Multi-Cell Modeling of Complex Biological Systems
Past, Now (CompuCell3D) and Future

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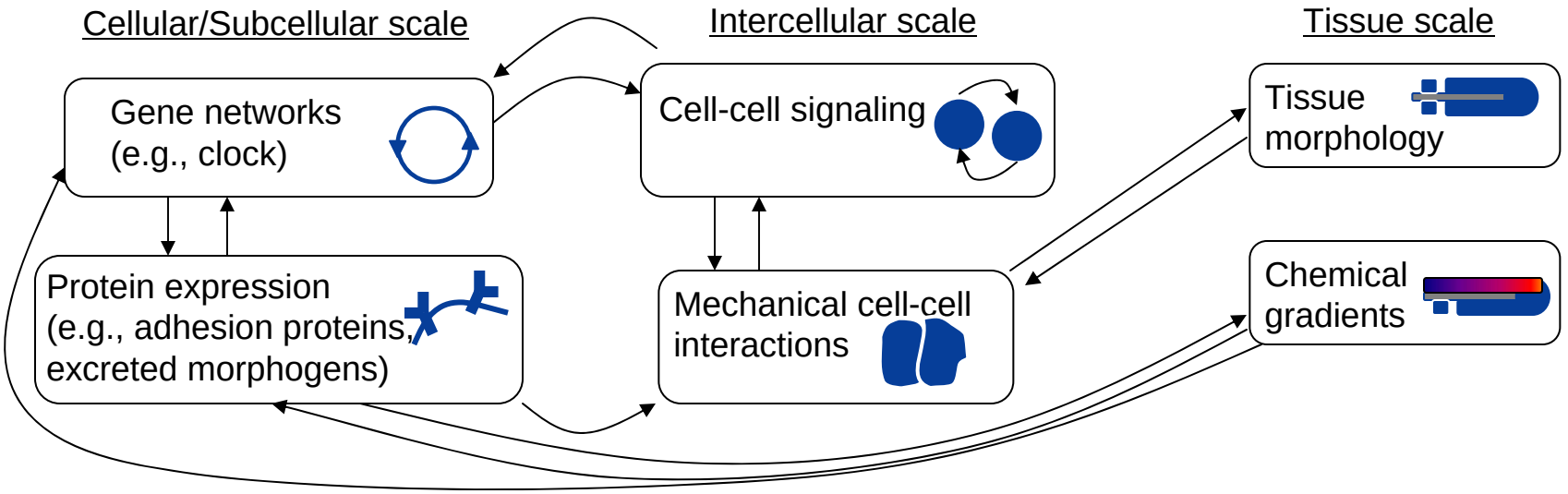
For papers, please visit http://www.biocomplexity.indiana.edu

To download software for model building, please visit
http://www.compucell3d.org

CompuCell3D is free, Open-Source tool

Google keyword: CompuCell3D

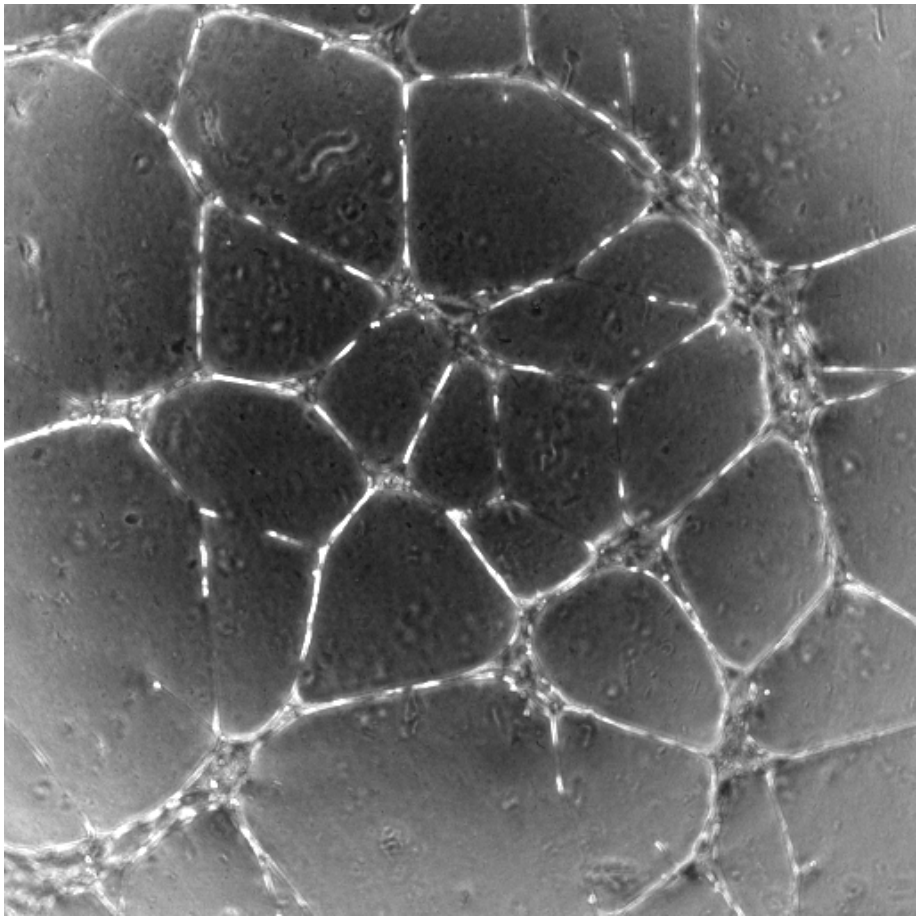
Biomedical Modeling at Multiple Scales



- More and more common pattern in modern biomedical modeling research
- Synthesis of information from multiple subfields to create truly multi-scale predictive models.
- Combining models from multiple scales is not a trivial “superposition” - we often discover “unintuitive” behaviors of complex systems only when we build truly multi-scale model.

Why single-scale models are often insufficient?
In vitro Capillary Formation

Abbas Shirinifard, Abdelkrim Alileche, Prof. Glazier's lab



An attempt to understand vascular network formation requires knowledge of gene regulatory networks, cell-cell signaling, cell level cellular mechanics, cell-morphogen interactions etc… - multi-scale problem

“Traditional” (past?) approach to building complex biomedical models (multi-scale, multi-cell)

- Hire a postdoc
- Train new employee (6 months- 1 year)
- Pick most fashionable programming language (often based on suggestion of an expert you have just met at the conference)
- Have a postdoc hard-code simulations using the latest and “the coolest” language
- Publish a paper (or few papers if working with exceptional individual)
- Inform a postdoc that funding is running out
- Throw farewell party for recently hired employee
- Get new funding
- Repeat the cycle (GOTO 1)

Typical cycle period is 2-5 years

Outcome

- Many excellent papers which are non-reproducible.
- Significant overhead for researchers who want to use / improve your model. They will have to go through the same research cycle that you have just successfully completed.
- Collaboration or competition? Choice between the two is not an excuse for inability to reproduce or validate models.

“Industrial” approach

Taken from various job-postings:

*“Utilize the **Matlab** program to prepare data... data. Run analysis programs in **Matlab**. Generate graphs utilizing **Matlab**. Generate reports in MS PowerPoint.. “*

“…including experience with Matlab, R, S-PLUS, SAS, or other major statistical system, experience with programming numerical methods, background in statistics and linear algebra, knowledge of time series, data analysis, finance is a plus”

*“…Experience in controlling equipment with external software such as Labview or **MATLAB**“*

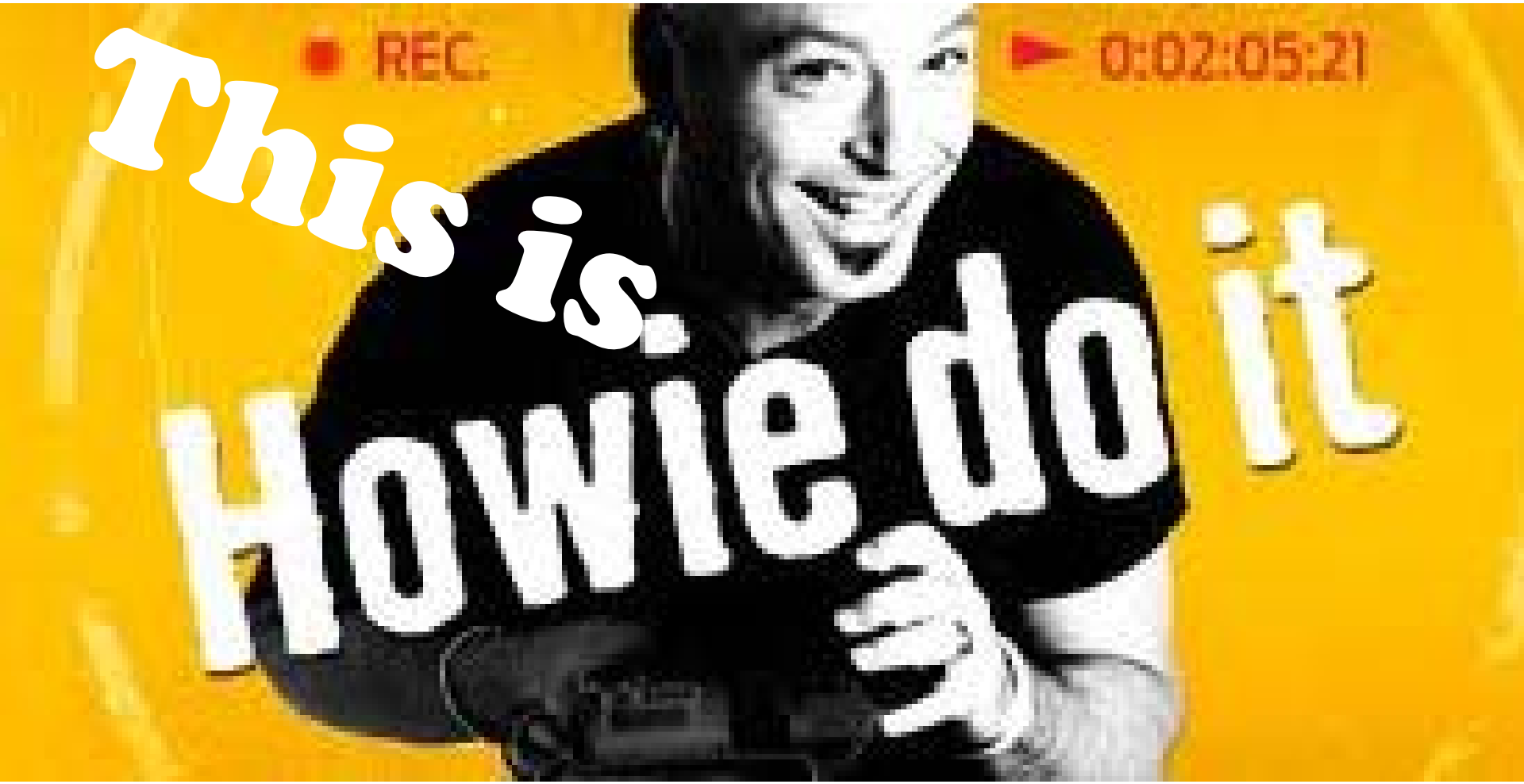
*“…expertise and experience in image processing, **Matlab**, CPU and GPU based algorithm acceleration. Further... 3 years experience with **Matlab** • 3 years experience”*

Improved “research” cycle

1. Hire a postdoc (job ad would ideally require knowledge of at least one of the standard modeling toolkits)
2. Train new employee (2 – 6 months)
3. Have a postdoc develop shareable simulations using standard tools
4. Publish multiple papers with full shareable model code
5. Engage postdoc in addition al activities such as experimental work
6. Write good recommendation letter and hopefully later congratulate postdoc on securing assistant professor job.
7. Get new funding
8. Repeat the cycle (GOTO 1)

Ingredients needed

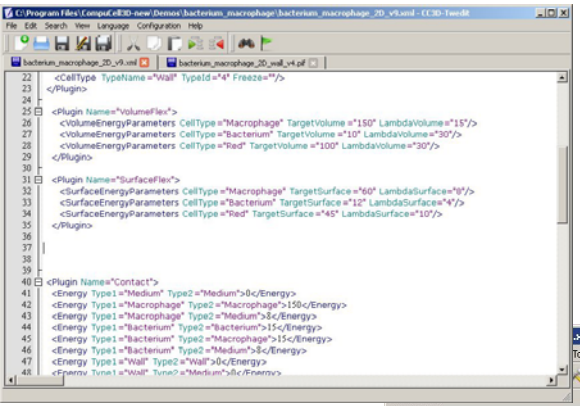
- Shareable and easy-to-use Simulation Environments.
- Standard way to represent multi-scale multi-cell biomodels – understandable by Simulation Environments.
- Curation and cross-validation of models (also helps with locate modeling artifacts specific to given modeling methodology)

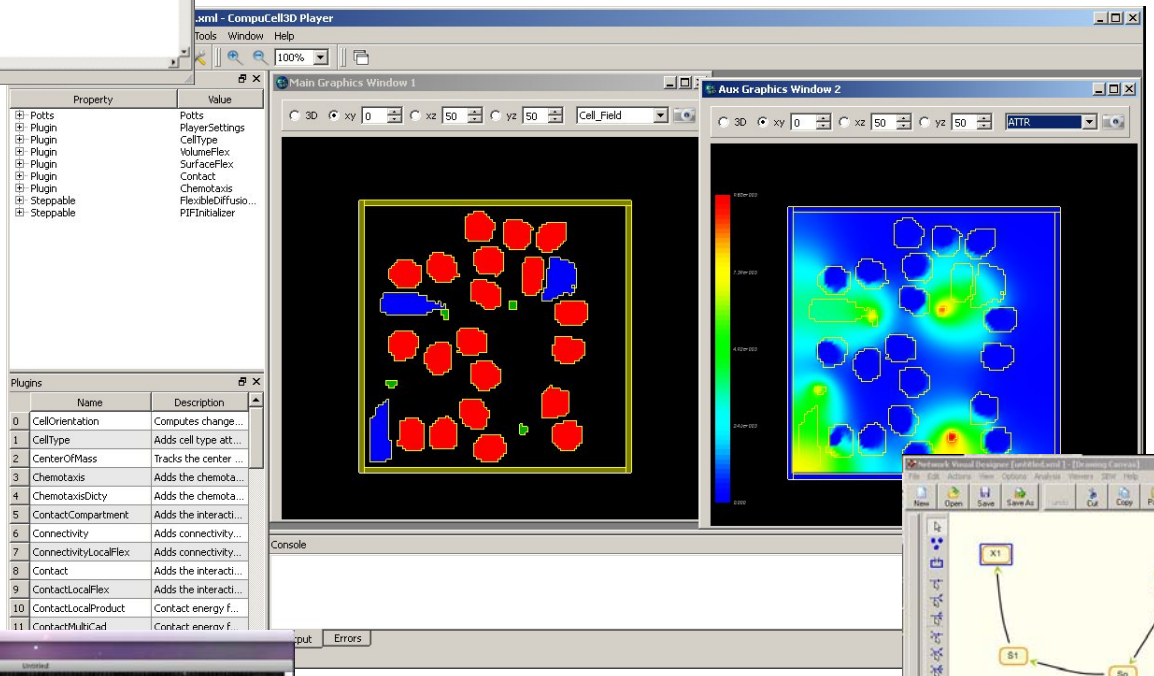


Source: seriimk.forumakers.com

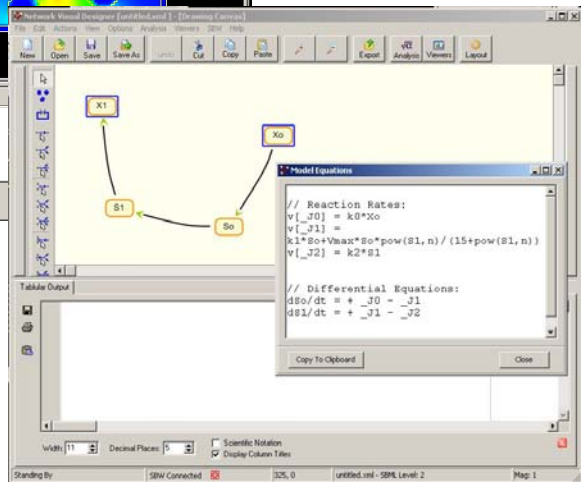
CompuCell3D Simulation Environment

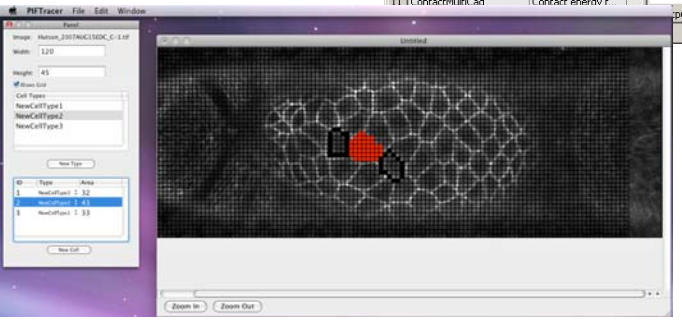
Python and XML model scripting





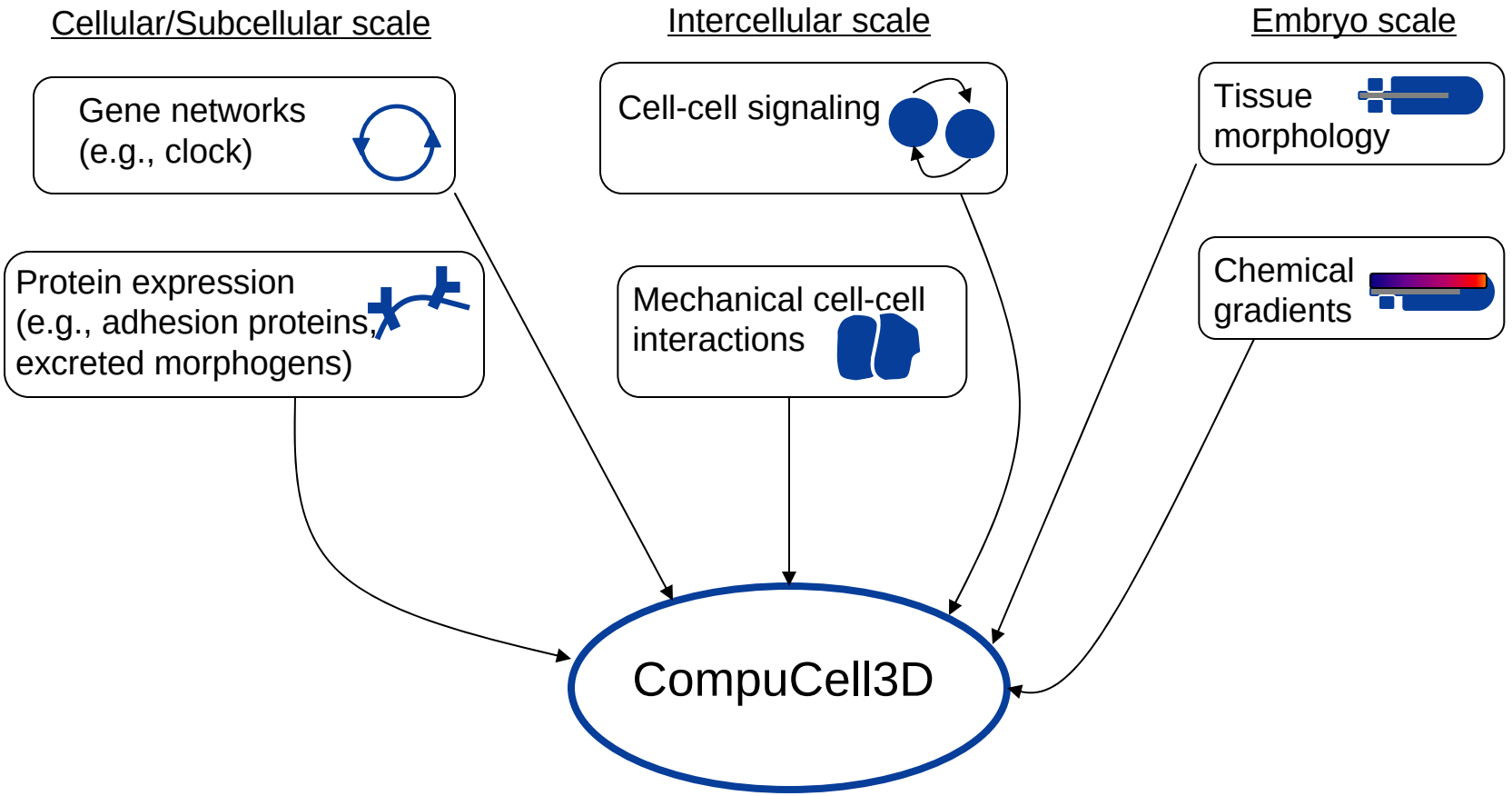
SBML models (e.g. defined using SBW)





Graphical specification of initial conditions

Multi-scale biomedical modeling framework



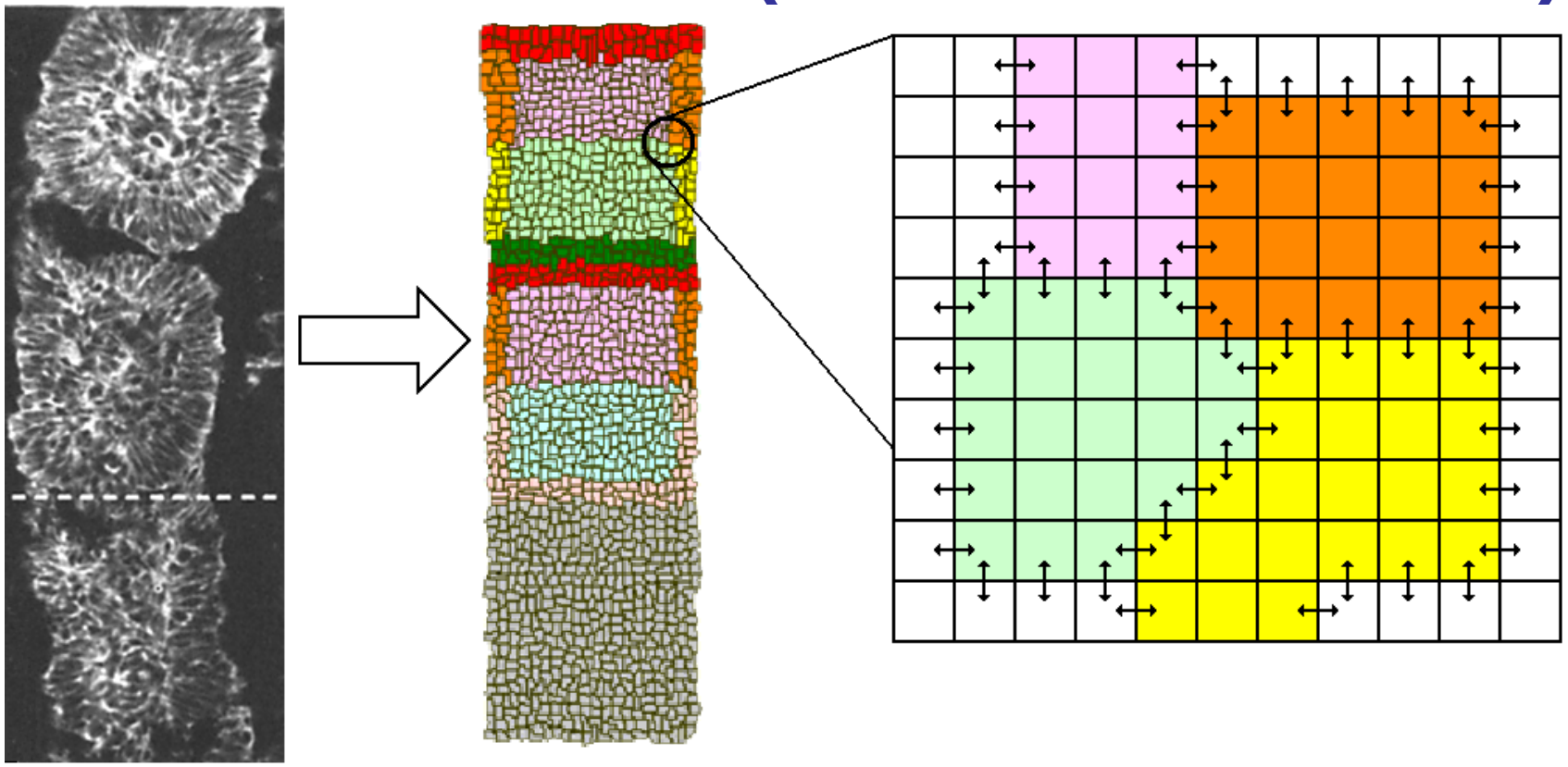
- The use of CompuCell3D as a framework makes handling and combining multiple scales tractable.

Model description is based on observed cell behaviors

- They also exhibit other behaviors such as:
  - **Grow,**
  - **Divide,**
  - **Change Shape,**
  - **Move Spontaneously**
  - **Move in Response to External Cues,**
  - **Stick,**
  - **Absorb,**
  - **Secrete,**
  - **Exert Forces**
  - **Change their local surface properties**
  - **(Send Electrical Signals)**

  A long list, but not compared to ~10^{10} gene-product interactions.
- Many cells have relatively simple phenomenological behaviors most of the time.

GGH(Glazier Graner Hogeweg) Model also known as CPM(Cellular Potts Model)



Cellular behaviors are represented as additive energy terms.

$$E = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}\left(1-\delta_{\tau(\sigma(x)),\tau(\sigma(x'))}\right)$$

$$+\lambda_s\left(s_\sigma - S_\sigma\right)^2 +$$

$$\lambda_v\left(v_\sigma - V_\sigma\right)^2$$

Acceptance probability

$$P(\Delta E) = 1,\ \Delta E \leq 0$$

Accept pixel copy attempt

$$P(\Delta E) = e^{-\Delta E/kT},\ \Delta E > 0$$

Conditionally accept pixel copy attempt

T in the above formula is NOT a physical temperature.

T is a measure of cell membrane fluctuations, or simply cell motility

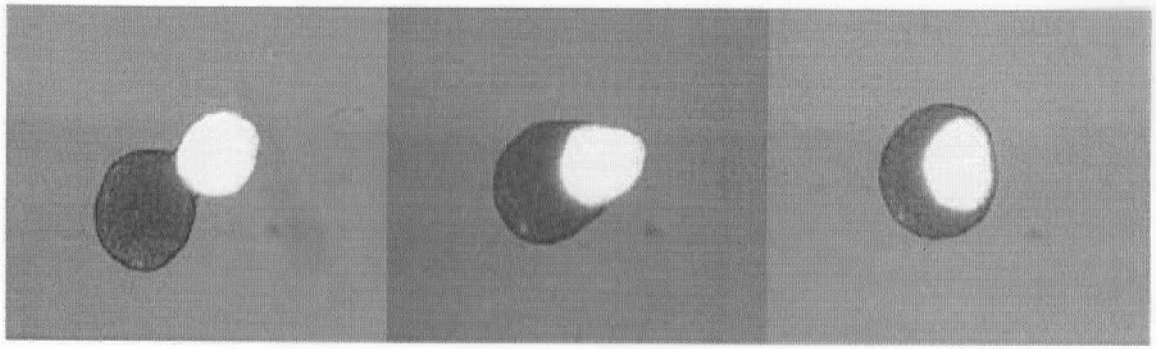
CompuCell3D Demo

Simple Example Cell Sorting/Engulfment

Engulfment

Use pairs of tissues of different types from chick embryo. Dissociate cells and reaggregate.

Engulfment of heart tissue (bright) by neural tissue (dark)

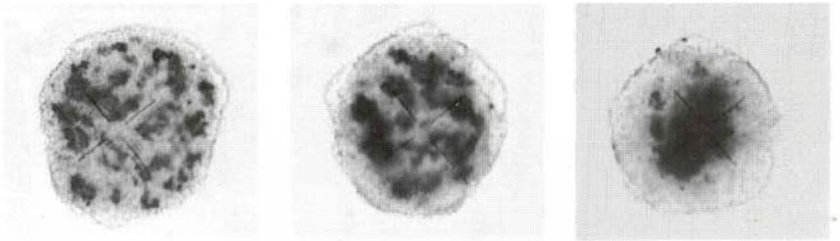


t = 1 hr t = 5 hr t = 10 hr

(Diameter of heart tissue is 325 μm.)

Neural: $\sigma_{NM} = 1.6$ dyn/cm. Heart: $\sigma_{HM} = 8.5$ dyn/cm.

Growth of pigmented clusters in neural retinal tissue



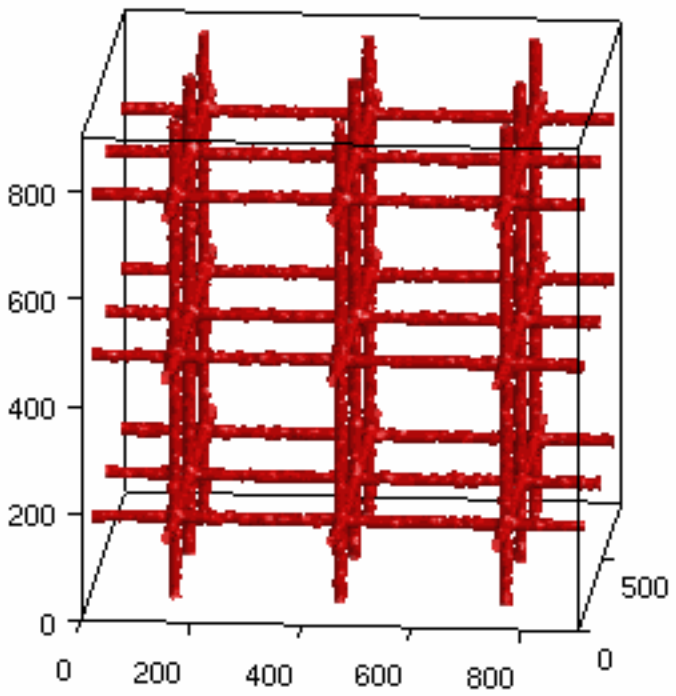
t = 38 hr t = 64 hr t = 88 hr

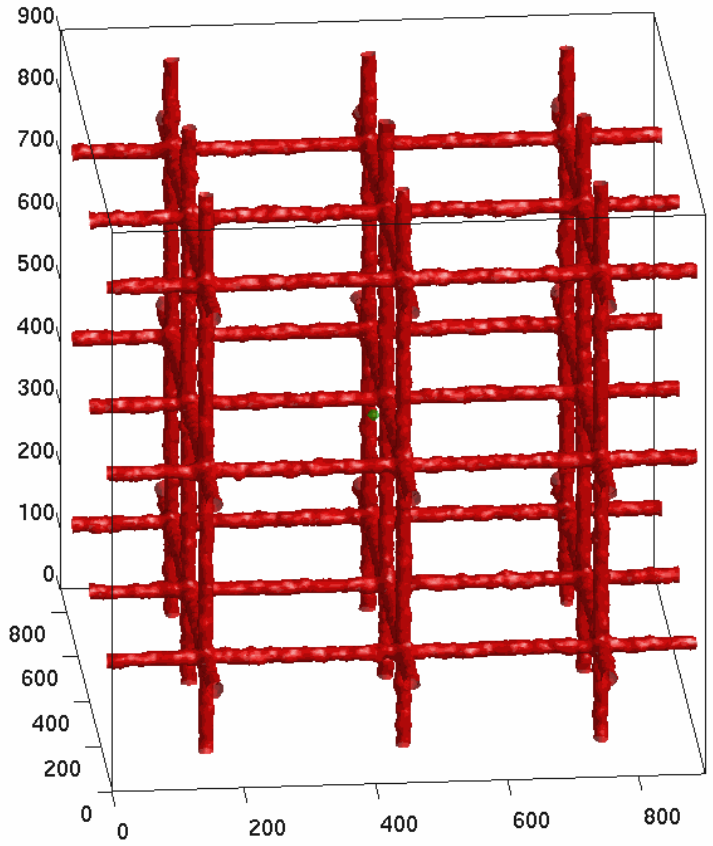
(Diameter of sorted aggregate is 260 μm.)

“Real” biology is more complex than cell sorting but…

- Starting with simple systems/models and gradually “dressing them up” seems natural
- Despite complexity of biomedical problems simulation tools and methods should be simple to use. Preferably building simulation should not me more difficult than describing time-lapse microscopy images.
- A natural building block of biological models of tissues, organs, organisms is cell. Try building models composed of many interacting cells

3D Vascular Tumor Growth





Simulation code can be found on PLoSOne website:

Abbas Shirinifard, J. Gens , Benjamin Zaitlen , Nikodem Poplawski , Maciej Swat , James Glazier, “3D Multi-Cell Simulation of Tumor Growth and Angiogenesis” PLoS ONE 4(10):e7190. doi:10.1371/journal.pone.0007190

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007190#s5

Case Study
Simulating Growth of Vascularized Tumor

Ingredients needed:

1. Cells
2. Cellular environment (ECM, diffusive fields, *etc*.)
3. Cell-Cell interactions
4. Cell growth and proliferation
5. Cell-environment interactions (secretion, chemotaxis, *etc*.)

All of the above depend in a complex way on molecular mechanisms inside each cell.

Why Use CompuCell3D? What Are the Alternatives?

1. CompuCell3D allows users to set up and run their simulations within minutes, maybe hours for complex models. A typical development of a specialized code takes orders of magnitudes longer time.
2. CC3D is parallelized (shared memory , multi-core) and we are constantly adding more performance enhancement features. It is also an Open-Source project.
3. CompuCell3D simulations DO NOT need to be recompiled. If you want to change parameters (in XML or Python scripts) or logic (in Python scripts) you just make the changes and re-run the simulation. Recompilation of every simulation is also error prone and often limits users to those who have significant programming background.
4. CompuCell3D is actively developed , maintained and supported. On www.compucell3d.org website users can download manuals, tutorials and developer documentation. CompuCell3D has approx. 4 releases each year – some of which are bug-fix releases and some are major
5. CompuCell3D has many users around the world. This makes it easier to collaborate or exchange modules and results saving time spent on developing new model.
6. The Biocomplexity Institute organizes training workshops and mentorship programs. Those are great opportunities to visit Bloomington and learn biological modeling using CompuCell3D. For more info see www.compucell3d.org

CompuCell3D Drawbacks

- Ad-hoc model description – terminology used in XML or Python API is often quite arbitrary and confusing for scientists
- Models are described in Python and/or XML – no standard model archiving standard. Single model may require multiple files in various formats
- Clunky simulation restart options
- Lack of model specification Graphical User interface
- No model annotation and ad-hoc formats for simulation result

Solution method:

While fixing CC3D drawbacks can be done immediately , establishing reasonable model description standards would greatly facilitate CC3D improvement, future-proof significant portion of source code and limit number of code alterations.