# Metabolic origins of spatial organization in the tumor microenvironment

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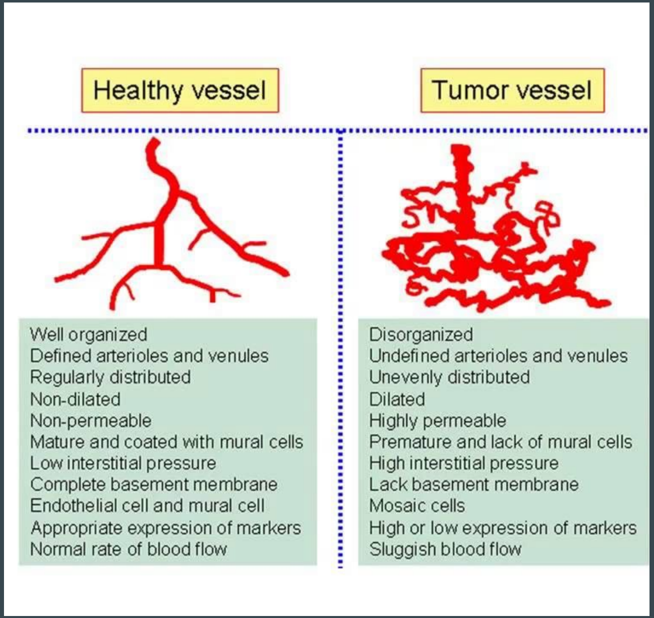
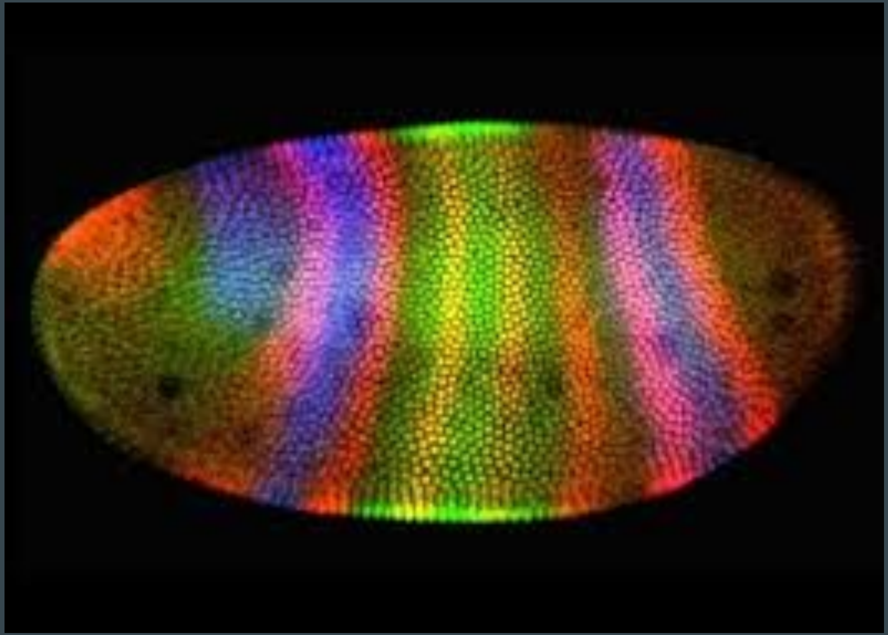
# Background & Motivation

Tumors are usually described as "disorganized", but the authors argue that metabolic processes lead to spatial structure, similar to the way that inter-cellular signalling leads to structure in embryonic development.

The authors suggest that this leads to higher efficiency.



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The rapid growth of tumors may result in some cells being too far from vessels to obtain resources or get rid of waste. This can trigger changes in gene expression.

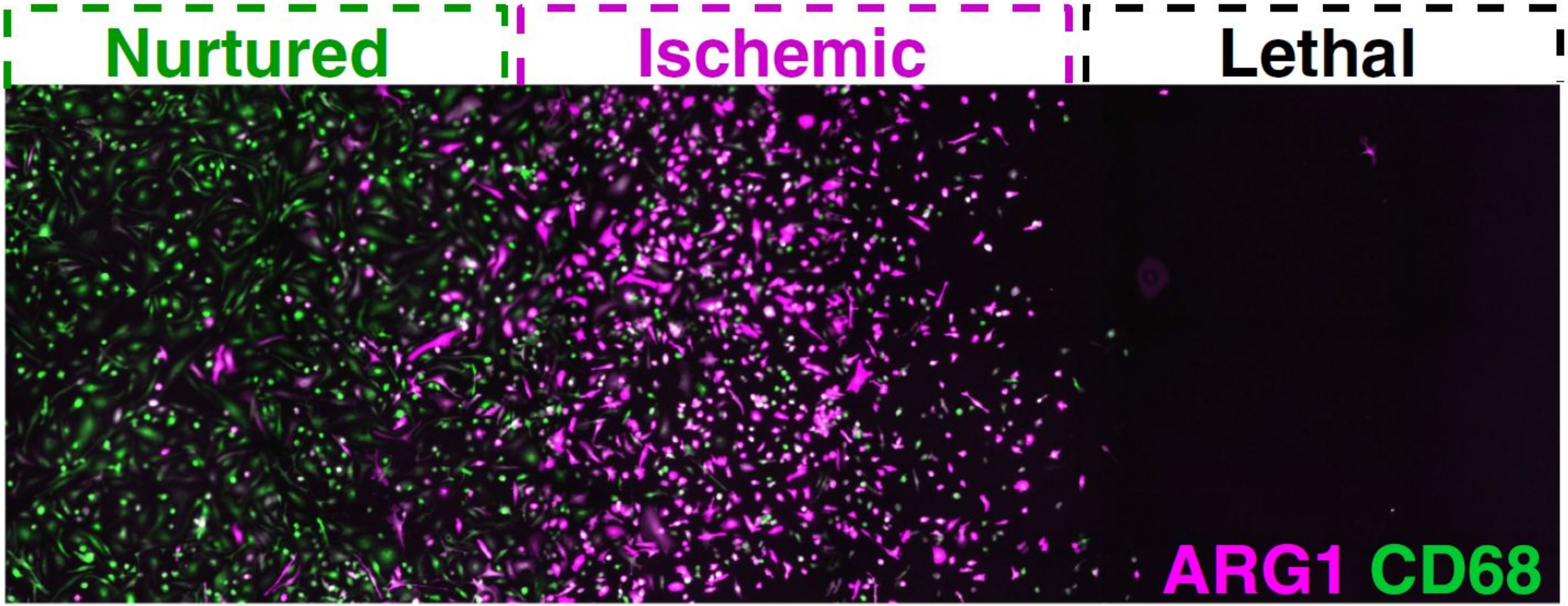
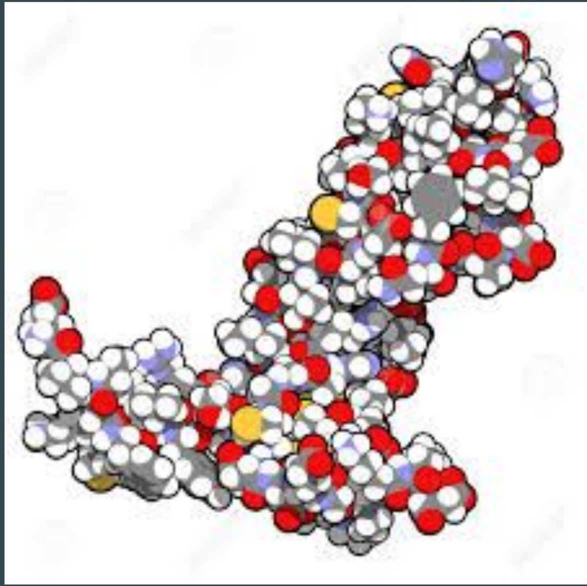


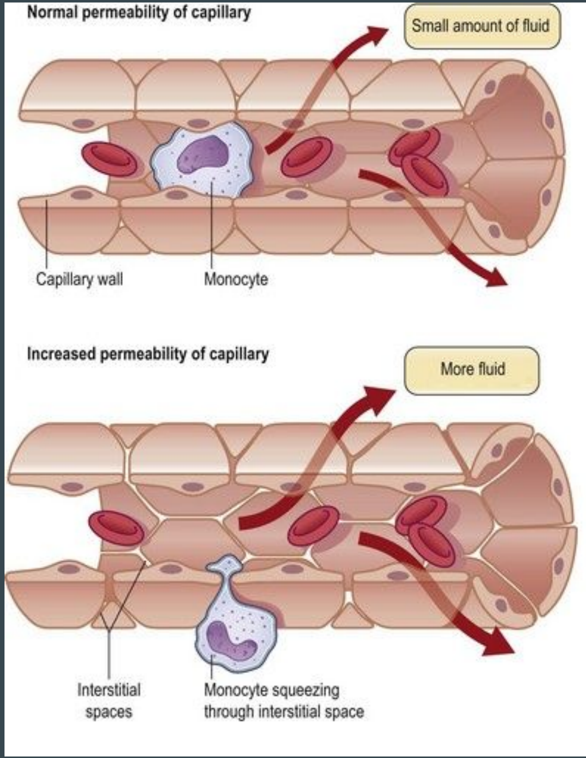

Image from: Carmona-Fontaine, C., Deforet, M., Akkari, L., Thompson, C. B., Joyce, J. A., and Xavier, J. B. "Metabolic Origins of Spatial Organization in the Tumor Microenvironment." Proceedings of the National Academy of Sciences of the United States of America 114, no. 11 (2017): 2934–2939.

The signalling molecule VEGF increases vessel permeability, causing vessels to deliver more resources to an area.

VEGF secretion is upregulated in many cancers, allowing them to sustain a high growth rate.

The authors argue that greater efficiency is achieved if VEGF secretion is spatially patterned rather than constitutive.



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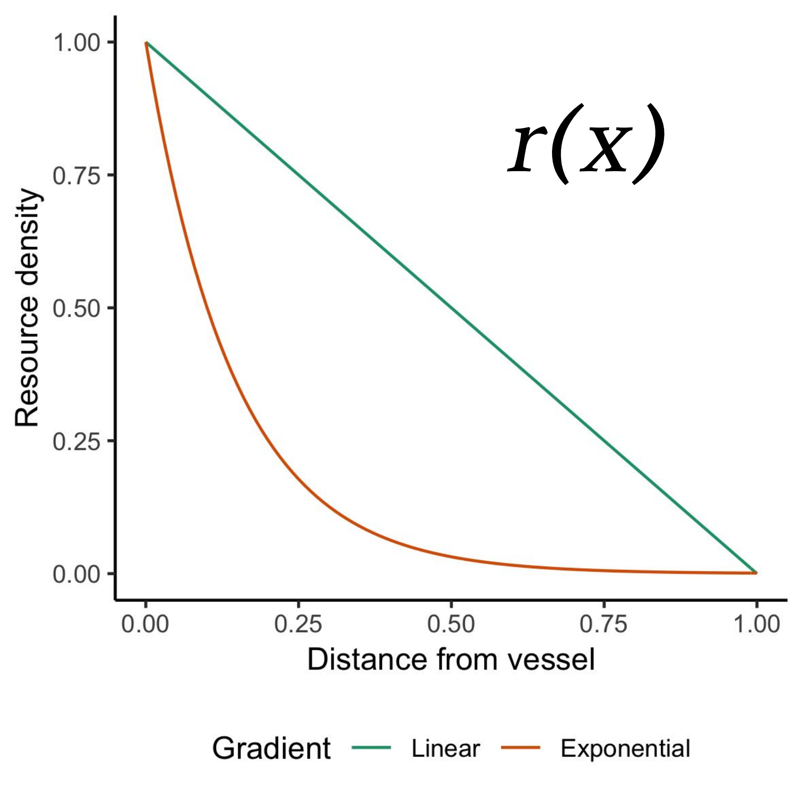
The authors used mathematical modelling and computer simulations in an attempt to show that the altered metabolism of cancer cells produces gradients of nutrients and metabolites. Their rationale was that this work would lead to a greater understanding of tumor heterogeneity and organization, and could be used to develop therapeutic targets.

We chose this paper because it offered multiple modalities that we could explore, and because of the potential therapeutic implications.

# Theoretical Model

# Theoretical model setup

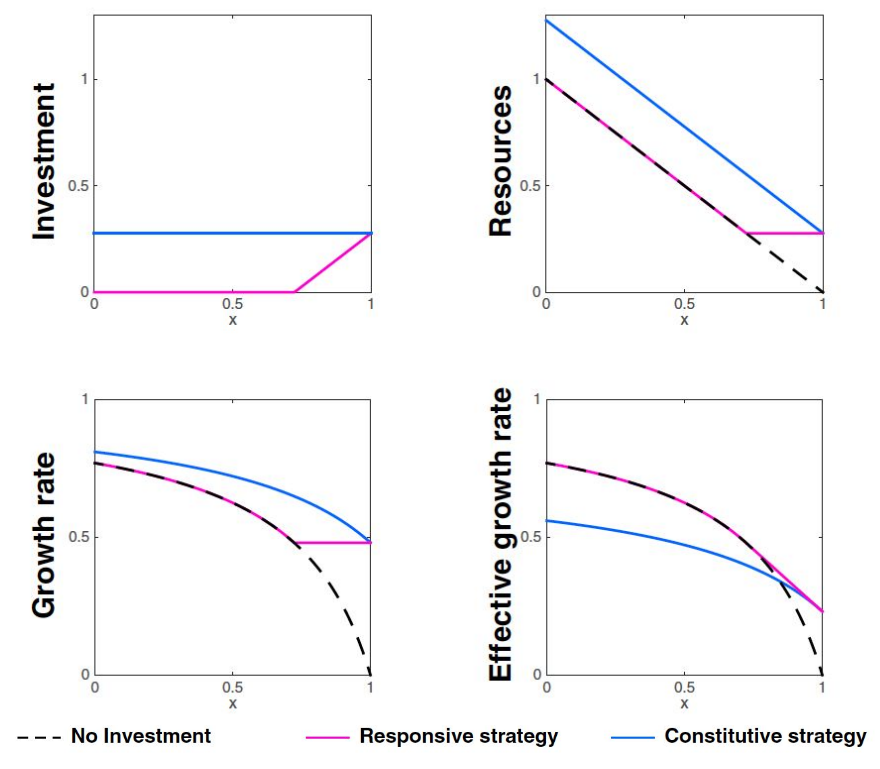



$$r^{opt} = r(x) + \Delta r^{opt}(x)$$

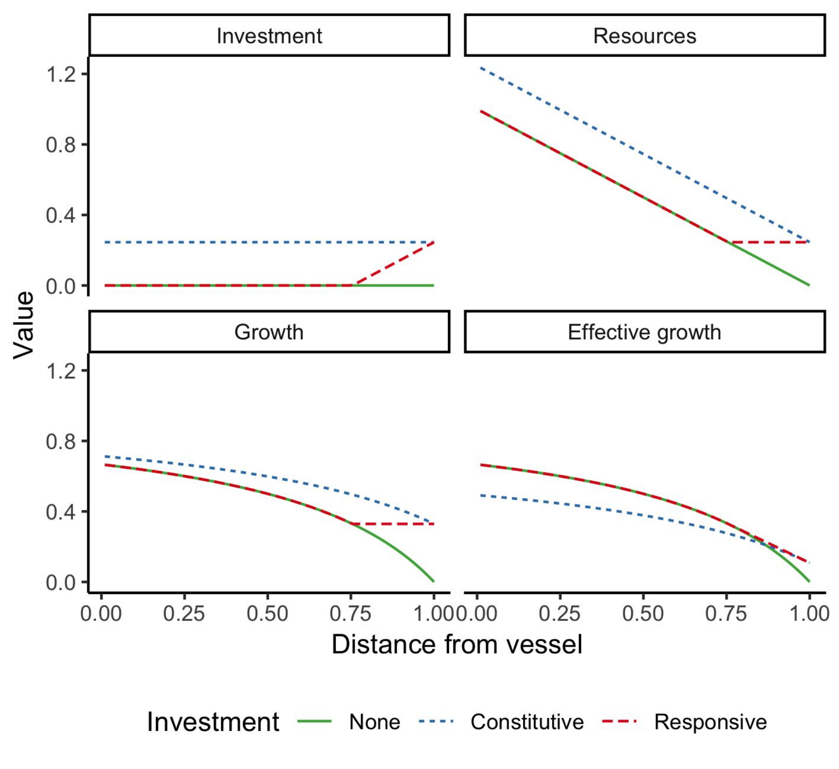
$$r^{opt} = \sqrt{\frac{\mu_{max} k}{c}} - k$$

$$\Delta r^{opt}(x) = \sqrt{\frac{\mu_{max} k}{c}} - k - r(x)$$

# Linear resource gradient

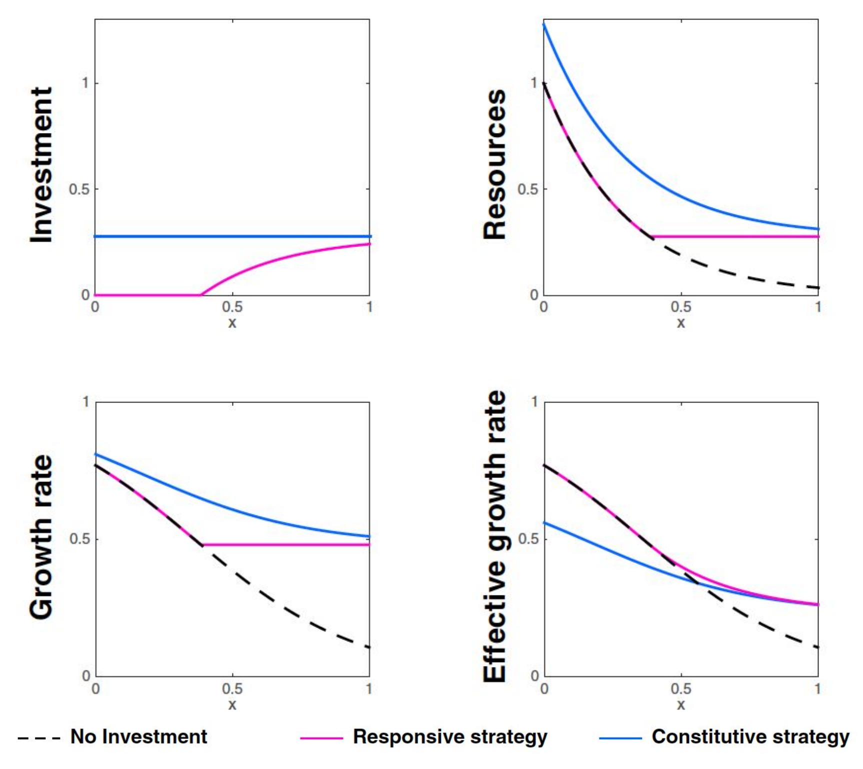



Carmona-Fontaine *et al.*, fig. S6 G

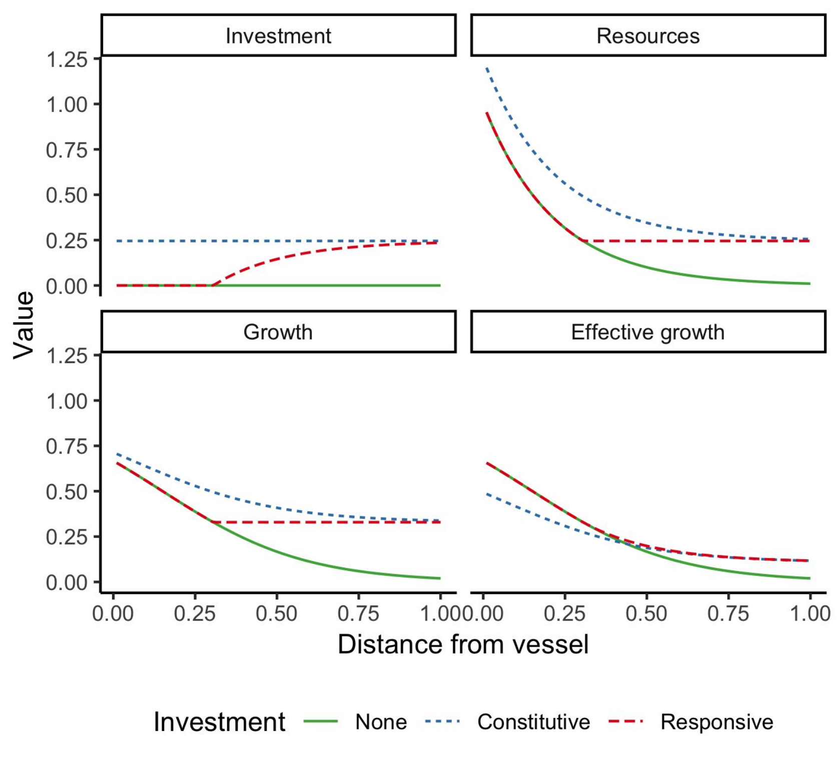



Reproduction

# Exponential resource gradient




Carmona-Fontaine *et al.*, fig. S6 G

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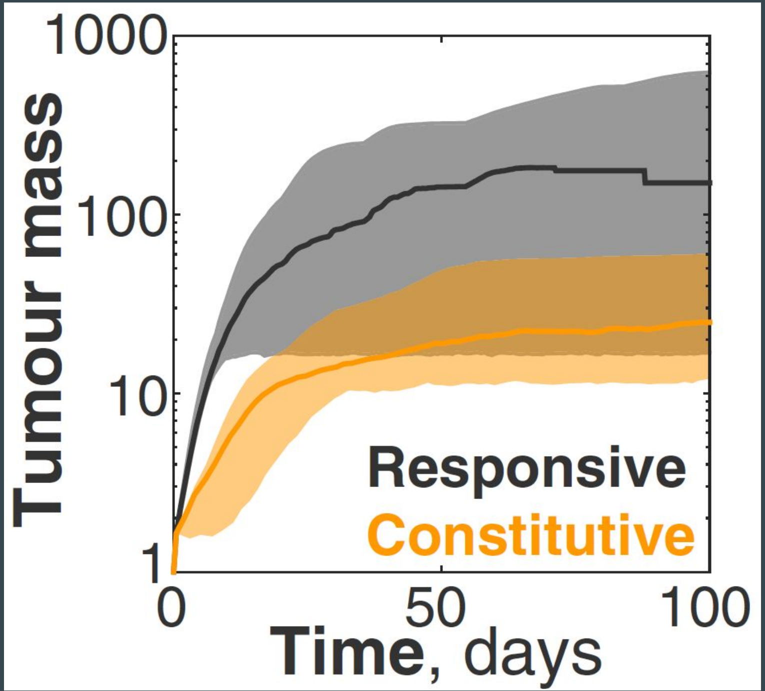
# Agent-Based Model

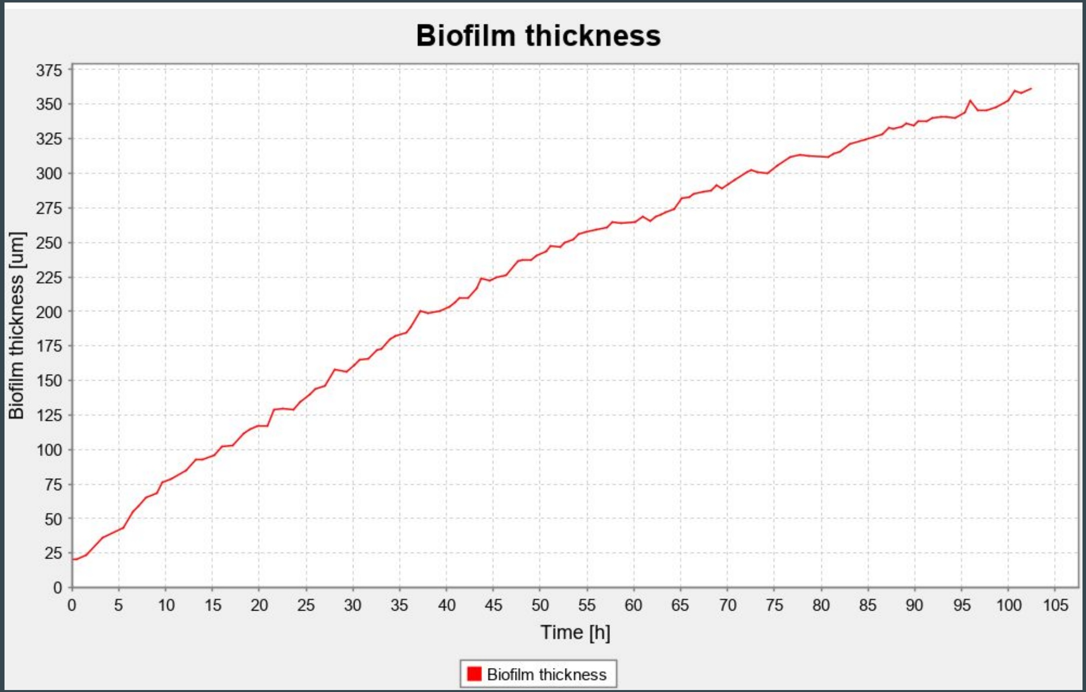
Xavier *et al*. 2005

Biofilm model

# Tumor growth curves

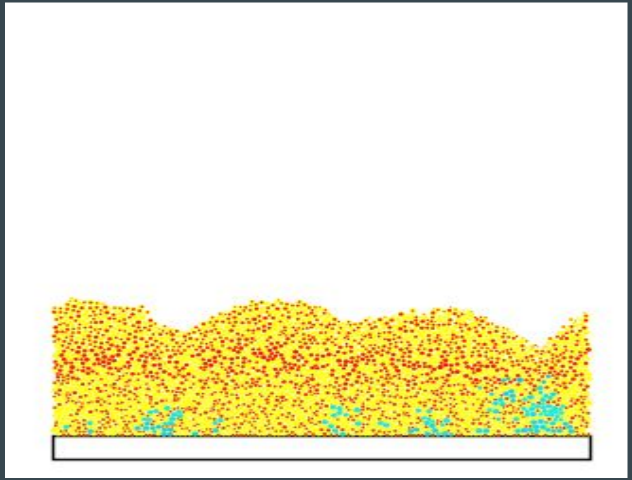


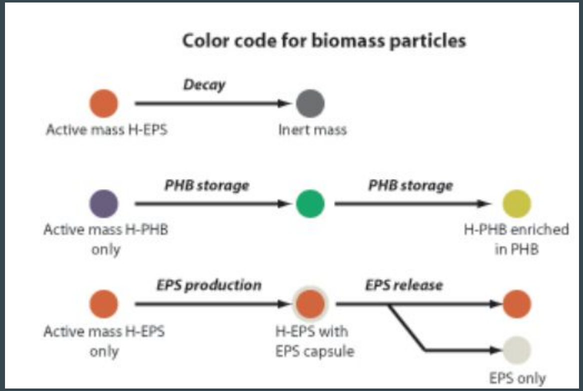

Carmona-Fontaine *et al.*, fig. 4 J




Reproduction (responsive growth only)

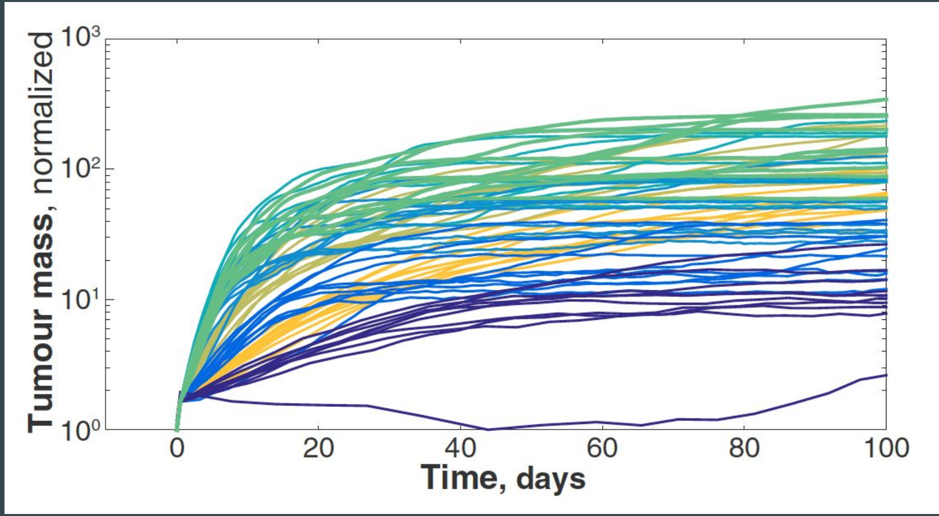
# Simulation: Hypoxia increases with distance from vasculature



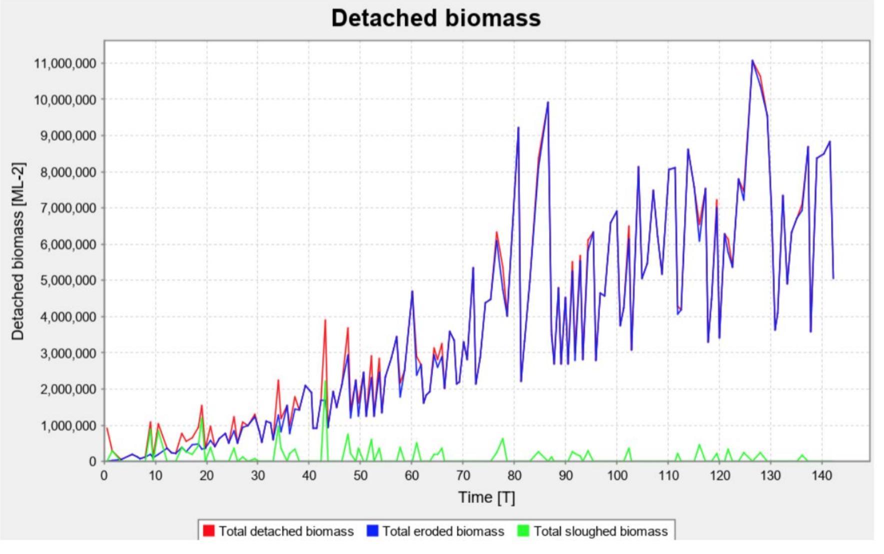



Carmona-Fontaine *et al.*, fig. 4 D

# Tumor mass simulations




Carmona-Fontaine *et al.*, fig. S6 D

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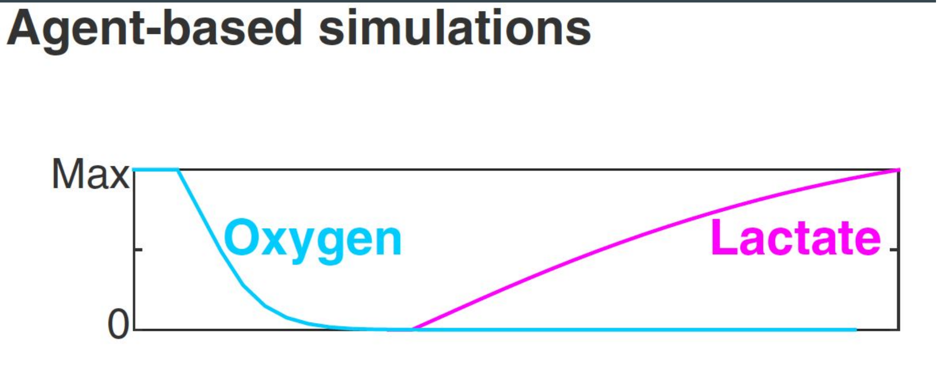
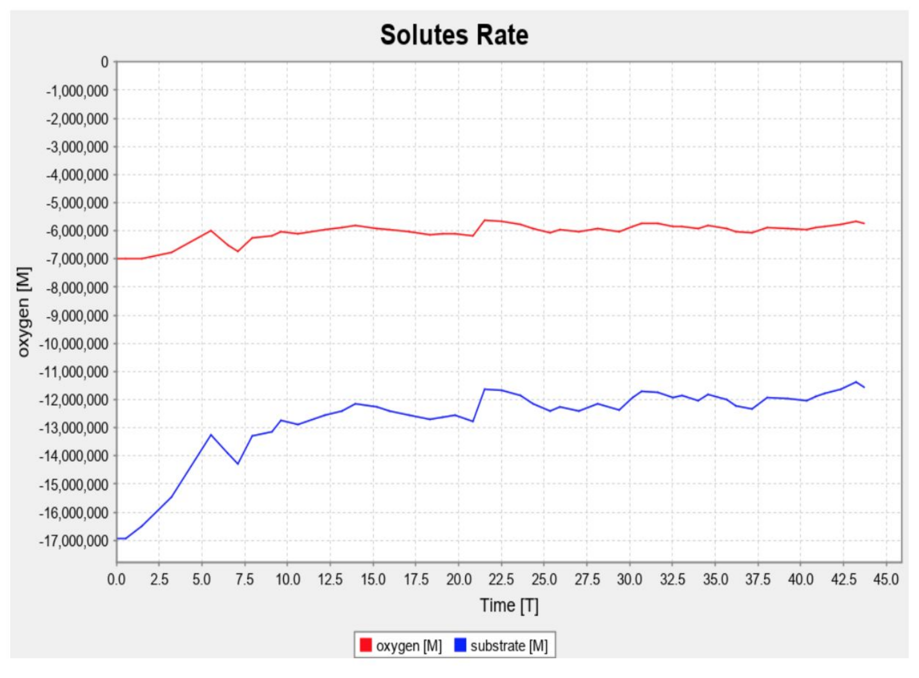
# Synergy between Oxygen and lactate(substrate) levels




Carmona-Fontaine *et al.*, fig. 4 D

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# Agent-Based Model

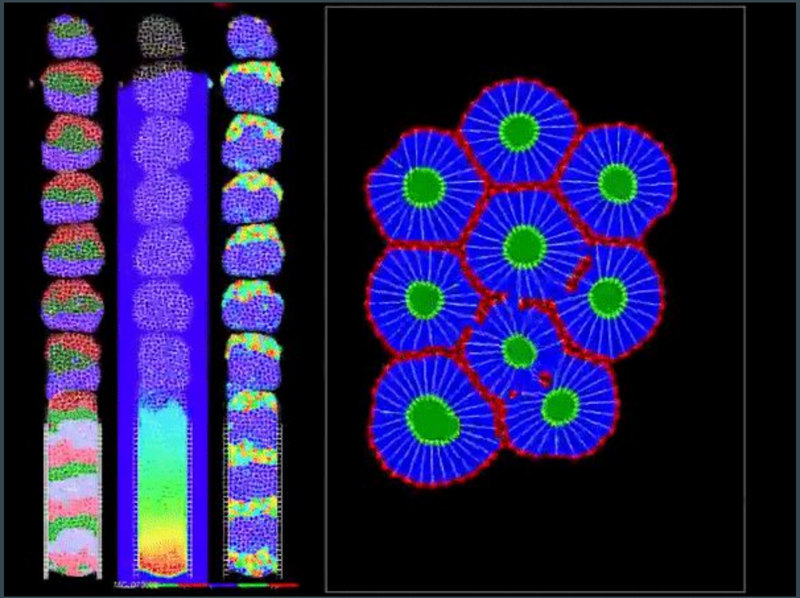
Swat *et al*. 2012

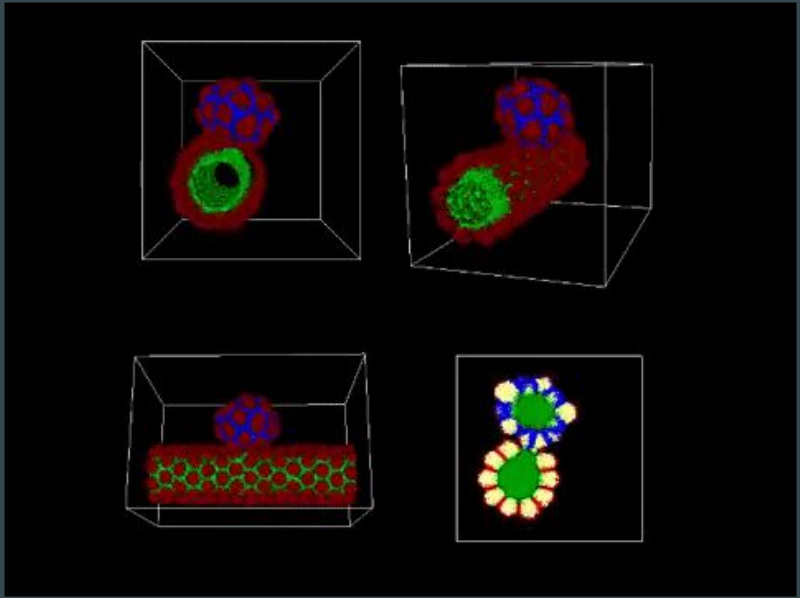
CompuCell3D

# CompuCell3D: multi-scale: intracellular and intercellular dynamics

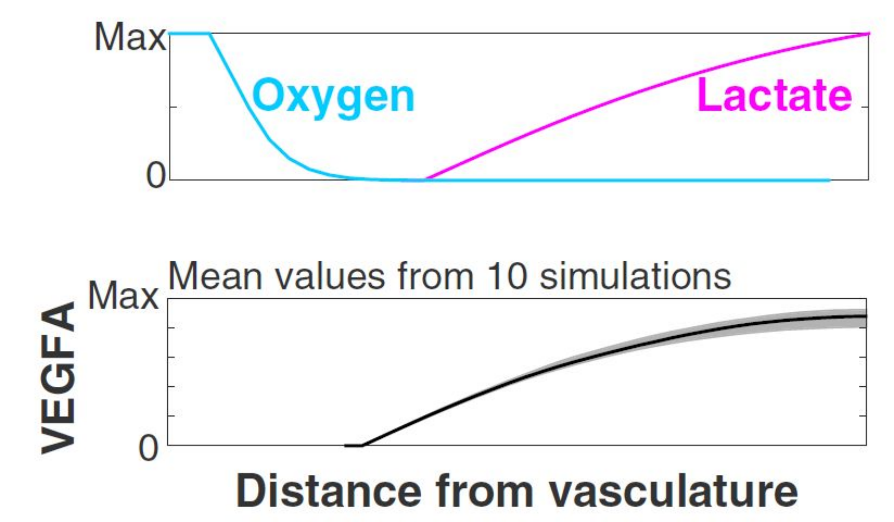
Advantages: scriptable; clear documentation and a number of examples exist

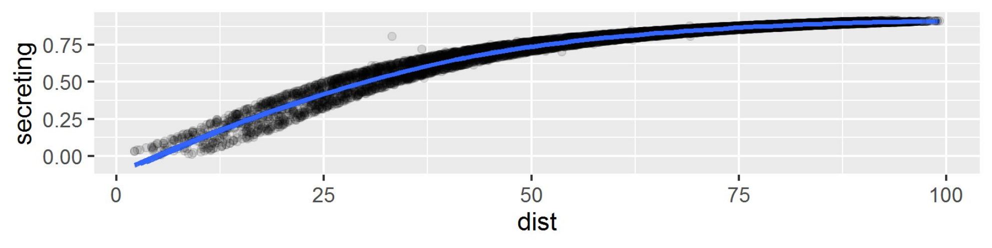
Disadvantages: lots of computation devoted to physical inter-cellular interactions. Simulations involving large numbers of cells can be computationally intensive and slow.





Images from: http://compucell3d.org/

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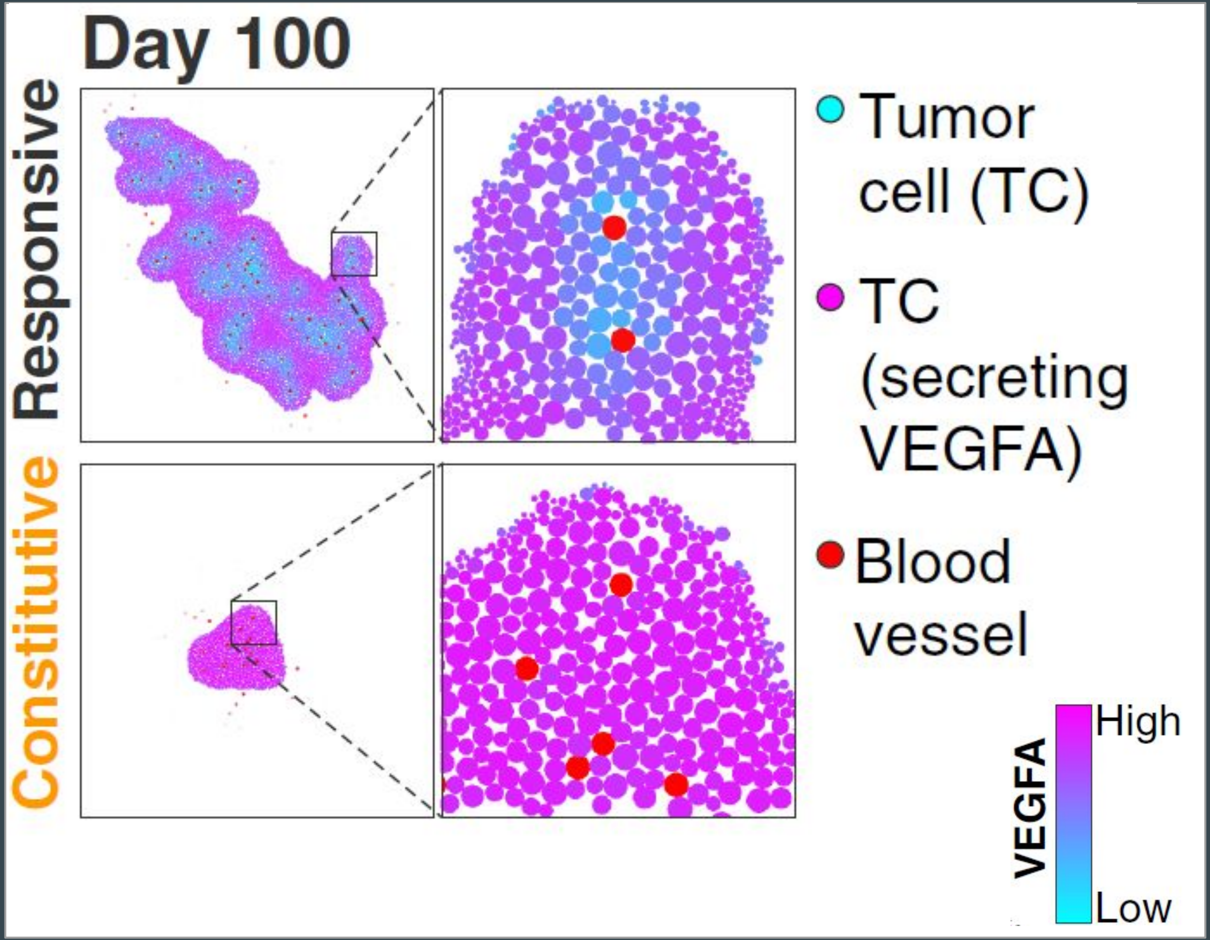
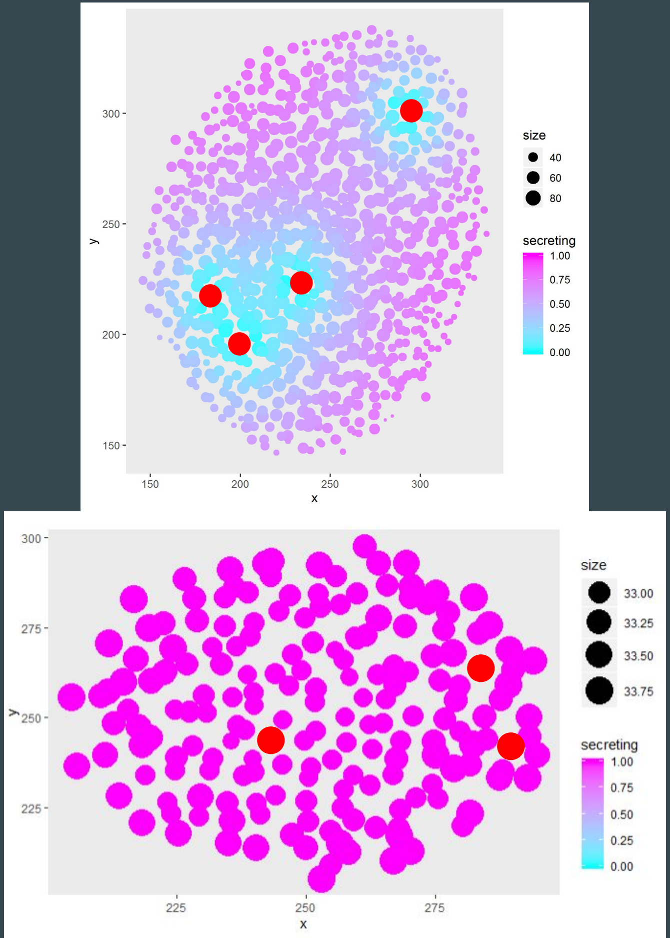
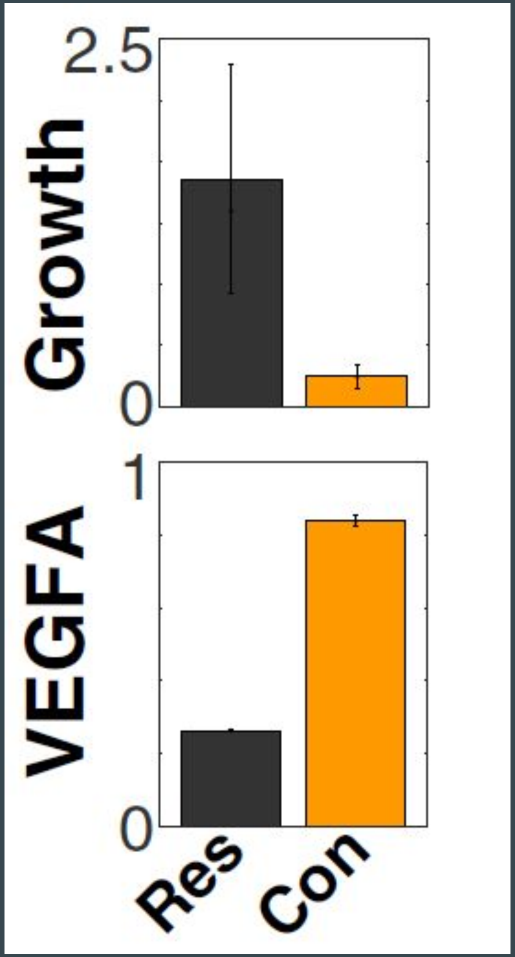


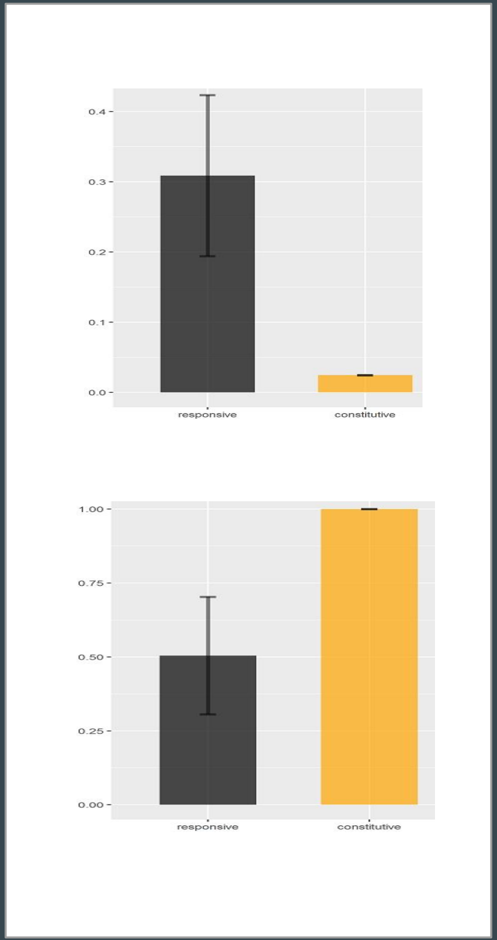

Carmona-Fontaine *et al.*, fig. 4 J




Reproduction (vessels drawn manually for clarity)




Carmona-Fontaine *et al.*, fig. 4 K

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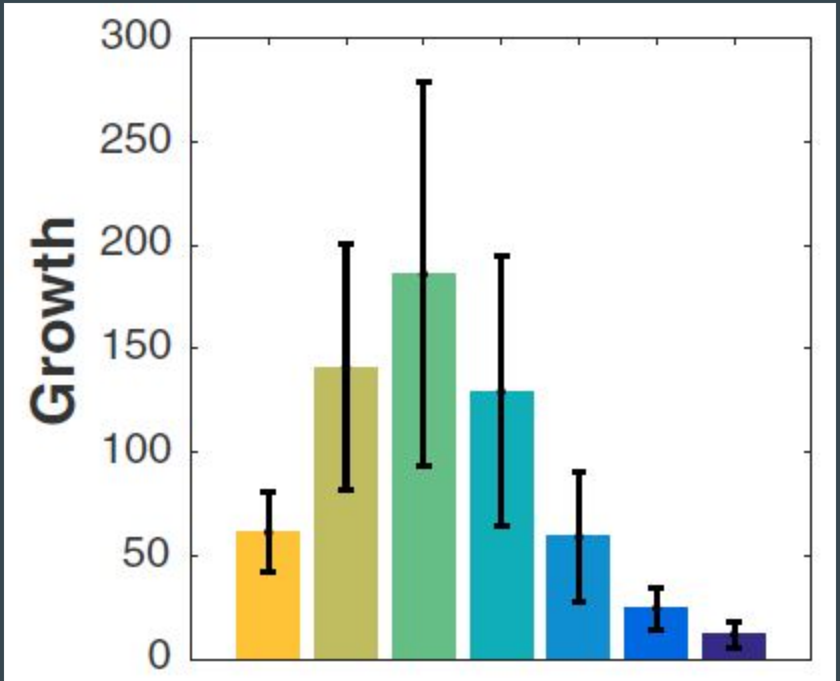
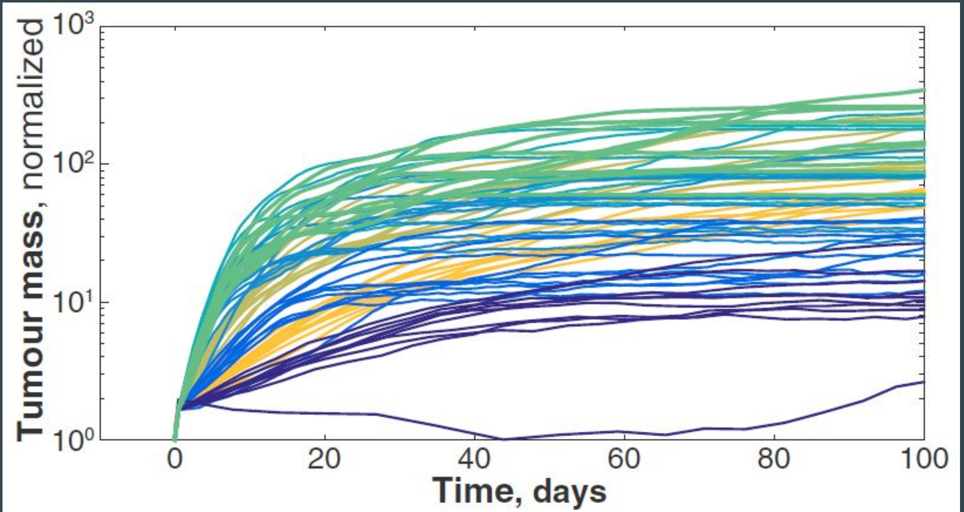



Carmona-Fontaine *et al.*, fig. S6 E




Carmona-Fontaine *et al.*, fig. S6 D

# Discussion & Future Prospects

# Were we able to replicate the authors' findings?

- Theoretical model
- Biomass
- VEGF secretion
- Growth strategies
- Growth speed
- VEGF Michaelis constant

# Do our findings call the authors' results into question?

Technical difficulties $\neq$ Contradictory results

(but they aren't replicable results either)

Are their parameters realistic?

We don't know.

# What can we conclude about reproducibility?

BLACK BOX + BLACK BOX = RESULTS

biofilm framework (~2015) | their modules

BLACK BOX + BLACK BOX = ?

biofilm framework (2018) | their modules

# References


- Carmona-Fontaine, C., Deforet, M., Akkari, L., Thompson, C. B., Joyce, J. A., and Xavier, J. B. "**Metabolic Origins of Spatial Organization in the Tumor Microenvironment**." *Proceedings of the National Academy of Sciences of the United States of America* 114 (2017): 2934–2939
- Swat, M. H., Thomas, G. L., Belmonte, J. M., Shirinifard, A., Hmeljak, D., and Glazier, J. A. "**Multi-scale modeling of tissues using CompuCell3D**." In *Methods in Cell Biology* 110 (2012): 325-366
- Xavier, J. B., Picioreanu, C., & Van Loosdrecht, M. C. "**A framework for multidimensional modelling of activity and structure of multispecies biofilms.**" *Environmental Microbiology* 7, no. 8 (2005): 1085-1103.

# Questions?