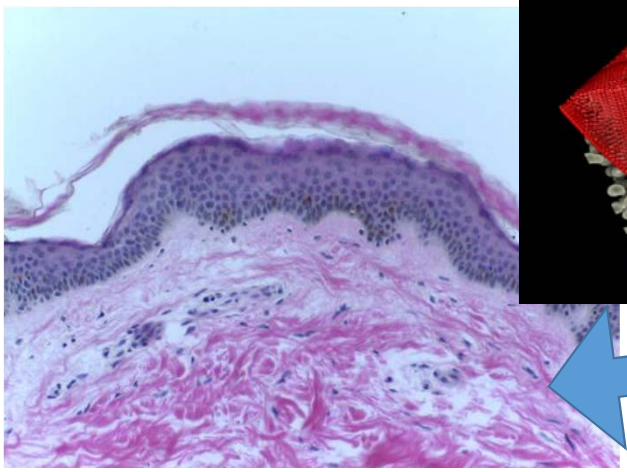




Model *in silico*



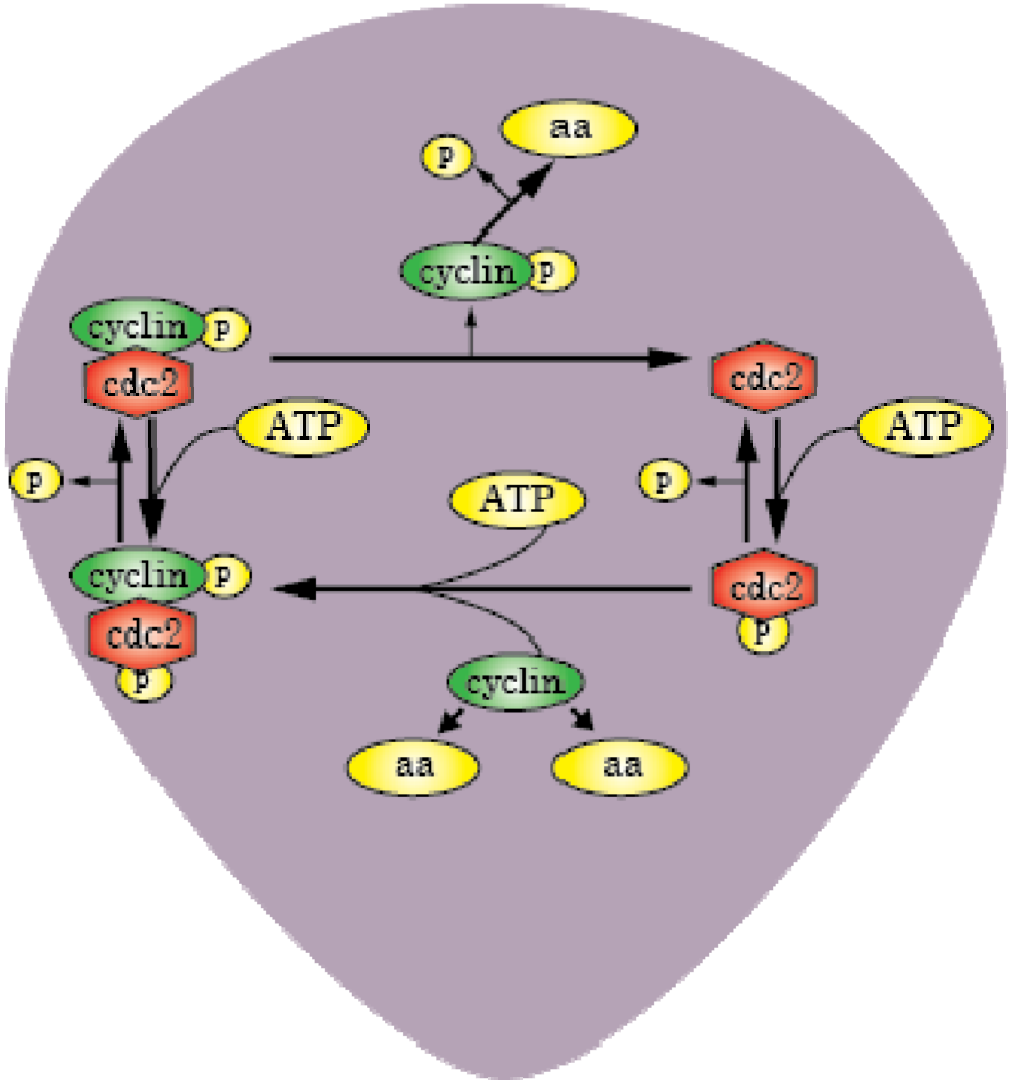
Innovation



Predict Clinical

Questions, comments, concerns?

Cell Cycle


aa
P
cyclin
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cdc2
ATP
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cdc2
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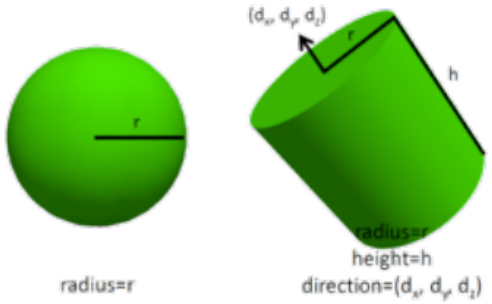
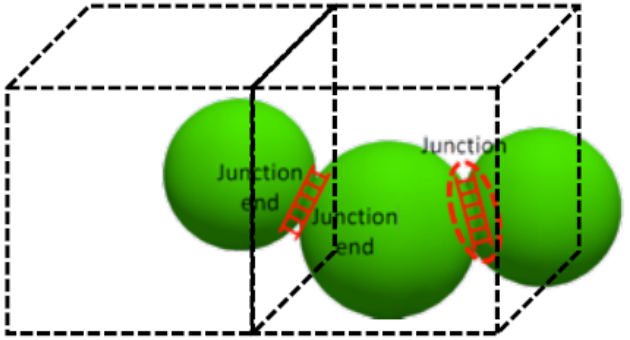
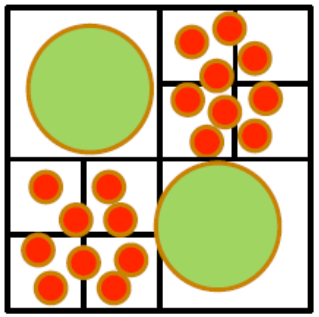
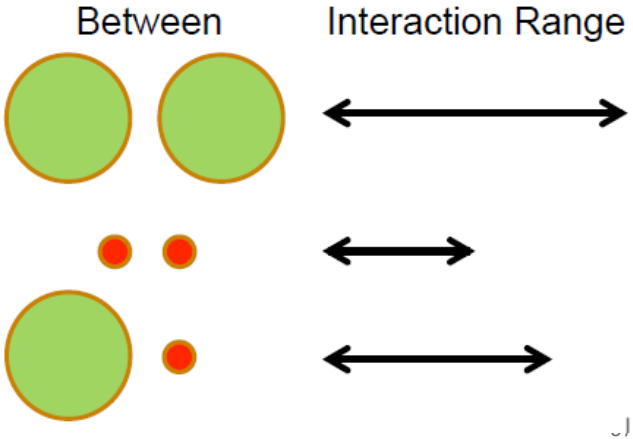
cyclin
aa
aa

Limited interaction ranges allow spatial partitioning



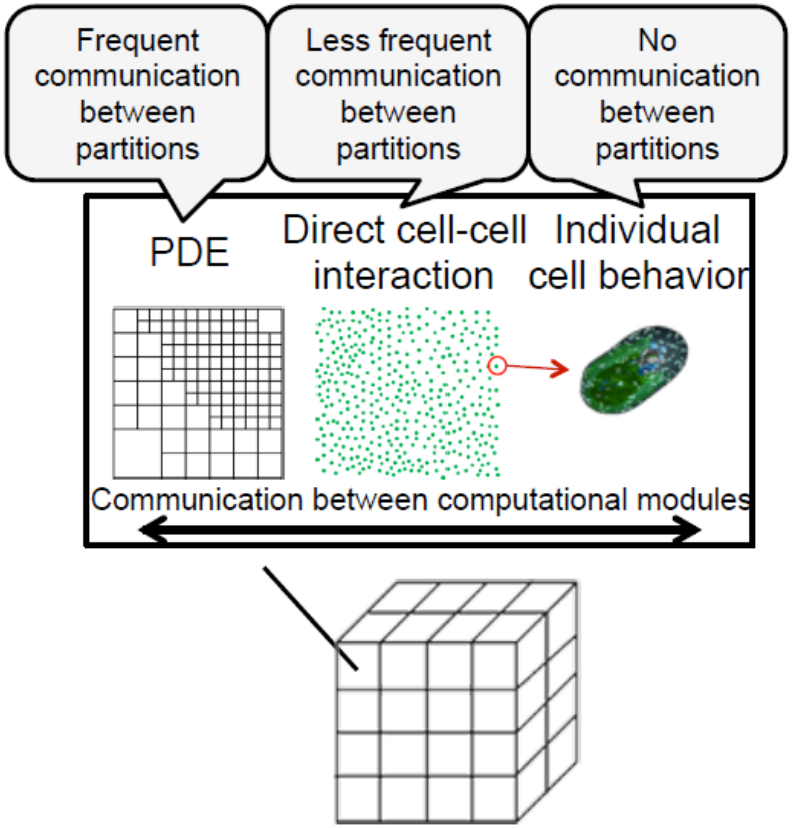






Different time scales allow temporal partitioning

- Baseline Time Step
  - Direct cell-cell interaction via physical contact
  - Couple all three computational modules
- State-and-grid time step
  - Couple the cell state update module and the grid update module
- PDE time step
  - Solve PDEs CHOMBO
  - Adaptive Mesh Refinement
- ODE's can also have different time steps
  - Intel's ODE solver
- Users set time step sizes, software manages parallelism & data movement
  - MPI for shared memory balancing
  - PNNL Global arrays across nodes



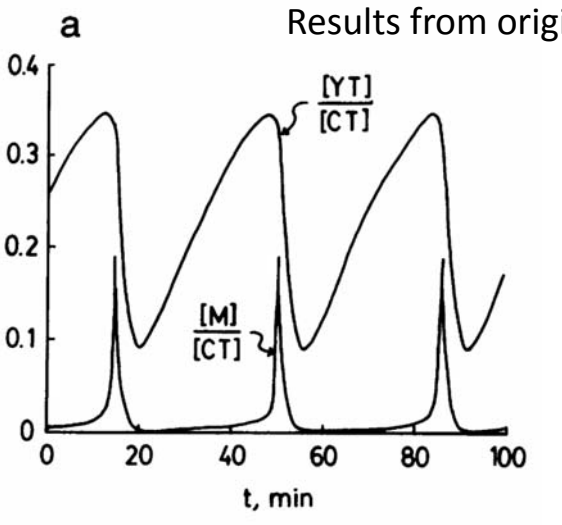
Validation studies

- We present validation results over serval modules.
- Not all modules are integrated on a single platform.
- This work is meant to be a qualitative validation.
  - More quantitative validation will be made a priority only when specific endpoints are chosen and appropriate resources, technologies, and/or knowledge sources are identified for determining parameter values, training and validation data.

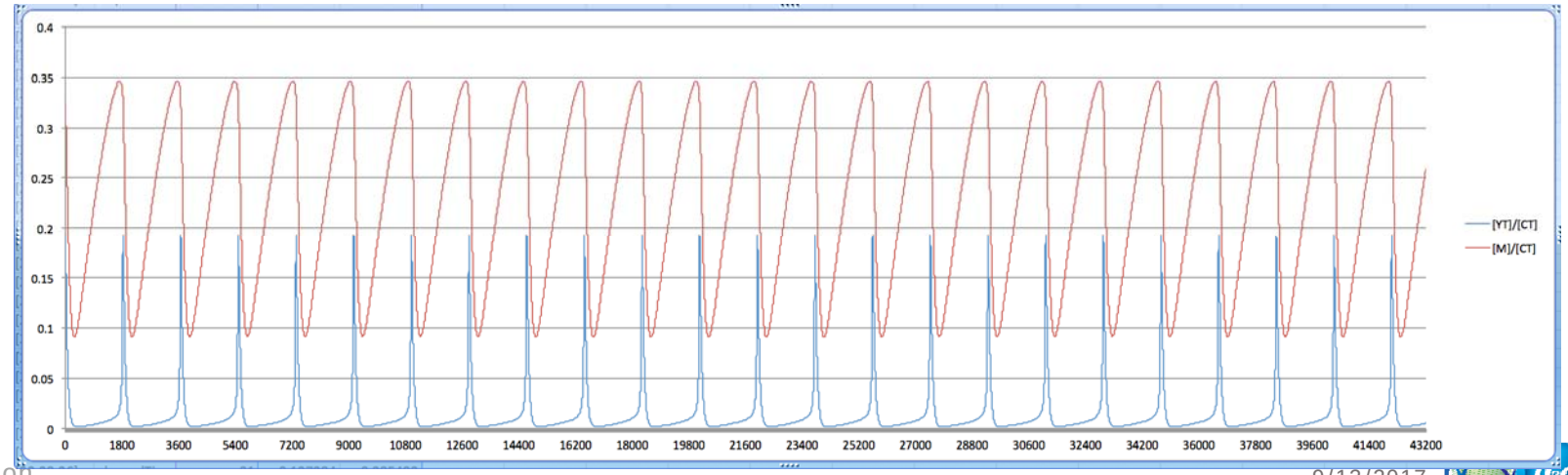
Biomolecular cell cycle module

- Tyson 1991 Modeling the cell division cycle: cdc2 and cyclin interactions
- Implemented in individual cells
- Tyson: 35 min interval
- Biocellion: 30 hours interval for stem cells and 15 hours interval for progenitor cells
- Scale d[var]/dt in ODEs by 35.0 / (30.0 * 60.0)
- Halt the cell cycle (d[var]/dt = 0) to model slower proliferation due to contact inhibition and barrier formation (low TEWL).

Results from original paper



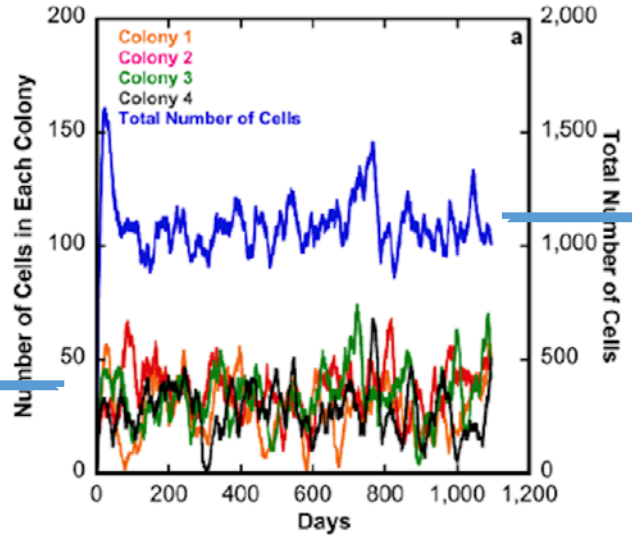
Results from current platform (period: 30 hours == 1800 min)



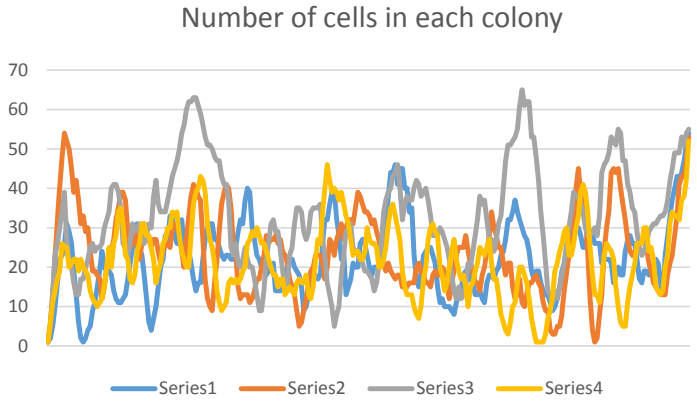
Agent-Based Barrier formation module

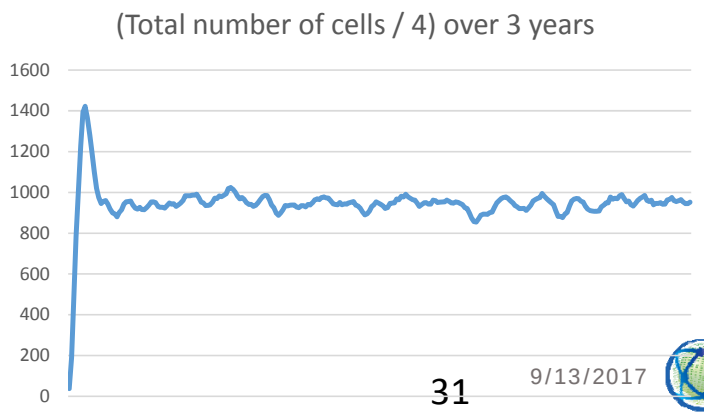
- Li 2013 Skin stem cell hypothesis and long term clone survival – explored using agent-based modeling
- Li2013: 100um by 100 um domain size, spheres
- Biocellion: 200um by 200um domain size, ellipsoids

Results from original paper

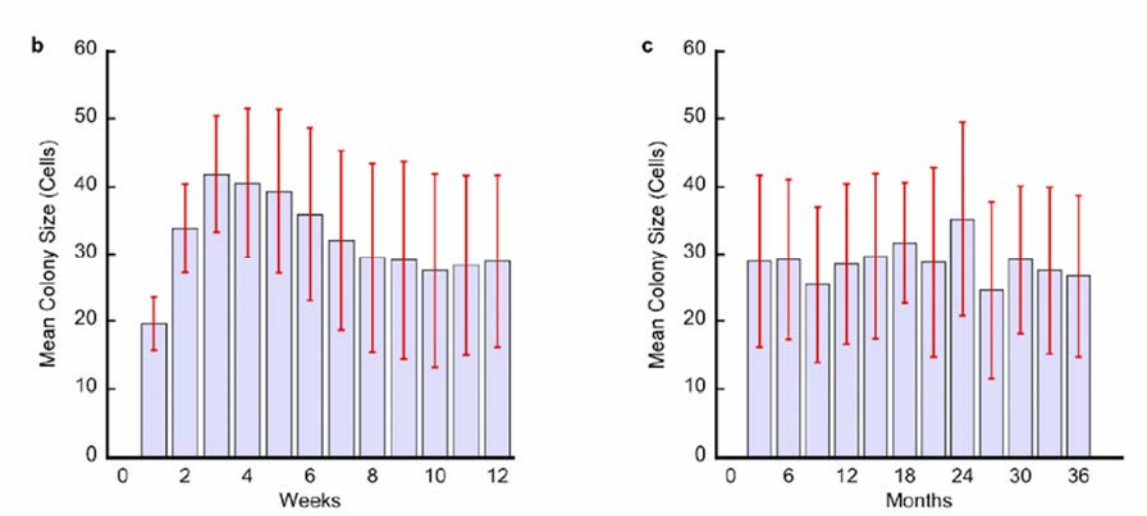


Results from current platform
(total number of cells divided by 4 considering that the simulation domain size is 4x larger)



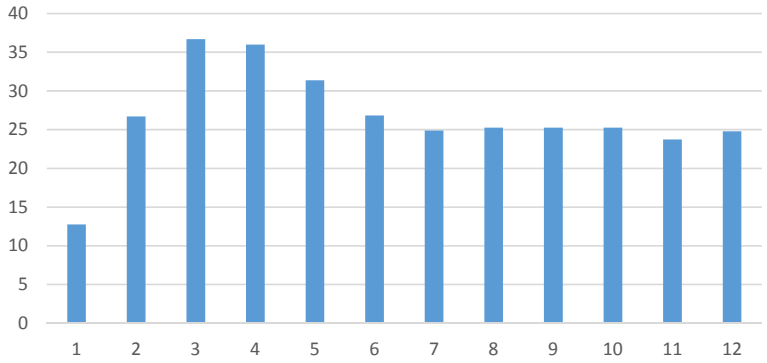


Results from original paper

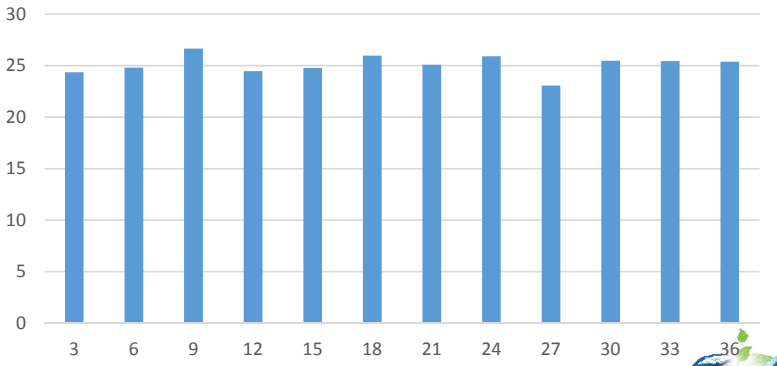


Results from current platform

Mean colony size (# cells) over 12 weeks

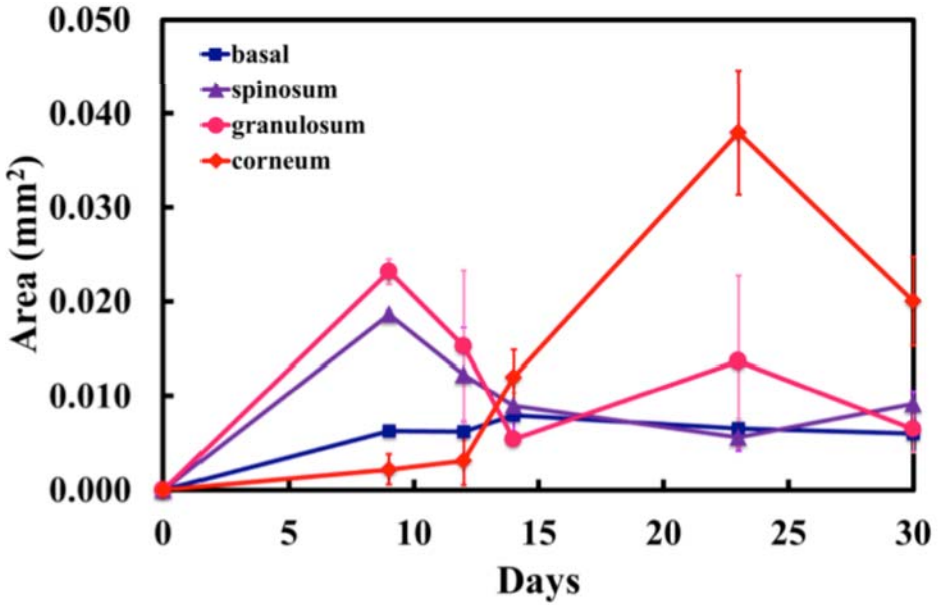


Mean colony size (# cells) over 3 years

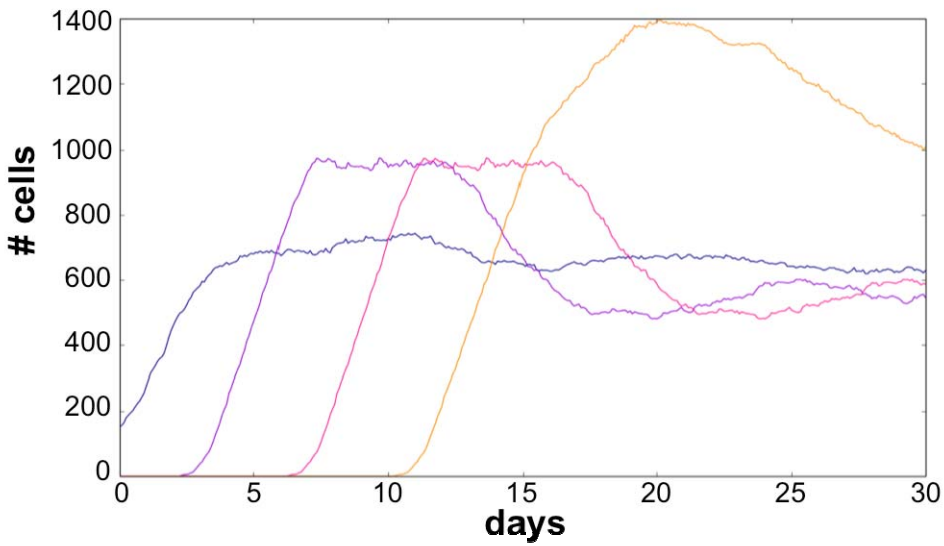


Dynamics of RE model (*in vitro)* Barrier formation comparable to simulation

In vitro, in house experimental results



model results



Slab style occlusion module

- Kasting 2015 Dynamics of water transport and swelling in human stratum corneum
- Different stratum corneum (approx. 40um at 0.05 RH) heights produced by the skin model on Biocellion, so the experimental setup is not identical
- Rough comparison (see the trends)

Results from original paper

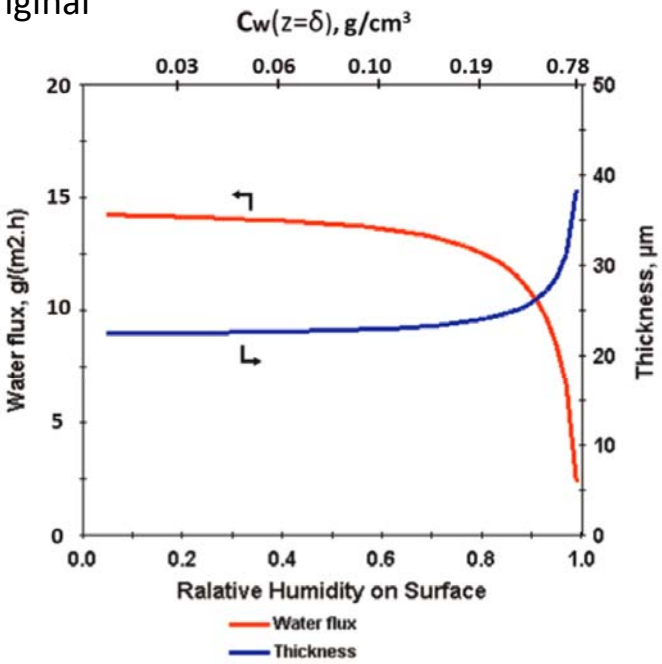
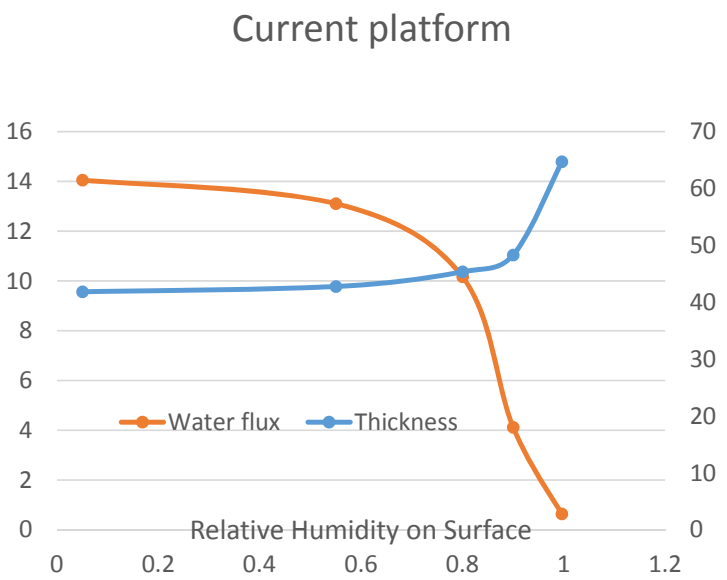


Fig. 3. Calculated water flux (TEWL) through SC and SC thickness at different relative humidities (RH) at steady state. The upper horizontal axis is $C_w(z=\delta)$, calculated from RH (or a_w) according to Eqs. (10) and (11).



Slab style skin pen module

- Kasting 2012 Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure
- Different stratum corneum (approx. 40um), viable epidermis (with rete pegs), and dermis heights produced by the skin model on Biocellion, so the experimental setup is not identical
- Rough comparison

Current platform Simulation (J_max):

- DPGME: 139.8 (close)
- Ibuprofen: 1.76913 (underestimates)
- Triclosan: 1.374 (overestimates)

DPGME is one of these

Experimental measurements in original paper

Table 4c
Experimental values of the cumulative amount measured at the end of the experiment (Q_{abs}) and maximum flux (J_{max}) to evaluate the large dose simulations. Values are obtained directly from the references or calculated as noted.

Compound	Q_{abs} [μg/cm^2]	J_{max} [μg cm^{-2} h^{-1}][b]	Reference
2-Ethoxyethanol	27,231[a]	1135	[33]
2-Butoxyethanol	24,211[a]	1009	
1-Methoxy-2-propanol	14,325[a]	597	
Malathion	1.89	0.546[b]	[72]
Ibuprofen	590	20	[34]
Flurbiprofen	74	17	
DPGME	609	106	[73]
EGnPE	2830	394	
EGiPE	1643	240	
EGMEA	6546	831	
DEGBEA	6546	59	
Triclosan	0.48	0.043	[74]

Original model results in paper