Endogenous electric fields: a tuneable consequence of ion homeostasis in functionally polarized cells

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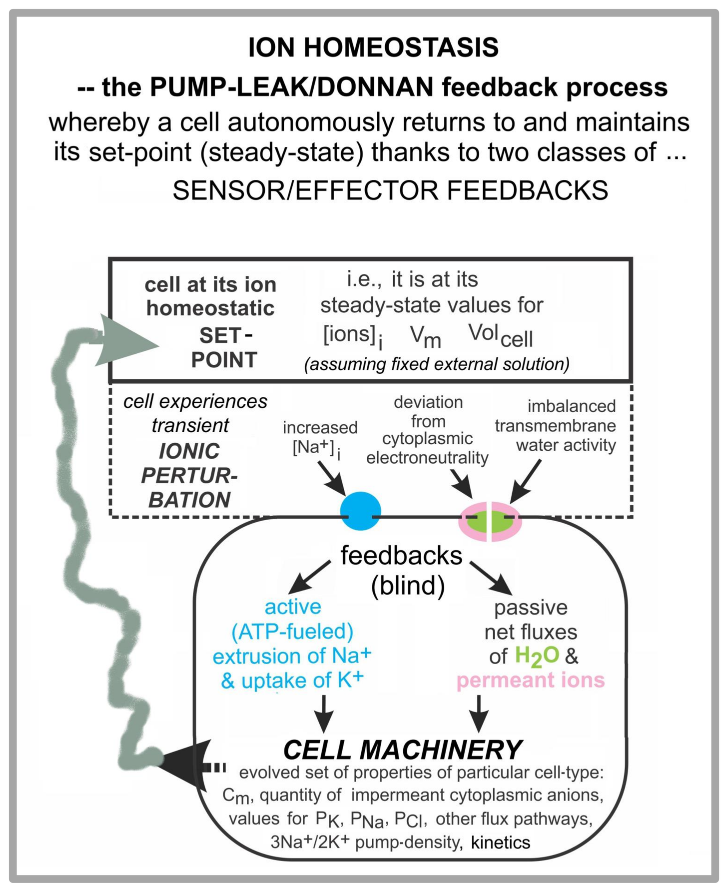
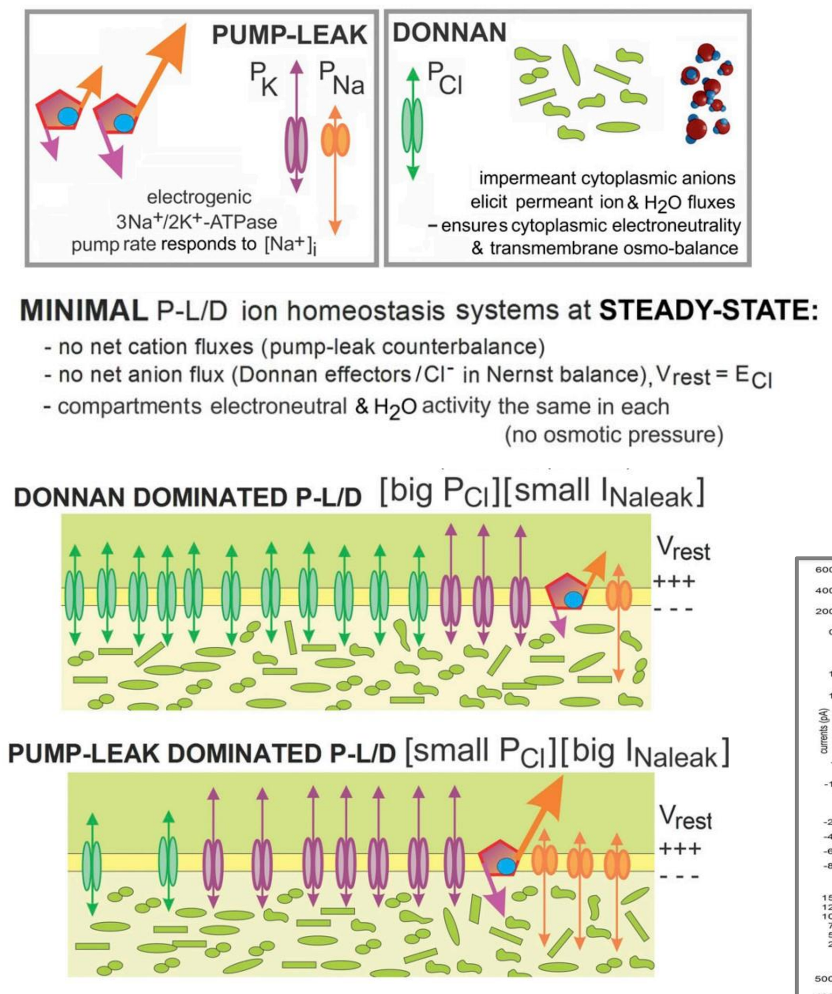
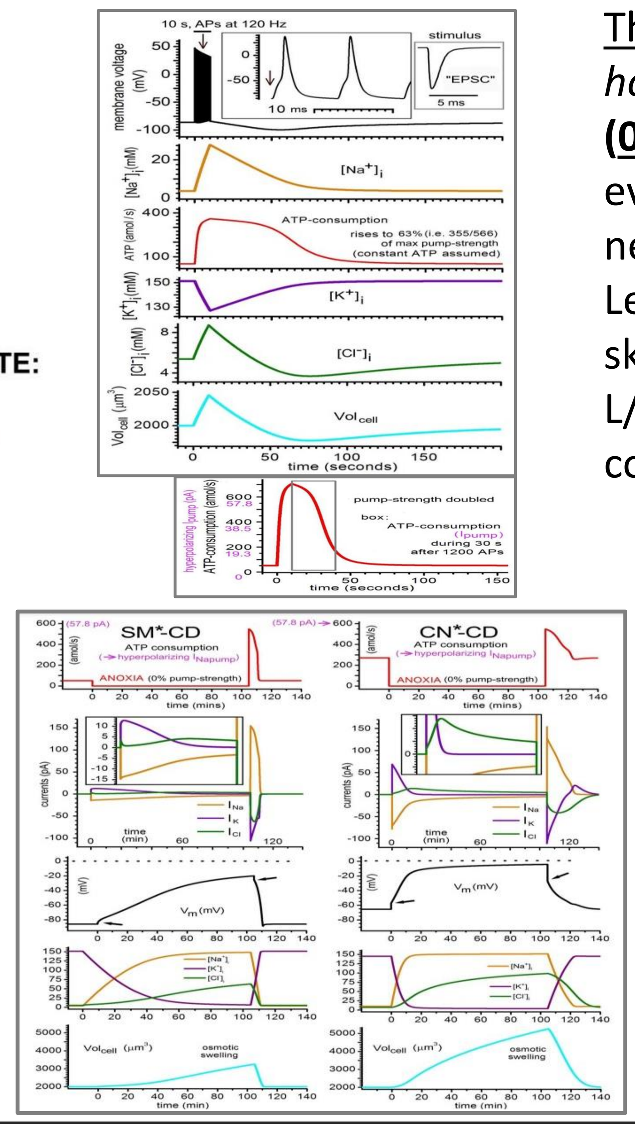
ABSTRACT Recently (Morris, Wheeler, Joos 2022 JGP 154:e202112914) we used the charge difference (CD) approach to model ion homeostasis **zero-dimensionally** (spatially uniform flux properties). Informative? For sure. BUT -- excitable cells' pumps, channels & transporters are spatially non-uniform and the cytomorphology of "battery-recharging" is not understood. In devising a **one-dimensional model** of the **P**ump-**L**eak/**D**onnan (ion homeostatic) process for **structurally polarized cells**, we realized that, for animal tissues, the steady-state axial currents of variously "symmetry-broken" polarized cells provide a robust explanation for the diverse, small, tuneable **Endogenous Electric Fields (EEFs)** that have come to be regarded as a feature of most tissues.

Take-home: **a simple 1D Nernst-Planck P-L/D framework for polarized cell ion homeostasis predicts the existence and general nature of "reprogrammable" EEFs.**







<u>This section (Morris et al 2022)</u>: *defines ion homeostasis as an autonomous* **P-L/D** *process* . **(<u>0D models</u>)**. P-L/D process gets evolutionarily-"tuned" to meet "life-style" needs of different cell-types. Neurons… Pump-Leak dominated, non-minimal P-L/D systems; skeletal muscle fibers…Donnan dominated P-L/D systems -- usually minimal (i.e. without co-transporters).

<u>Top panels</u>…**0D, minimal** muscle model (SM-CD) response to a realistic **STRESS-TEST** – last panel (with 2X max pump-strength) is extremely close to expt'l rat fiber condition.

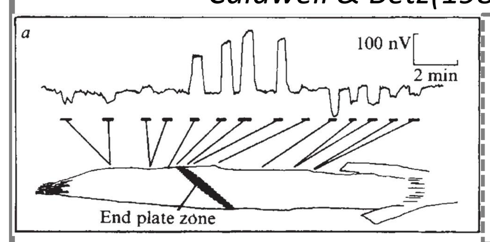
<u>Bottom 2 sets</u>… SM*-CD & CN*-CD **Anoxic RUNDOWN/RECOVERY** (*= **no** VGCs) *<u>Shows</u>*: skel muscles' Donnan dominated strategy (tho' "dumber") is safer & cheaper than neurons' P-L dominated strategy.

(CN-CD = Cortical Neuron CD; it is non-minimal)

A half-century of EEFs *… 1970s & 1980s …*

Jaffe LF, Nuccitelli R (1974) *An ultrasensitive* ***VIBRATING PROBE*** *for measuring steady extracellular currents. J Cell Biol. 63:614.*

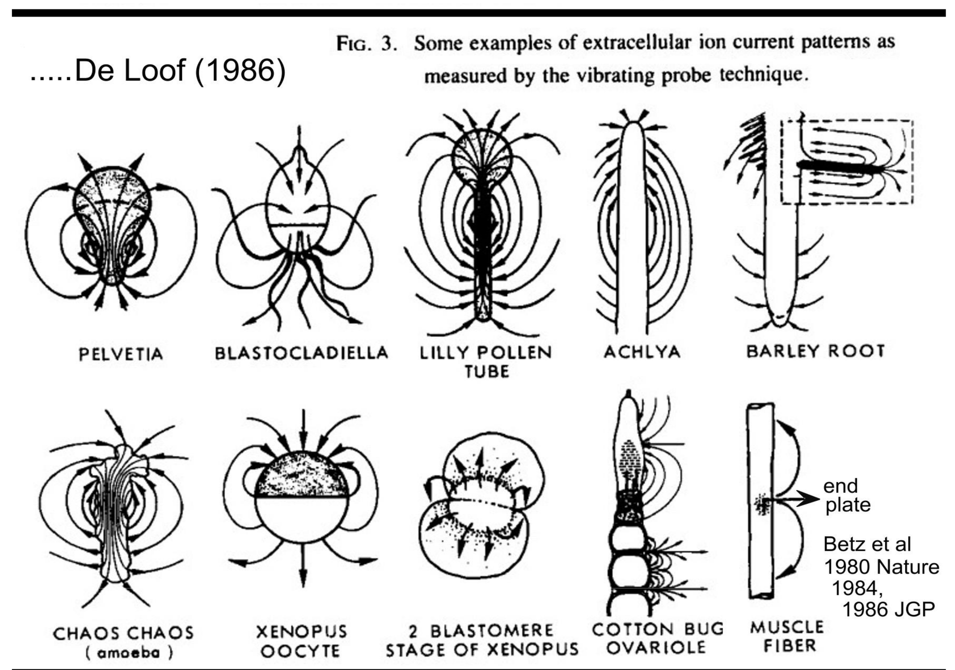
Betz WJ et al (1980) ***Endogenous electric field*** *around muscle fibres depends on the Na+-K+ pump. Nature 287:235-7. (has an* ***oops!*** *…* ***BUT…****)* *Betz & Caldwell (1984) JGP83:143. and Caldwell & Betz(1984)JGP 83:157.*



Betz et al papers…vibrating probe..
<u>TWO</u> classes of EEF .. rat skeletal muscle fibers…(*data shown for 1*)
1) asym gCl plus cotransporters
2) asym'ly Na⁺-loaded → asym electrogenic pumping (~10X bigger)

De Loof A (1986) The electrical dimension of cells: the ***cell as a miniature electrophoresis chamber****. Int Rev Cytol. 104:251.*

…..De Loof (1986)



… a few-decade hiatus……

….but more recently …. ……

<u>…. the issue of EEFs has been heating up …..</u>

Funk RH (2015) *Endogenous electric fields as guiding cue for cell migration.* **Front Physiol**. 6: 143.

Savtchenko, Poo, Rusakov (2017) *Electrodiffusion phenomena in neuroscience: a neglected companion.* **Nat Rev Neurosci**. 18:598.

Levin M (2021) *Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer.* **Cell** 184: 1971.

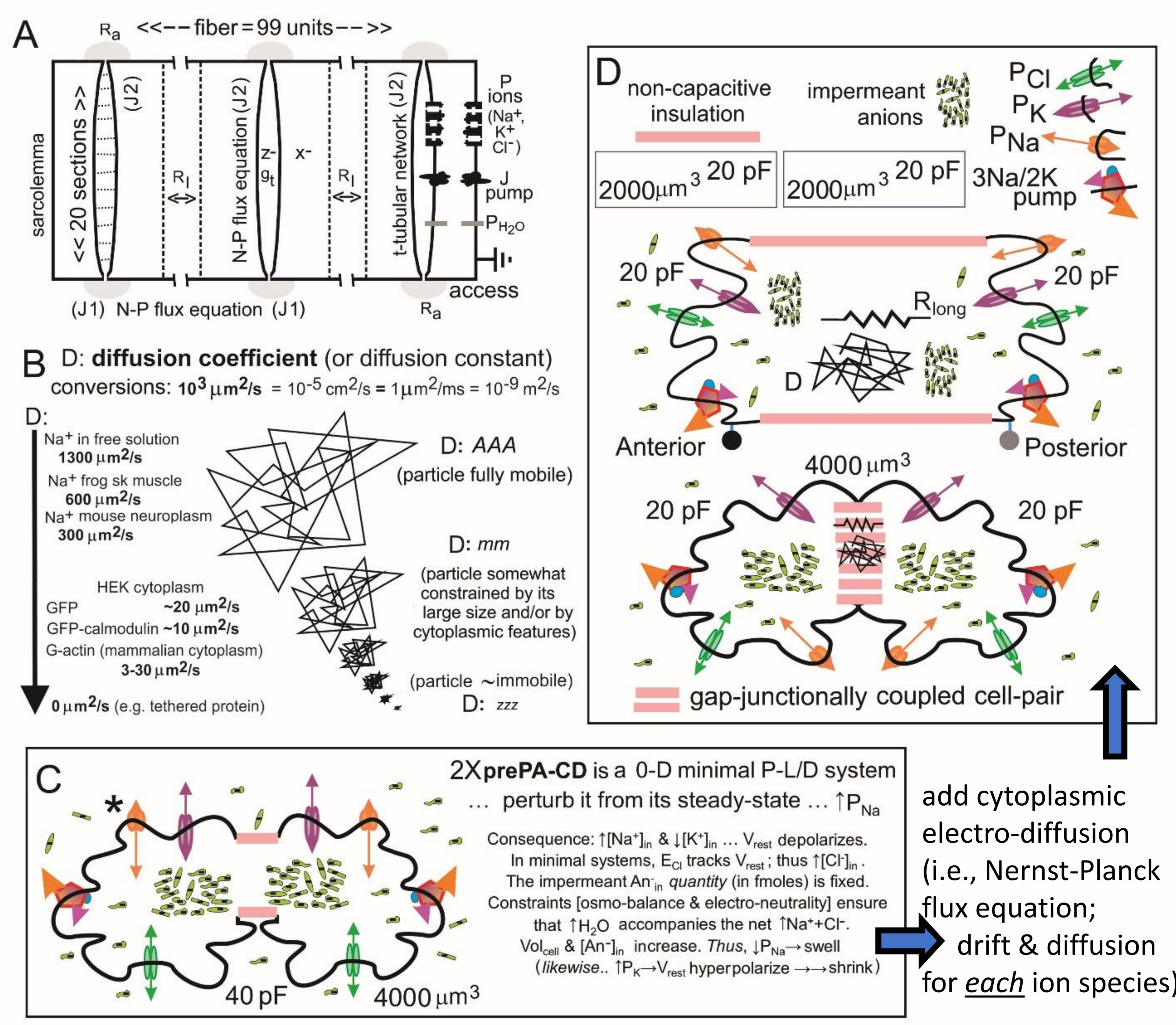
<u>Recent Experimental (plus modeling) Work:</u>

McNamara HM et al (2020) *Bioelectrical domain walls in homogeneous tissues.* **Nature Physics** 16:357.

Rebollo B et al (2021) *Modulation of intercolumnar synchronization by endogenous electric fields in cerebral cortex.* **Sci Adv.** 7:eabc777.

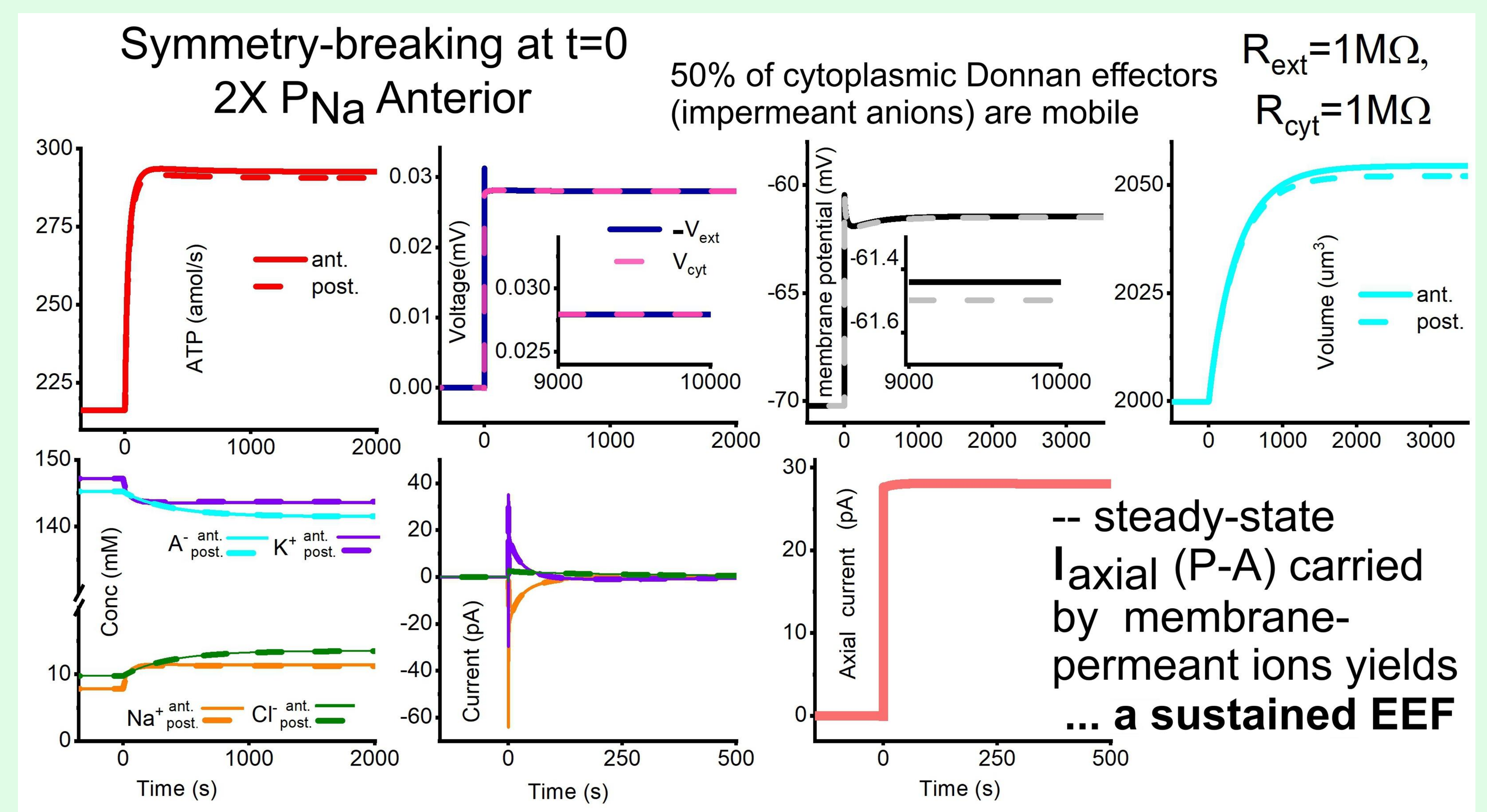
Setting up PA-CD model (*going 1 Dimensional*) (**P**osterior **A**nterior - **C**harge **D**ifference)

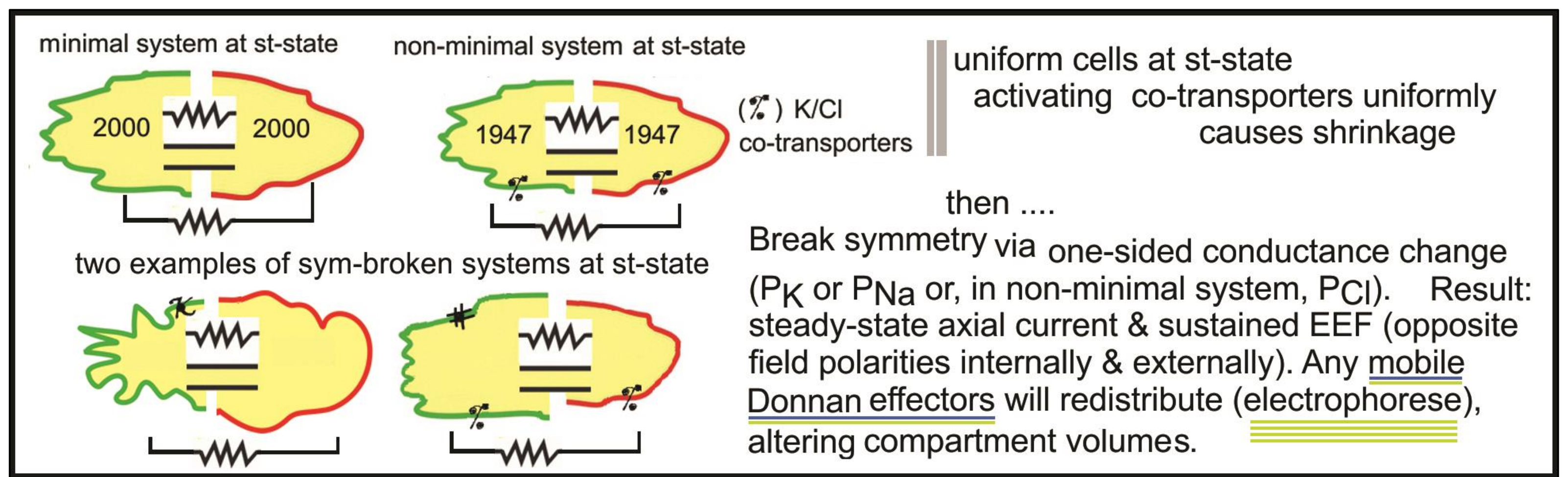
A) Summarizes Fraser et al (2011)'s hybrid 0D/1D model **B)** info re Diffusion coefficients **C)** 0D ("pre-1D") version of PA-CD **D)** two ways to envisage PA-CD



add cytoplasmic electro-diffusion (i.e., Nernst-Planck flux equation; drift & diffusion for *<u>each</u>* ion species)

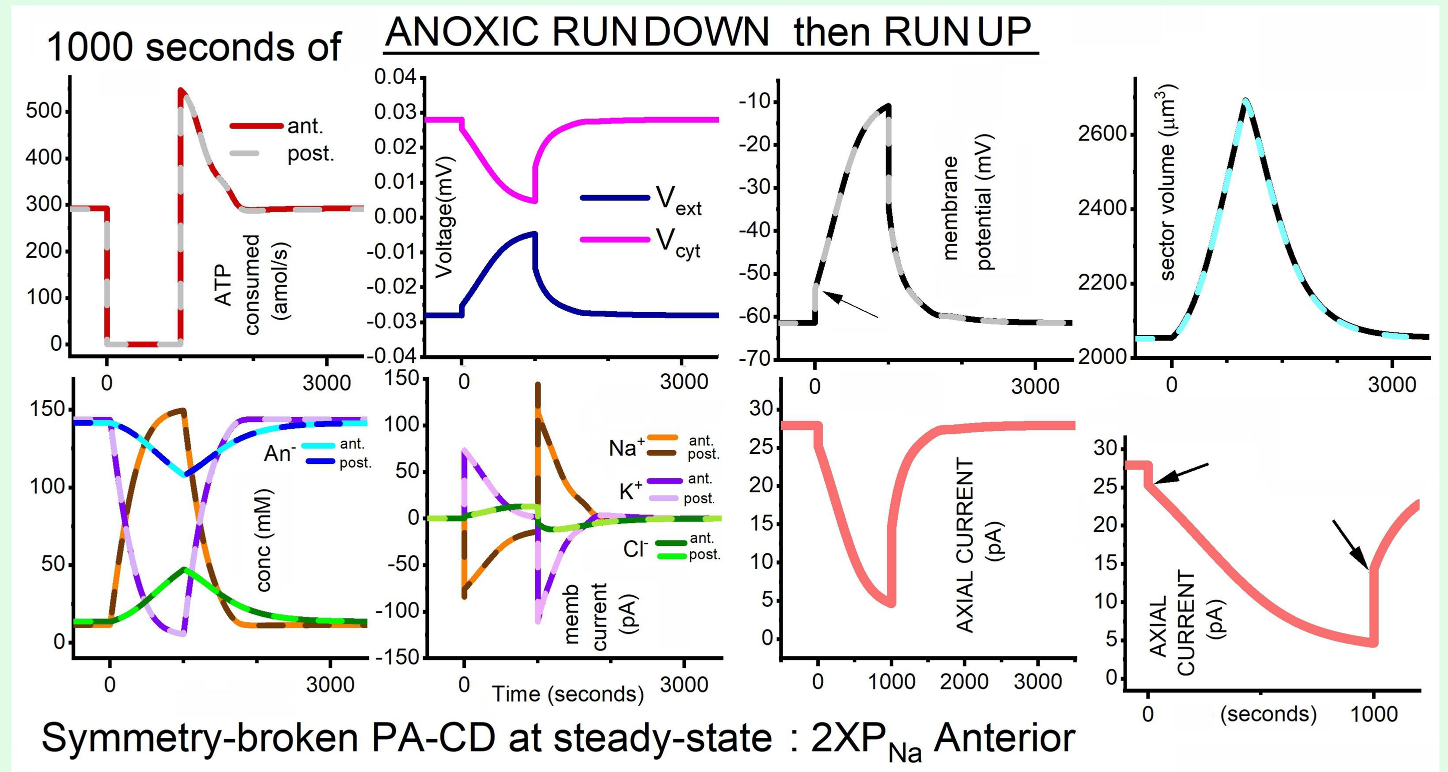
<u>PA-CD</u>: minimal P-L dom'd system. $R_{external(\mathbf{P-A})}$ =1MΩ ; $R_{(cytoplasm=\mathbf{axial})}$ =1MΩ (given **D**=90µm²/s for membrane-perm ions &10 µmX200µm²). **<u>Trajectories</u>** for **<u>"0D→1D"</u>** upon **<u>symmetry-breaking:</u>** Post & Ant sector parameters, plus I_{axial}. *This* **sustained I_{axial}** yields a **sustained EEF** of **~30 µV/10µm** or **~3 V/m .**





(from Kay & Blaustein 2019 JGP 151:407)

Figure 4. **Joseph Hoffman (left) and Daniel Tosteson (right).** Photograph from 1955 or 1956 at the Museum of National History, Frederiksborg Castle, Hillerød, Denmark, taken when Tosteson was a postdoctoral fellow in Hans Ussing's laboratory in Copenhagen before he moved to join Alan Hodgkin's laboratory at the University of Cambridge, UK. Photo courtesy of Dr. Magdalena Tosteson.



(if pump & leak densities are uniformly higher, then sym-break by 2XPNa Ant yields bigger Iaxial, thence more intense EEFs …e.g. 4XPNa,PK,PCl & 2XPump... yields a sustained 89 pA)

(Posterior–Anterior value differences are too small to show - plot lines overlap – but – see resultant ***AXIAL CURRENT****).*

In steady-state sym-broken PA-CD, 28 pA of I_{axial} flows in a loop (*Ant memb, axial R, Post memb, external R, Ant m..*), generating a **sustained EEF** (opposite polarity for external & axial i.e. cytoplasmic EEF). Anoxic rundown = pump shut-off = "computational ouabain". EEF shows a *small* immediate drop then a slow decay, at the rate of ion-gradient rundown. Recovery: big initial jump because the now Na⁺-loaded cytoplasm hyper-stimulates the pump.

REFERENCES: Dijkstra et al (2016) J Neurosci 36:11881. ❶ Fraser & Huang (2004) J Physiol 559:459. ❶ Fraser et al (2011) JGP 138:95. ❶ Joos… Morris (2018) PloS One 13: e0196508. ❶ Mondragão…Rose CR (2016) J Physiol 594:5507. ❶ Morris (2018) Curr Top Membr 81:457. ❶ Morris, Wheeler, Joos (2022) JGP 154:e202112914.