A mathematical and computational model of the calcium dynamics in *Caenorhabditis elegans* ASH sensory neuron

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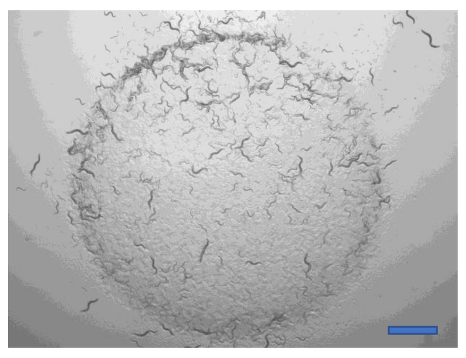
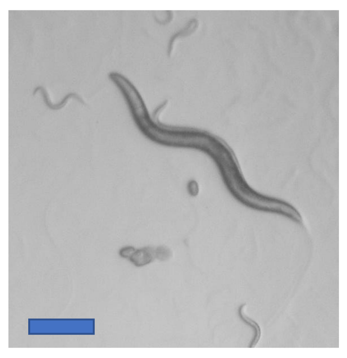
Background & Introduction



C. elegans on a petri dish, scale bar:2mm

C. elegans is a tiny nematode, broadly used as a model organism in neuroscience.

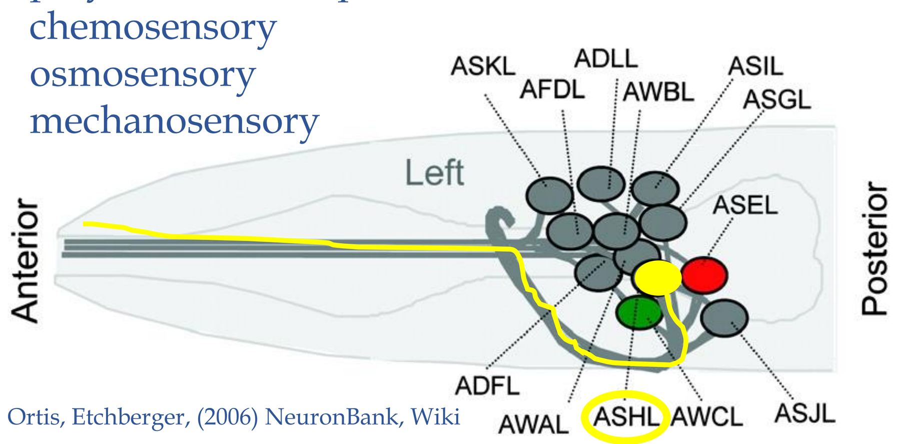
Its nervous system (305 neurons) is fully mapped and the wiring diagram is known.



C. elegans adult, eggs and larvae, scale bar:0.25mm

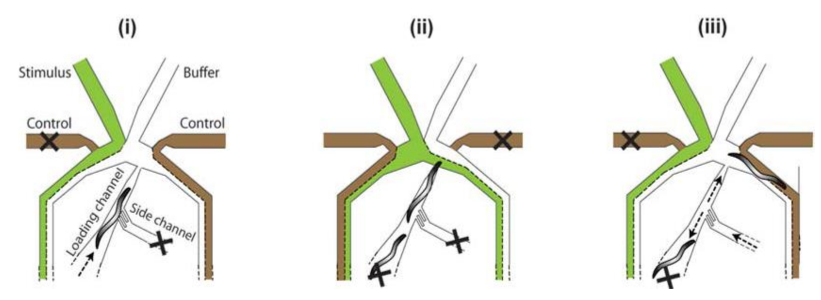
The ASH pair of sensory neurons

polymodal nociceptor:
chemosensory
osmosensory
mechanosensory



Ortis, Etchberger, (2006) NeuronBank, Wiki

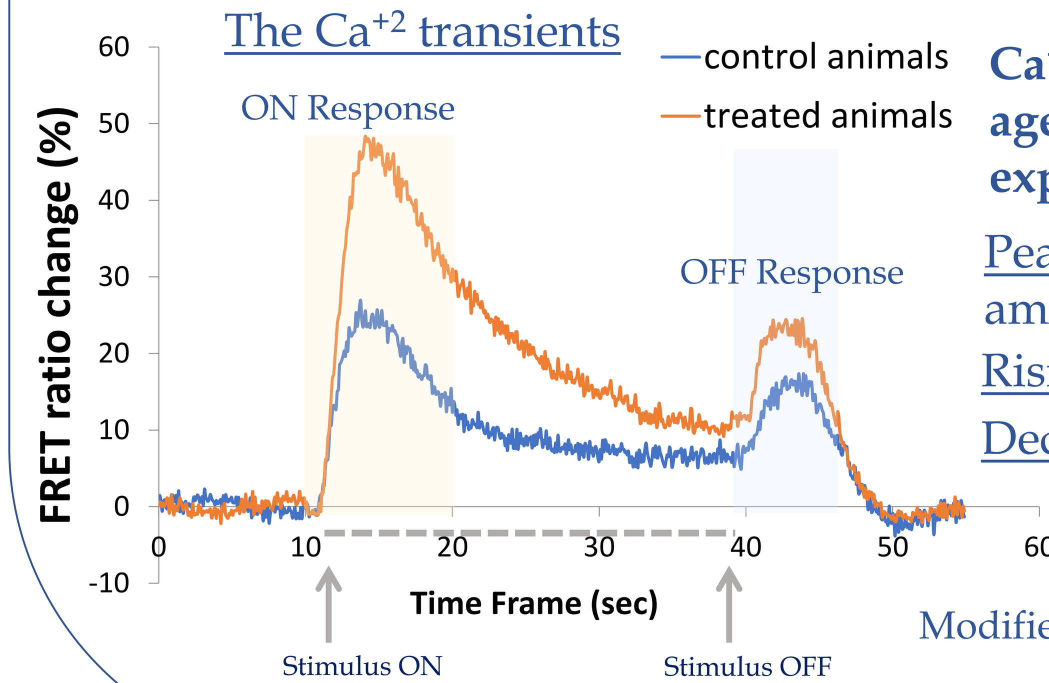
The microfluidic platform



Chokshi et al, *LabChip*, 2011

Worms are trapped in the microfluidic channel, stimulus is delivered to their nose, Ca^{2+} transients are recorded.

The Ca^{+2} transients



Ca^{+2} transients are recorded for young & aged animals, untreated (control) and exposed to oxidative stress (OS)--4 cases.

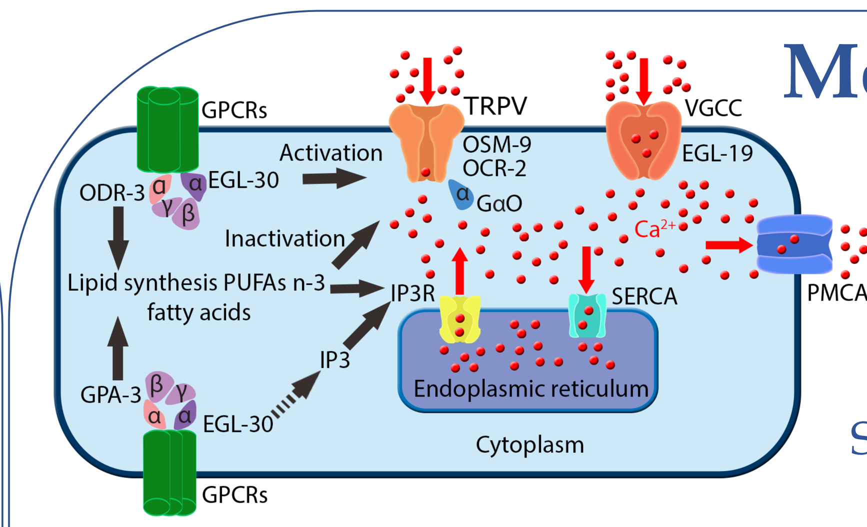
Peak: magnitude of response, total amount of incoming Ca^{+2} ions

Rising slope: time rate of Ca^{+2} influx

Decaying slope: time rate of Ca^{+2} efflux

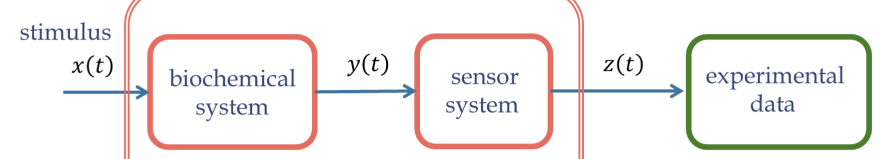
Modified from Gourgou & Chronis, 2016

Methods



Components of the Ca^{2+} homeostatic machinery that are included in the model

The system to be modeled:



Sensor equation: $\Delta R\% = \frac{R - R_{min}}{R_{max} - R_{min}} = R_{max} \frac{Ca^n}{Ca^n + K_d^{\prime n}}$

Sensor : FRET, genetically encoded Ca^{2+} indicator

Model equations

$$\frac{dCa}{dt} = (J_{Stores} + J_{ER})(Ca_{ER} - Ca) - J_{SERCA} - J_{Pump} + JTRPV + J_{VGCC} + J_{Leak}$$

$$\frac{dCa_{ER}}{dt} = \gamma\big(J_{SERCA} - (J_{Stores} + J_{ER})(Ca_{ER} - Ca)\big)$$

$$J_{Pump} = V_{pump} \frac{Ca^2}{Ca^2 + K_{Pump}^2}$$

$$J_{SERCA} = V_{SERCA} \frac{Ca^2}{Ca^2 + K_{SERCA}^2}$$

$$J_{TRPV} = V_{TRPV}\, OI^3 (Ca_{ext} - Ca)$$

$$J_{Stores} = V_{Stores}\, IP3.Ca.\left(\frac{1 - Y}{(IP3 + K_1)(Ca + K_5)}\right)^3$$

$$J_{VGCC} = V_{VGCC}.m_{Ca}^2.V.\frac{-Ca\exp(-V) + Ca_{Ext}}{1 - \exp(-V)}$$

$$\frac{dP_0}{dt} = k_0.\frac{Stim}{Stim + K_0} - k_0^-.P_0$$

$$\frac{dP_1}{dt} = k_1.P_0 - k_1^-.P_1$$

$$\frac{dP_2}{dt} = k_2.\frac{P_0}{P_0 + K_1} - k_2^-.P_2$$

$$\frac{dO}{dt} = k_o.P_1.(1 - O) - k_O^-.O$$

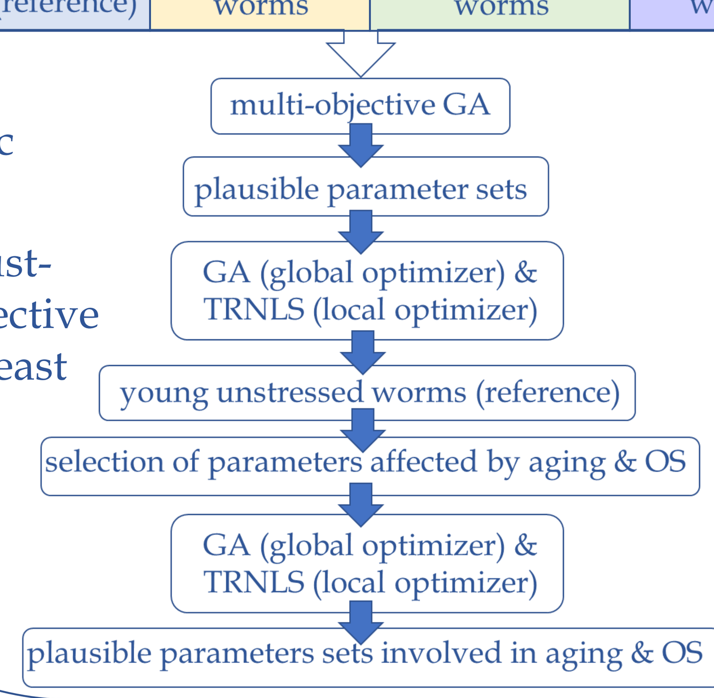
$$\frac{dI}{dt} = k_I.(1 - I) - k_I^-.P_2.I$$

$$\frac{dIP3}{dt} = k_{IP3}.\frac{P_1}{1 + (K_{IP3}.P_2)^4}.\frac{Ca^2}{Ca^2 + K_{Ca}^2} - k_{IP3}^-.IP3$$

$$\frac{dV}{dt} = k_V(V_{max} - V) - k_V^-(V - V_{rest})$$

Parameter estimation

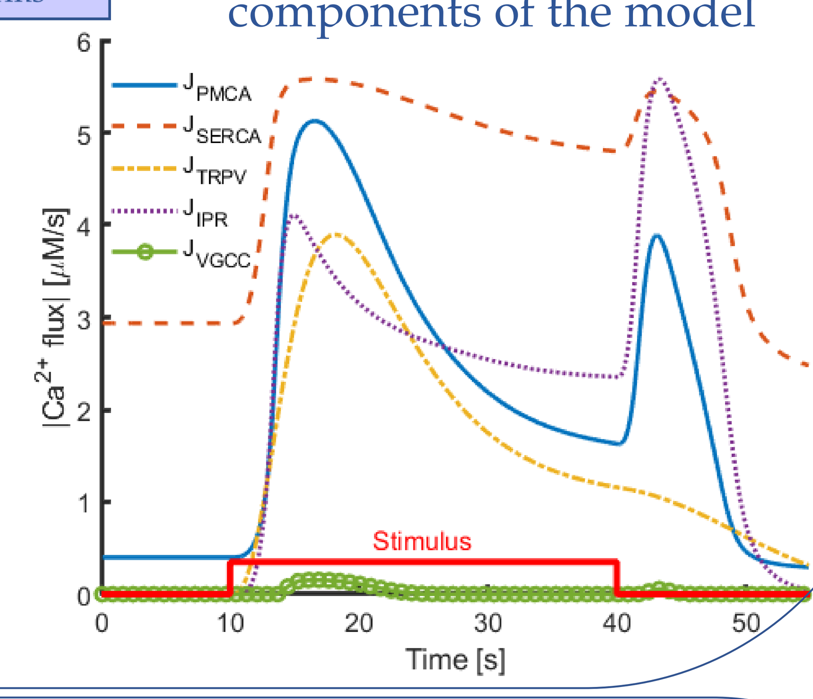
young unstressed worms (reference)	young stressed worms	aged unstressed worms	aged stressed worms



GA: genetic algorithm

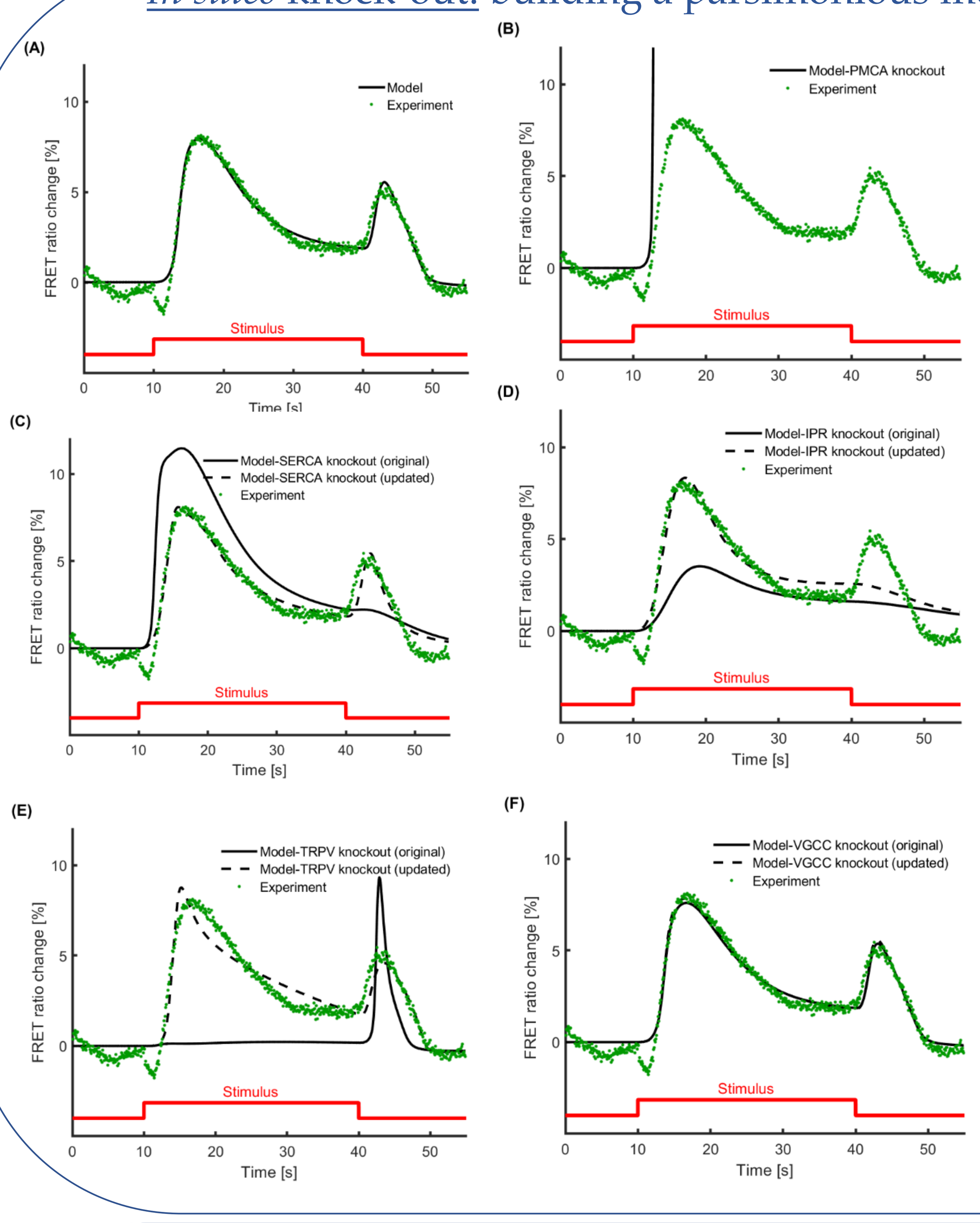
TRNLS: trust-region-reflective nonlinear least squares

The Ca^{2+} fluxes for different components of the model

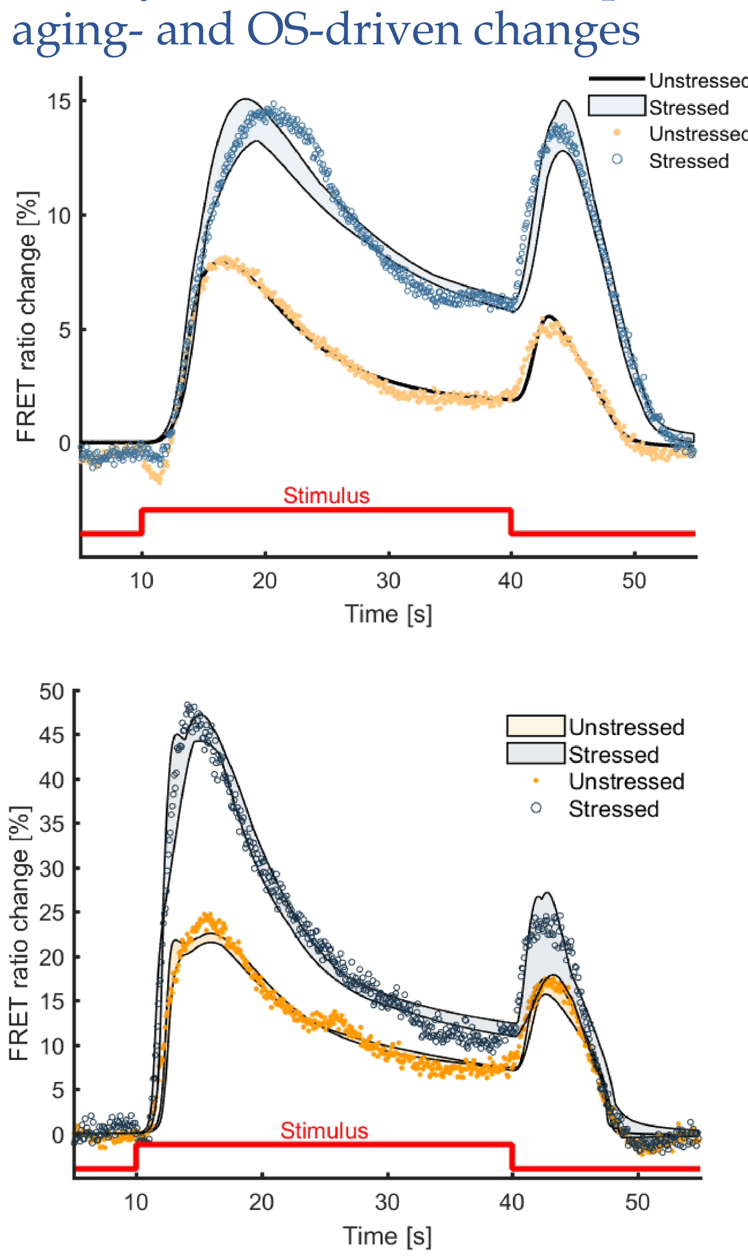


Results

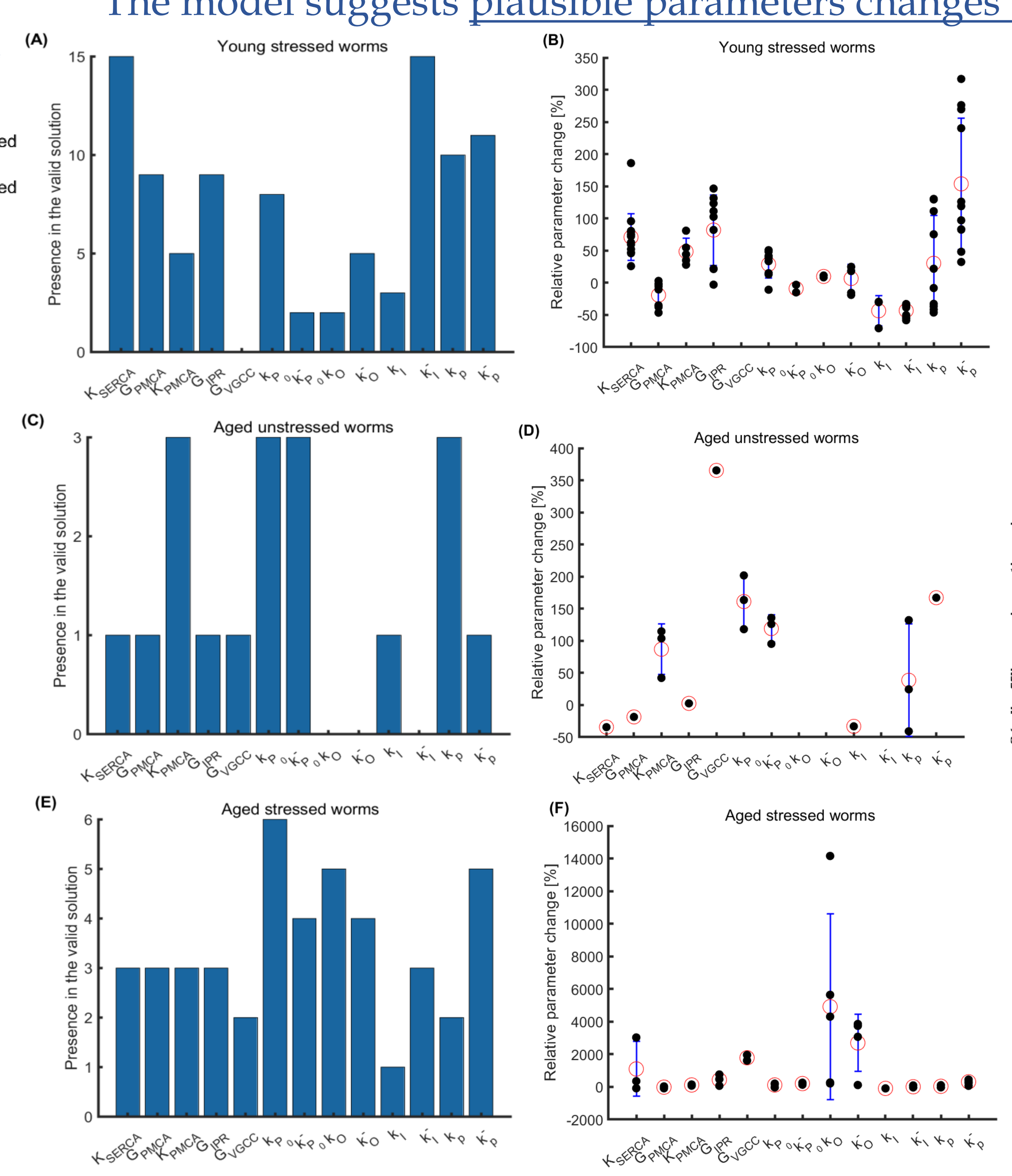
In silico knock-out: building a parsimonious model



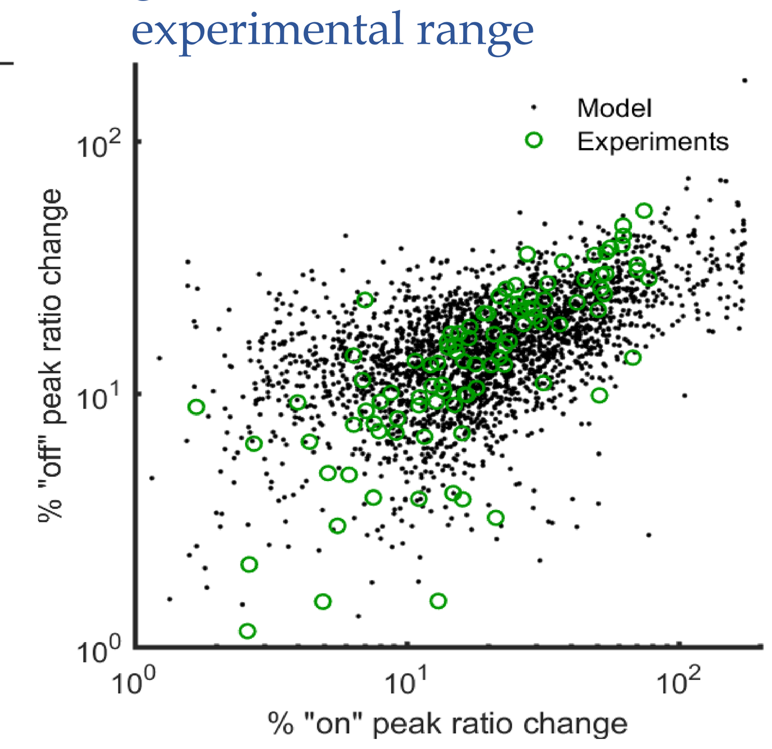
Ca^{2+} dynamics: the model captures aging- and OS-driven changes



The model suggests plausible parameters changes due to aging and OS



Sensitivity: the model generates results within the experimental range



Conclusions

We propose a model for the Ca^{2+} dynamics in the *C. elegans* ASH polymodal neuron, based on intracellular events that unfold as part of the Ca^{2+} signaling machinery.
Our model:

- captures for the first time the dynamics of both the "on" and "off" responses.
- can account for changes in the ASH Ca^{2+} dynamics due to age and exposure to oxidative stress, reflecting, confirming and sometimes predicting the role of each molecular player modeled in the cellular mechanism that generates Ca^{2+} transients.
- can be used to propose and guide future experimental work, targeting specific molecular players involved in Ca^{2+} dynamics.

Acknowledgments

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References

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