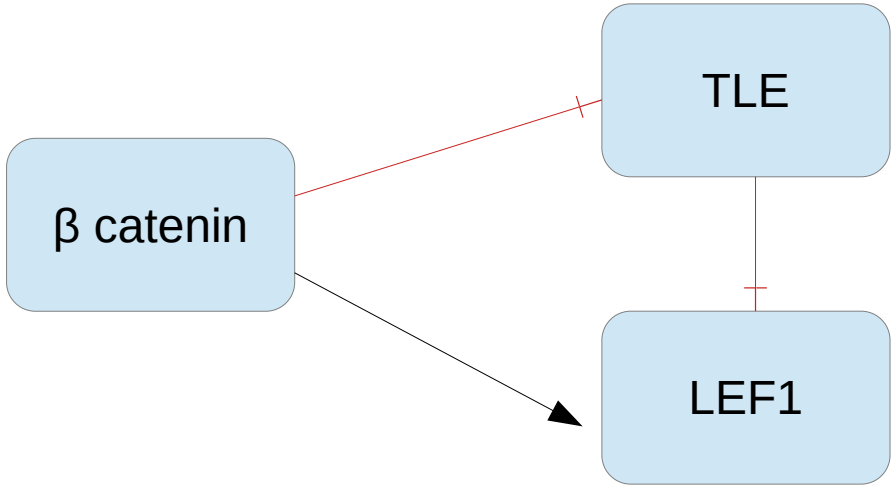
SHINE model dynamic behavior analysis

The present analysis is based on the attractors reached from 100,000 initial states (Out of the 2^{205} possible) using the version shine_1.bnet.txt which includes the changes suggested by our initial analysis. Which we interpreted as observable endothelial behaviors corresponding to quiescent or dysfunctional pulmonary microvascular endothelial cells (ECs). These atractors where also include an interpretation of glycocalyx damage and oxidative stress.

Nathan Weinstein 05/01/2025

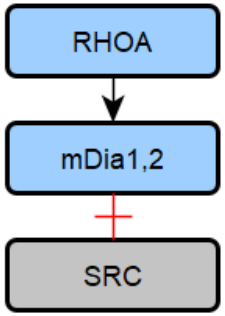
LEF1

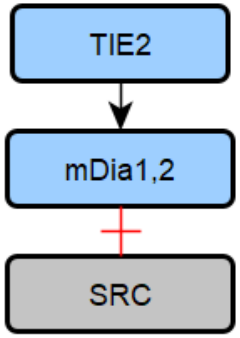


β catenin forms a complex with LEF1 to activate the transcription of WNT targets. TLE1 binds LEF1 preventing it from binding β catenin (https://www.cell.com/AJHG/fulltext/S0960-9822(06)02259-7, https://link.springer.com/article/10.1186/1471-2407-9-159)

Old: TLE1, Bcatenin
New: TLE1, !Bcatenin

Pathways that need some thought





Ang1 promotes the activation of mDia through RhoA, inhibiting SRC-mediated VE-cadherin phospphorylation. In our model RHOA activity is associated with incrreassed permeability, perhaps a diirect interaction from TIE2 to mDia skiping RhoA would be less problematic here.

https://doi.org/10.1016/j.devcel.2007.10.019

Old:
mDia, RHOA
RHOA, !PKGIB & !CDC42 & !ArhGAP29 & !RhoGDIa & (GEFH1 | TIE2 | SRC | G12)
New:
mDia, TIE2
RHOA, !PKGIB & !CDC42 & !ArhGAP29 & !RhoGDIa & (GEFH1 | SRC | G12)

Another option would be:
TIE2 --| RHOA --| mDia
However, see:

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0023448

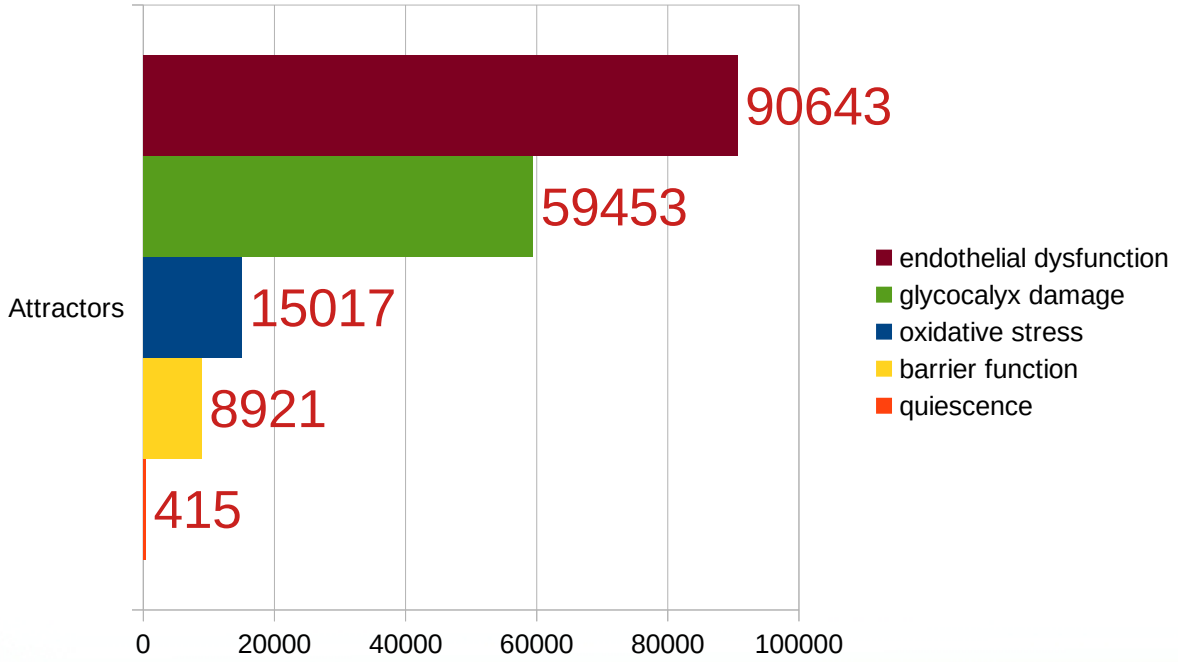
Hypoxia causes oxidative stress

- Suggesed new update rules where even under very hypoxic conditions, the basal concentration of oxygen is sufficient to activate the NOX enzymes:
- NOX2, (p47phox | PKC) & (!NRF2 | !propionylLcarnitine)
- NOX4, HIF1
- NOX5, Ca2 & PIP2
- O2 represents normoxia in our model. Hypoxia actually causes oxidative stress(https://ri.conicet.gov.ar/bitstream/handle/11336/40230/CONICET_Digital_Nro.41f41e84-3f10-4ca8-b942-c13b0338f4f3_A.pdf?sequence=2
  see page 19 “under hypoxia, the mitochondrial complex III suffers a conformational change that would facilitate the interaction between O2 and ubisemiquinone, resulting in an increase of O2•− formation (Guzy et al., 2005). Others also consider complex II as relevant for ROS formation during hypoxia exposure (Paddenberg et al., 2003). It was proposed that this complex switches its catalytic activity from succinate dehydrogenase to fumarate reductase at diminished oxygen levels. This would not only cause succinate to accumulate but additionally will cause ROS generation because fumarate reductase has been demonstrated to be a powerful O2•− generator”)
- Also, HIF1 directly activates NOX4 (https://www.molbiolcell.org/doi/10.1091/mbc.e09-12-1003)

Changes to explore PGI2 synthesis

- **Old: a_ketoglutarate, 1**
- **New: a_ketoglutarate, a_ketoglutarate**

99192 Attractors, almost 1 for each initial state



Conclusions

- **Oxidative stress is now possible**
- **In quiescence, adrenergic receptor signaling is still active in some but not all attractors.**
- **In quiescence, LEF1 is active.**
- **In quiescence, RHOA is inactive. However now ANG1 can inhibit SRC through mDia in some of the attractors.**
- **Now in some of the endothelial dysfunction attractors PGI2 is absent.**

Next steps

- Now that we have quiescence, barrier function, oxidative stress, glycocalyx damage, and endothelial dysfunction trap spaces we need to analyze the summary of their characteristics.
- Next, we need to find the perturbations that cause transitions from each behavior to the others.
- Then, we need to analyze each possible gain and loss of function mutations, agonists, and inhibitors to compare the simulated effect with the effect reported in the literature (most are available).