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Towards the combination of computational modeling and imaging-based machine learning models for female-specific long-term blood pressure regulation

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Context & Aims

- **Hypertension is a major global health issue**, affecting over one billion individuals worldwide and contributing to a significant burden of cardiovascular diseases. Even though **blood pressure differences exist between sexes**, antihypertensive treatment strategies remain largely uniform across sexes, despite evidence that women respond differently to such therapies [**2**].
- Recent research has identified **hormonal influences as key contributors to sex differences in blood pressure regulation**. The model by [**5**] has incorporated sex-specific parameters; however, it does currently not account for dynamic hormonal variations and endothelial contributions.
- Given the **pivotal role of nitric oxide (NO) in vascular function and its regulation by estradiol (E2) and progesterone (P4)**, integrating these elements into computational models is crucial for advancing sex-specific hypertension management strategies. The cellular mechanisms of actions and pathways of E2 and P4 have been characterized (Figure 2).
- We aim to study the effect of healthy menstrual cycles and post-menopausal hormone levels on blood pressure regulation by **relating the sex-specific parameters to dynamic changes in E2 and P4 hormone levels** and
- To include the vasodilatory effect of NO into the model proposed by [**5**] by extending it with a **sub-model for endothelial function depending on E2 and P4**.

Material & Methods

- We **verified** a submodel of the NO signaling model developed by [**1**] 'Shear stress induced **calcium influx and eNOS activation** - Model 1' (Figure 3A) using COPASI.
- The model was then implemented in Python following the same kinetic equations but structured for **numerical simulation using an ODE solver** (scipy.integrate's solve_ivp function with the ODE solver 'LSODA').
- We **tested the accuracy** of the Python implementation by validating it against the original COPASI simulations under identical conditions through the **average squared difference** between the two resulting datasets, allowing us to assess overall deviation. Additionally, we measure the **percentage difference** between corresponding values from the two models **over time** (Table 1).
- To explore existing research on machine learning models in vascular imaging and the influence of female-specific sex hormones, we conducted a short, **targeted literature review** with the goal to identify studies that integrate **AI-driven vascular imaging analysis with hormonal regulation** of endothelial function, particularly focusing on E2 and P4.

Results

- The Python **implementation accurately replicates the NO production dynamics** described by [**1**], making it a reliable foundation for further analysis and extensions.
- Our analysis identified a **gap in current research** regarding the use of machine learning, specifically including the usage of **imaging data**, to model the **female-specific hormonal regulation of vascular function**. We found one paper that focuses on using machine learning to analyze high-content imaging data from 3D MCF7 microtissues to predict estrogenic effects [**4**].

Discussion

- **Machine learning** can identify complex patterns in imaging data, but it often requires large, **high-quality datasets** and **often lacks interpretability** [**6**]. While **computational biochemical models** can be leveraged to **explain molecular mechanisms**, they do **not account for biological inter-patient variability** seen in vascular imaging.
- A **hybrid approach**, where computational models inform machine learning models and vice versa, could enhance female-specific cardiovascular research by incorporating hormonal effects on endothelial function and integrating computational models with imaging biomarkers could additionally enhance patient-specific vascular assessments.
- One possible reason for the scarcity of literature is the **challenge of obtaining high-quality imaging data of vascular tissue** while simultaneously measuring hormone levels. Hormonal fluctuations occur over varying timescales, and capturing their direct effects on vascular function requires carefully controlled studies with **synchronized imaging and biochemical data collection**. The complexity of such studies, along with ethical and logistical constraints, may explain the limited availability of relevant datasets in this field. **Challenges remain in data availability, model interpretability, and clinical applicability**.
- A major challenge in hypertension research is the lack of models that dynamically incorporate hormonal variations and their downstream effects on endothelial function. The envisioned thesis project aims to bridge this gap by constructing a model that includes E2- and P4-dependent NO production and its impact on arterial resistance.
- **Future studies** could include e.g. **training machine learning algorithms** on vascular imaging datasets to enhance endothelial function assessment and **validate them using computational predictions** or developing machine learning-driven predictive tools for personalized therapy based on computational model outputs and patient-specific imaging data.

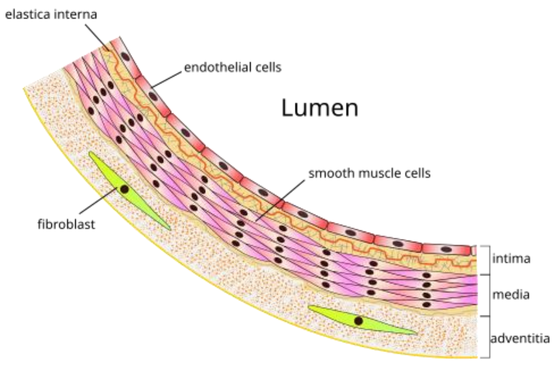
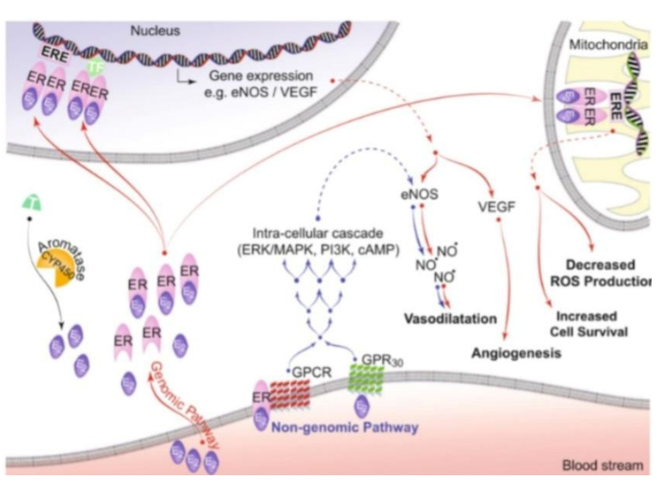
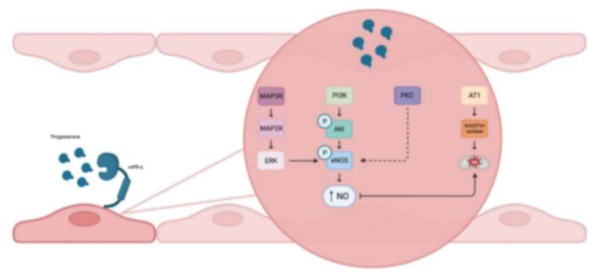


Figure 1. Vessel walls, Figure taken from [**7**]. The endothelium is a thin layer of single flat (squamous) cells that line the interior surface of blood vessels (and lymphatic vessels). Endothelial cells are involved in many aspects of vessel function, including blood clotting, inflammation, angiogenesis (i.e. formation of new blood vessels), and blood pressure control through vasoconstriction and vasodilation [**3**]. The endothelium uses nitric oxide (NO) to signal the surrounding smooth muscle to relax, resulting in vasodilation and increasing blood flow.



(**a**) E2 pathway.



(**b**) P4 pathway.

Figure 2. Schematic diagrams of pathways for E2 (left, from [**8**]) and P4 (right, from [**9**]). E2 and P4 have been linked to the bio-availability of NO; their cellular mechanisms of actions and pathways have been characterized in (**a**) and (**b**). However, there are contradictory results on their interactions with NO due to the nature of the experiments. Many experiments that discuss the cardio-protective role of E2 and P4 are performed in postmenopausal women during Hormonal Replacement Therapy (HRT), which differs from the actions from endogenous produced hormones [**8, 9**]. Such experiments lead to contradictory conclusions regarding premenopausal women. The extrapolation from one group to the other does not hold, since the body undergoes systemic changes during peri-menopause, including loss of sex hormone receptors.

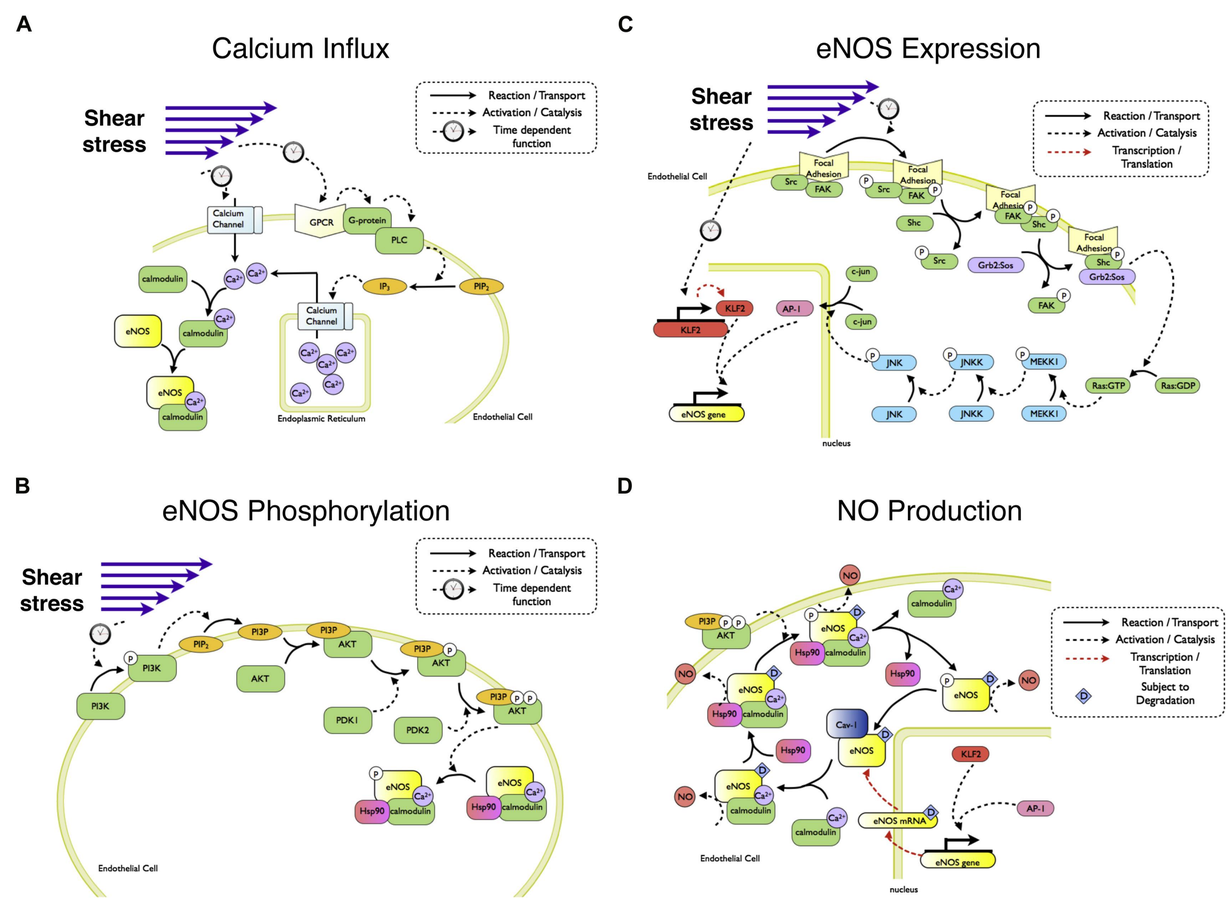


Figure 3. The four models of the shear-stress-induced NO production system (from [**1**]). (***A***) The calcium influx model. This submodel describes how endothelial nitric oxide synthase (eNOS) activation leads to NO production and how factors like substrate availability and oxidative stress influence NO bioavailability. (***B***) The eNOS phosphorylation model. (***C***) The eNOS expression model. (***D***) The NO production model.

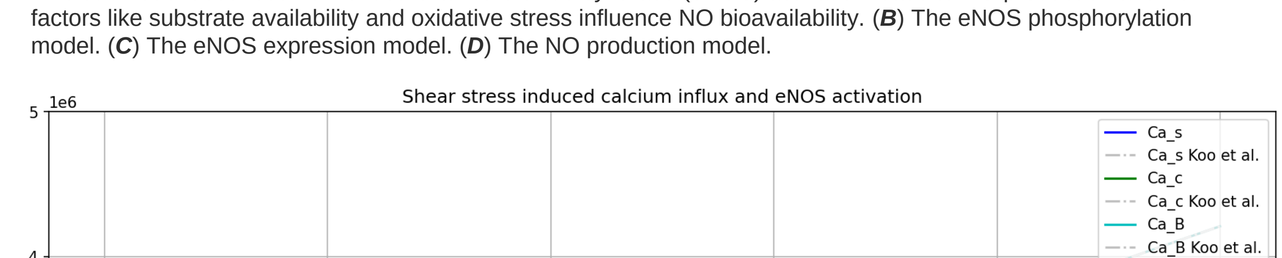


Figure 4. The simulated shear stress-induced calcium influx and eNOS activation over a simulation period of 1000 seconds. The plotted species include calcium concentrations in different cellular compartments (Ca_s, Ca_c, Ca_B), inositol trisphosphate (IP3), and downstream signaling molecules (s8, s9, s10). The lines represent simulation results from the Python implementation, while the dashed lines (grey) indicate reference data from the model by [**1**] simulated in COPASI. The close overlap between the two sets of curves demonstrates the accuracy of our model in reproducing the expected biochemical dynamics. The implementation is available on GitHub: https://github.com/ElenaHeinze/Female-specific-long-term-blood-pressure-regulation.

Species	MSE (nmol/L)	Mean relative error
Ca_c	1.315e-6	1.951e-06
Ca_B	0.0009309435	1.189e-06
IP3	5.457e-10	1.725e-06
s8	0.0001180843	2.359e-06
S9	1.1642422124	1.537e-06
s10	3.7613719039	1.590e-06

Table 1. Results of a quantitative validation of the Python implementation by comparing the simulated species concentrations with reference values from the model by [**1**] simulated in COPASI. The mean squared error (MSE) and mean relative error for each species are reported.

References

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