School of Biological Sciences

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Towards a whole-cell model of the human platelet

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Why model a platelet?

Whole-cell models account for every molecule in a cell mechanistically, and they exist for bacteria but not for any human cell. The platelet is the most tractable human candidate: anucleate, as there is no transcription or replication to model; clinically central to thrombosis; and backed by excellent proteomic data (Burkhart 2012).

A model could allow us to run *in-silico* experiments, and the act of building a model verifies understanding of the biology.

What we built

We took the wcEcoli model from Macklin (2020), the Covert lab's published bacterial whole-cell framework, stripped out the *E. coli* biology, and rebuilt the platelet calcium-release pathway in its place: agonist to Gq to PLC-beta to IP3 to IP3-receptor store release, with SERCA re-uptake, PMCA extrusion, store-operated entry, and mitochondrial buffer. Fig. 1 shows a schematic of the systems covered. Every protein is counted from platelet proteomics, and every rate constant carries a primary-source citation in the code.

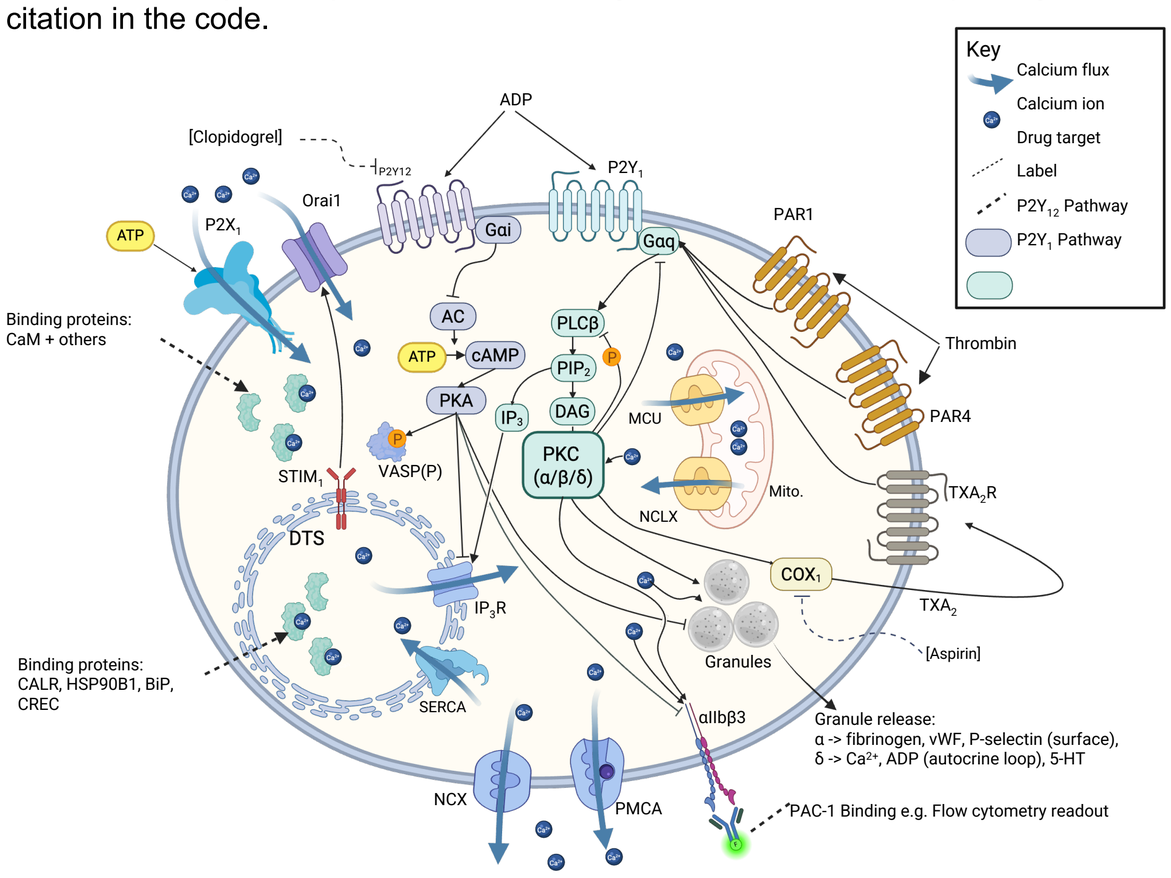

Figure 1. Schematic representation of the platelet systems modelled.

The model reproduces the calcium transient

The model holds a stable resting state and reproduces the agonist-evoked cytosolic Ca^{2+} levels against Dolan & Diamond (2014). Removing extracellular Ca^{2+} (the EDTA condition) disables store-operated entry, so the paired results show its contribution. Under EDTA the transient level self-limits at 276 nM, inside Dolan's band; with calcium present, entry sustains a 521 nM plateau. In this model the dense tubular store (DTS) depletes almost entirely on activation. See Fig. 2.

We also varied both agonist levels and determined that the Ca^{2+} level rapidly saturates in the presence of either agonist, see Fig. 3.

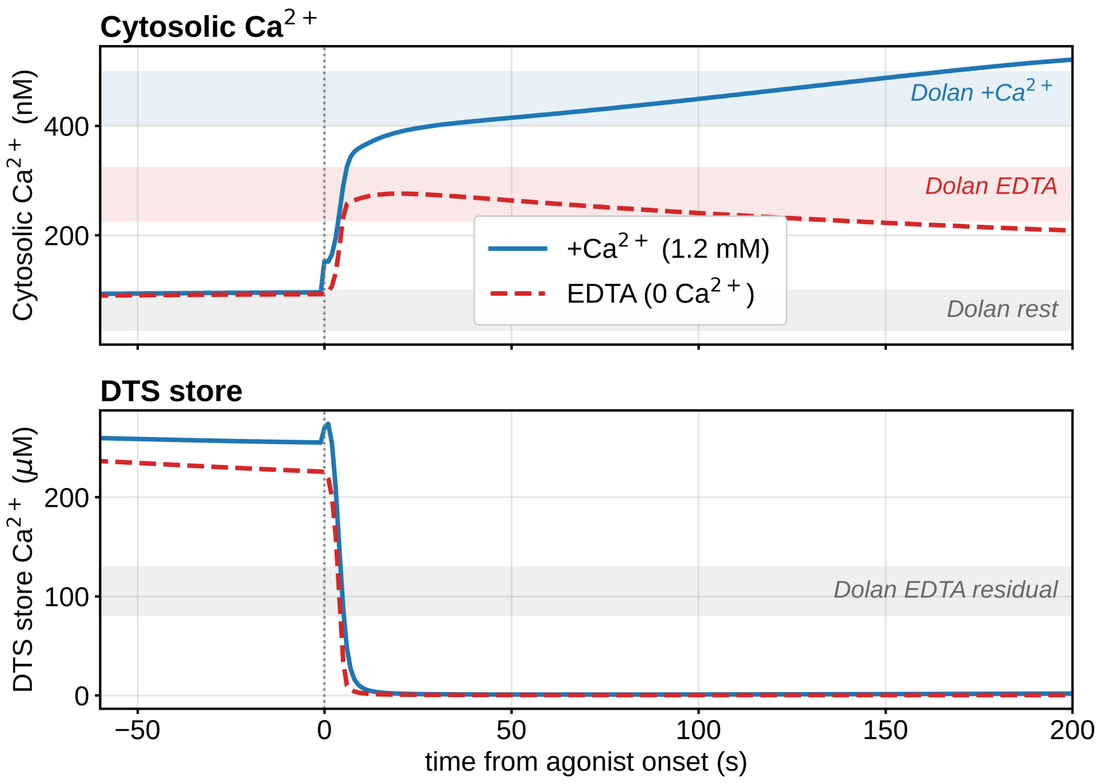

Figure 2. Cytosolic and DTS Ca^{2+} levels after agonist treatment at t=0. Cytosolic levels increase, DTS depletes to almost zero.

Dose response

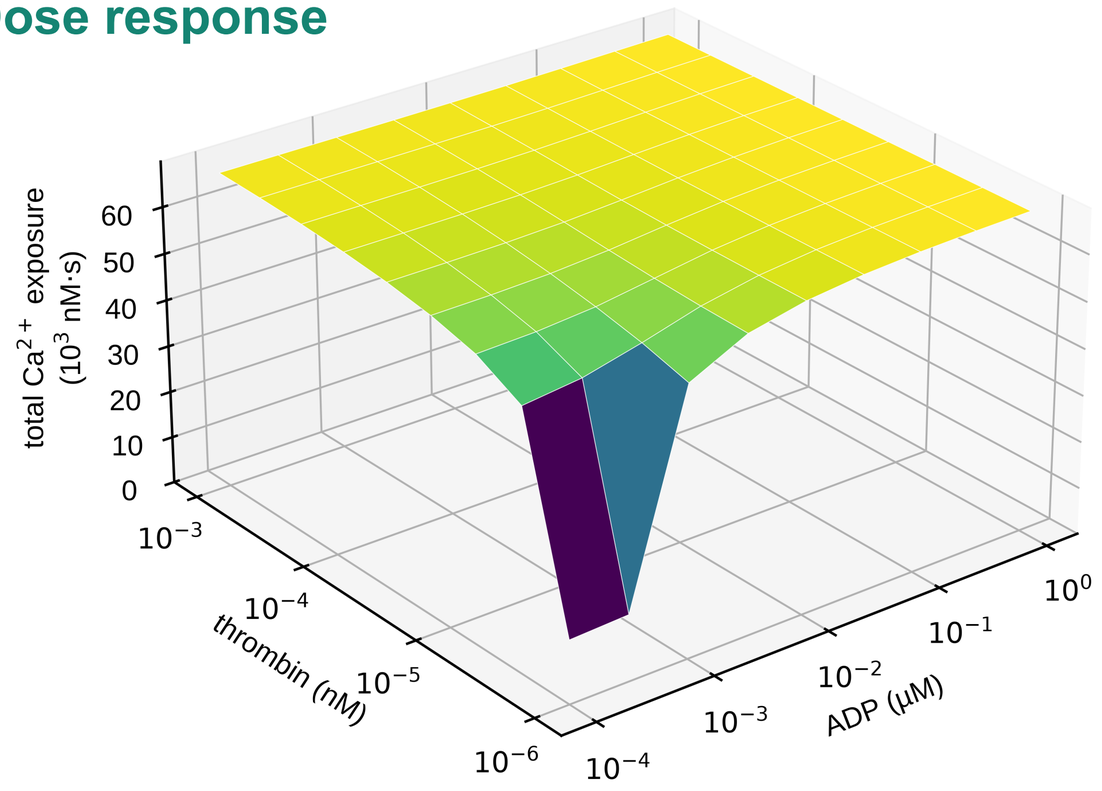

Figure 3. Cytosolic Ca^{2+} levels by varying agonist (thrombin, ADP) concentrations. Either agonist is alone is sufficient in this model and level saturates as the DTS depletes.

Drug simulations

Three drug simulations were added to the calibrated core model and reproduce expected antiplatelet responses. Fig 4 plots the first 2 of these.

- prostacyclin - reduces Ca^{2+} release from DTS, so Ca^{2+} rises to 0.90 then relaxes to 0.66, i.e. drug halves the peak (Hollopeter 2001).
- Clopidogrel blocks $P2Y_{12}$ and lowers the peak to 0.76, also delays it from 124 s to 201 s

We also ran other experiments, e.g. treating with Aspirin, modelled as COX-1 knockout, abolishes thromboxane, and anMCU (mitochondrial calcium uniporter) knockout experiment which reproduced the literature (Chatge 2026). Further details available.

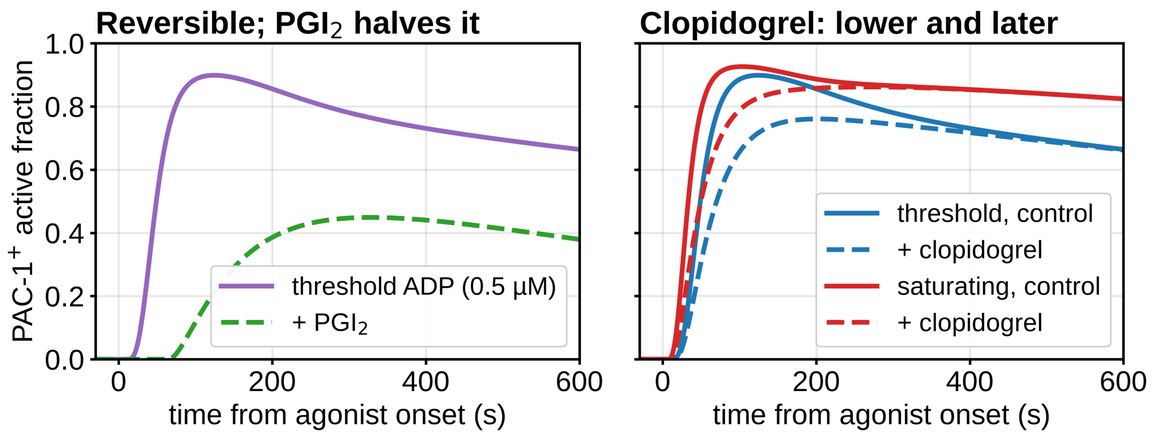

Figure 4. Simulations of prostacyclin and clopidogrel treatments.

Conclusions

A mass-balanced, mechanistic model of a human cell can be built and then extended without breaking. The calcium core is store-limited, giving an all-or-none type response to agonists. The obstacle to a more complete model is the availability and consistency of quantitative data, not computation.

References

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AI statement: I acknowledge the use of Claude (Anthropic) to re-render figures from my own analysis code and to check grammar and spelling. The text is my own. I confirm that no output generated by GenAI has been presented as my own work.