

Introduction

Impermeable molecules within cells create a higher intracellular osmolarity relative to the extracellular space. This difference in intracellular concentrations drives a water flux into a cell. With no other mechanisms in place, a cell will swell until lysis. While plant cells and bacteria have evolved to have a rigid cell wall, animal cells possess pumps and channels to regulate ionic concentrations. This pump-leak mechanism (PLM) utilizes ionic channels to move ions along an electrochemical gradient while Na⁺/K⁺-pumps consume adenosine triphosphate (ATP) to pump out 3 Na⁺ out and in 2 K⁺. The PLM can be modelled mathematically using a system of algebraic differential equations, called Pump-Leak Equations (PLE). However, this model does not capture the behavior of an epithelial cell which presents the need for a mathematical model of the PLM that also includes multiple compartments. We extend PLE to model ion transport through a multi-compartment epithelial layer and study the effect of Na⁺/K⁺- pump and other parameters in cell regulation.

Pump-Leak Equations (PLE)

Here, we consider three main ions, Na⁺, K⁺, and Cl⁻ as well as impermeable molecules in the extracellular space Y_e and intracellular space X_i with an average valence of z_Y and z_X , respectively. In the PLE, ion concentrations $[ion]_i$ and cell volume w are modeled with differential equations. Membrane potential V is modeled using a difference in charge where we assume electroneutrality of the extracellular space.

$$\begin{aligned} F \frac{d(w[Na^+]_i)}{dt} &= -g_{Na}(V - E_{Na}) - 3P_{NKA} \\ F \frac{d(w[K^+]_i)}{dt} &= -g_K(V - E_K) + 2P_{NKA} \\ F \frac{d(w[Cl^-]_i)}{dt} &= g_{Cl}(V - E_{Cl}) \\ \frac{dw}{dt} &= \nu(\mathcal{O}_i - \mathcal{O}_e) \\ V &= \frac{Fw}{C_m} \left([Na^+]_i + [K^+]_i - [Cl^-]_i + z_X \frac{X}{w} \right). \end{aligned}$$

We assume that the extracellular space is an infinite bath so that $[ion]_e$ is constant.

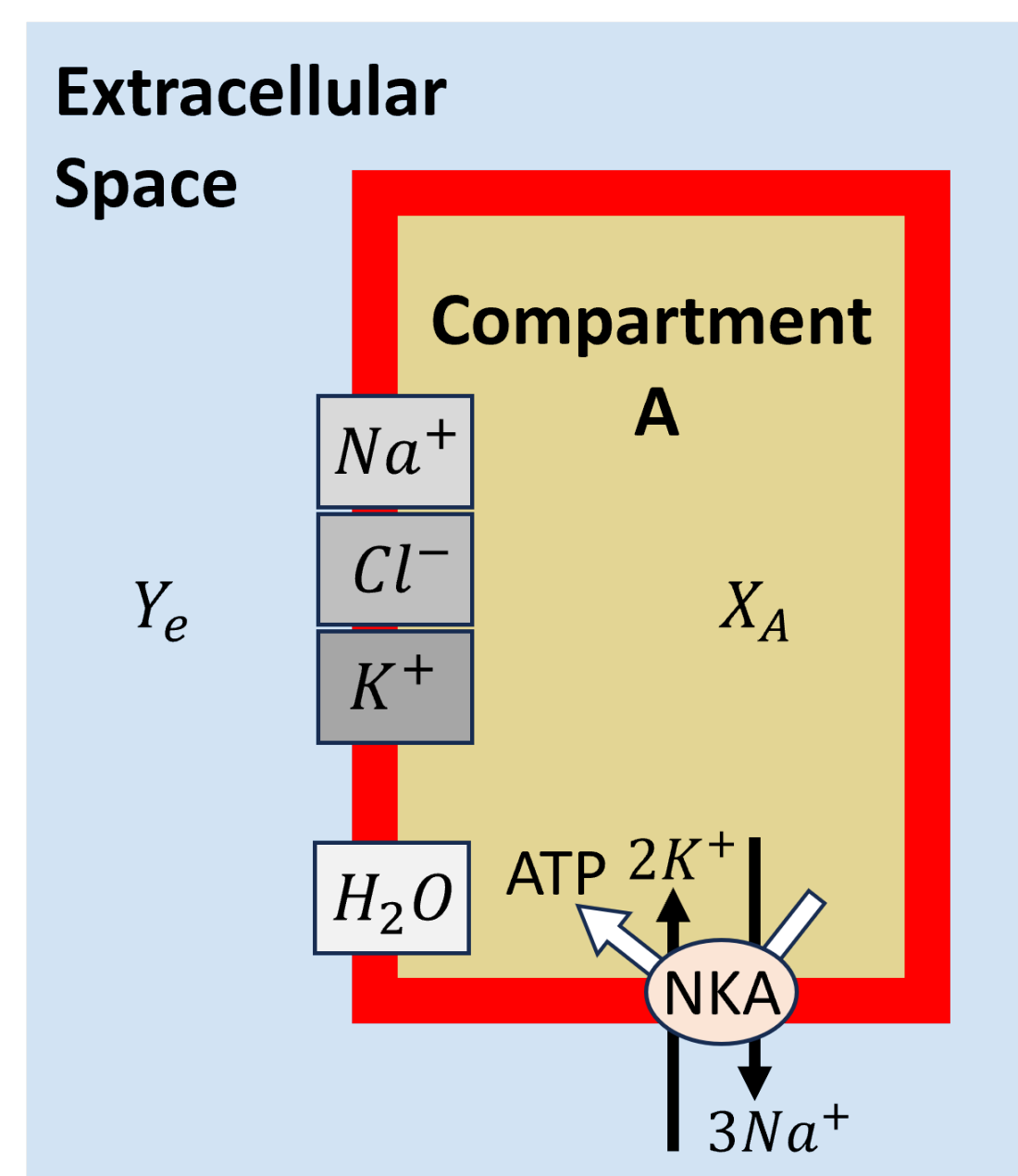
The passive ionic flux between the two spaces (intra- & extra-cellular) is driven by their electrochemical difference using Ohm's law.

The Nernst potential is given by $E_{ion} = \frac{RT}{z_{ion}F} \ln \left(\frac{[ion]_e}{[ion]_i} \right)$.

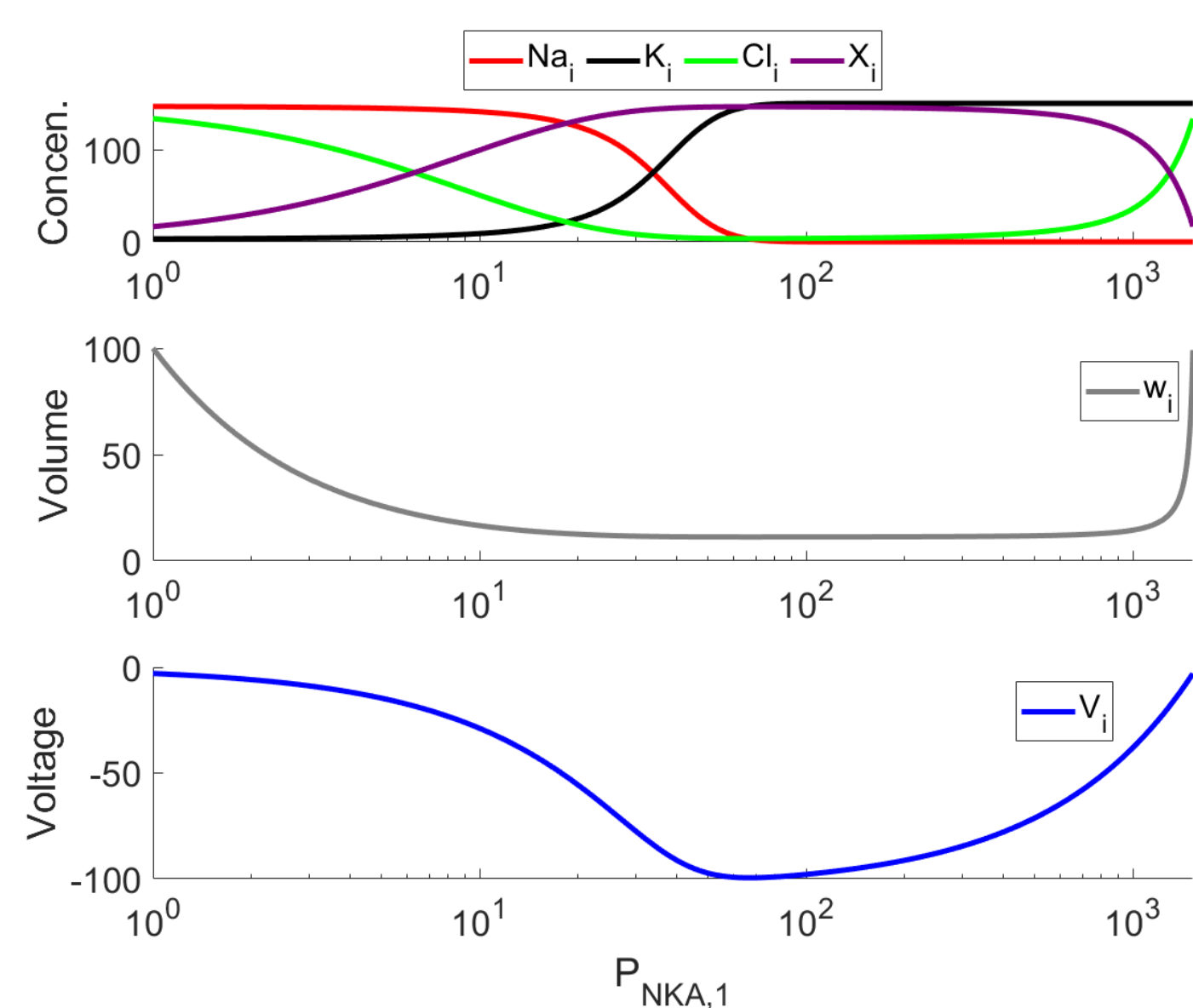
Water w is driven towards the space of greatest osmolarity, with the osmotic difference between the two spaces being $\mathcal{O}_i - \mathcal{O}_e$ where $\mathcal{O}_i = [Na^+]_i + [K^+]_i + [Cl^-]_i + [X]_i$ and $\mathcal{O}_e = [Na^+]_e + [K^+]_e + [Cl^-]_e + [Y]_e$.

In these equations, g_{ion} is the ionic conductance, ν is the membrane permeability to water flux, and P_{NKA} is the density of Na⁺/K⁺-pump multiplied by the rate of ATP hydrolysis.

Steady State Behavior of Single Compartment



A schematic of the single compartment model cell with Na⁺/K⁺-pump, intracellular X_i and extracellular Y_e impermeant molecules, and Na⁺, K⁺, and Cl⁻, and water channels.



Steady state values of a single compartment system as a function of the pump rate. At steady state, net ionic flux across the membrane is zero.

Acknowledgments

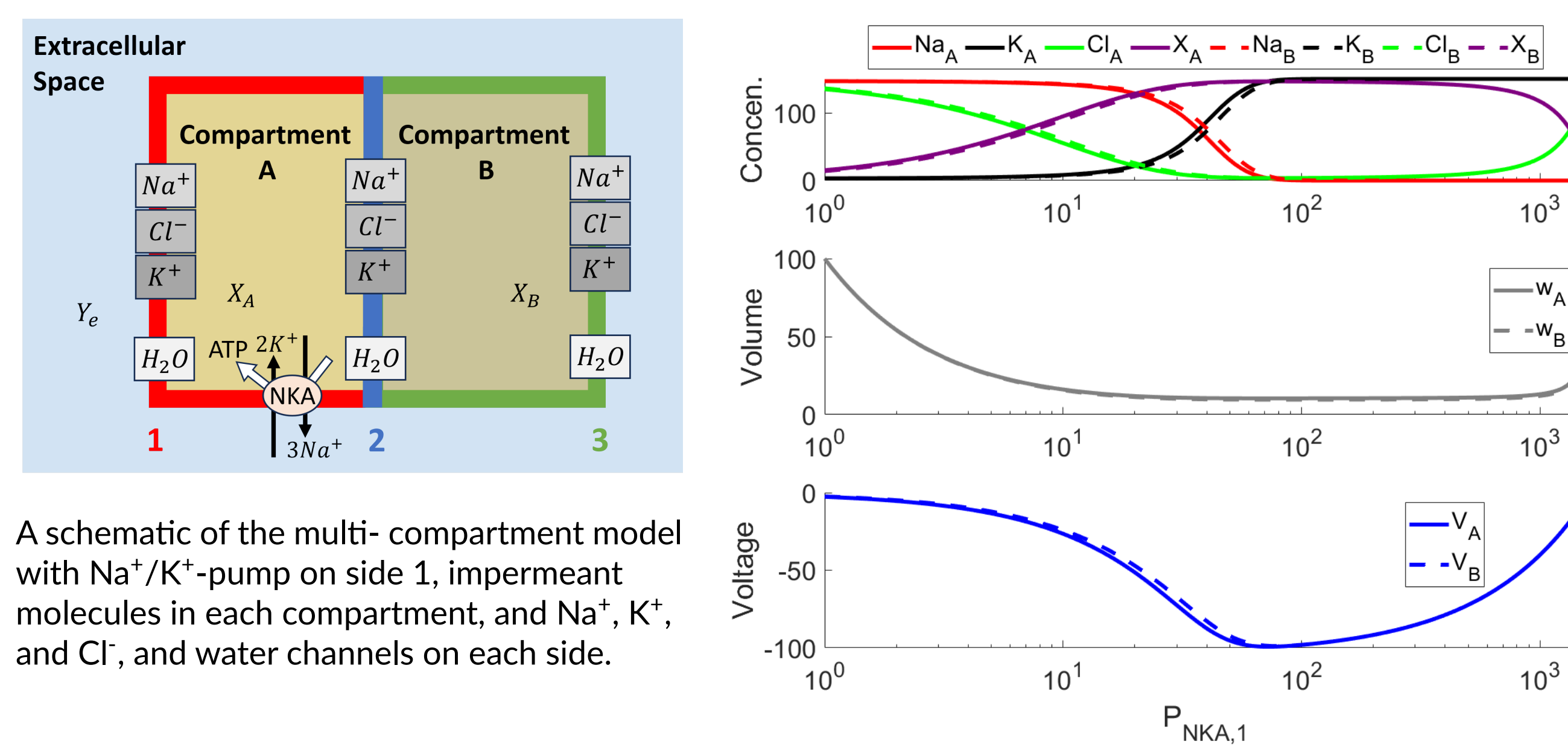
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Coupled Compartment PLE

We extend PLEs to a 10-dimensional algebraic differential equation to model a two-compartment epithelial layer (as well as other biological systems) which are coupled through *gap junction*. We consider two biologically relevant configurations for the N⁺/K⁺ pump: (1) the pump is located on the basolateral membrane (side 1, red), and (2) the pump is on the apical surface (side 2, blue).

Steady State Behavior of Coupled PLE with Pump on Side 1

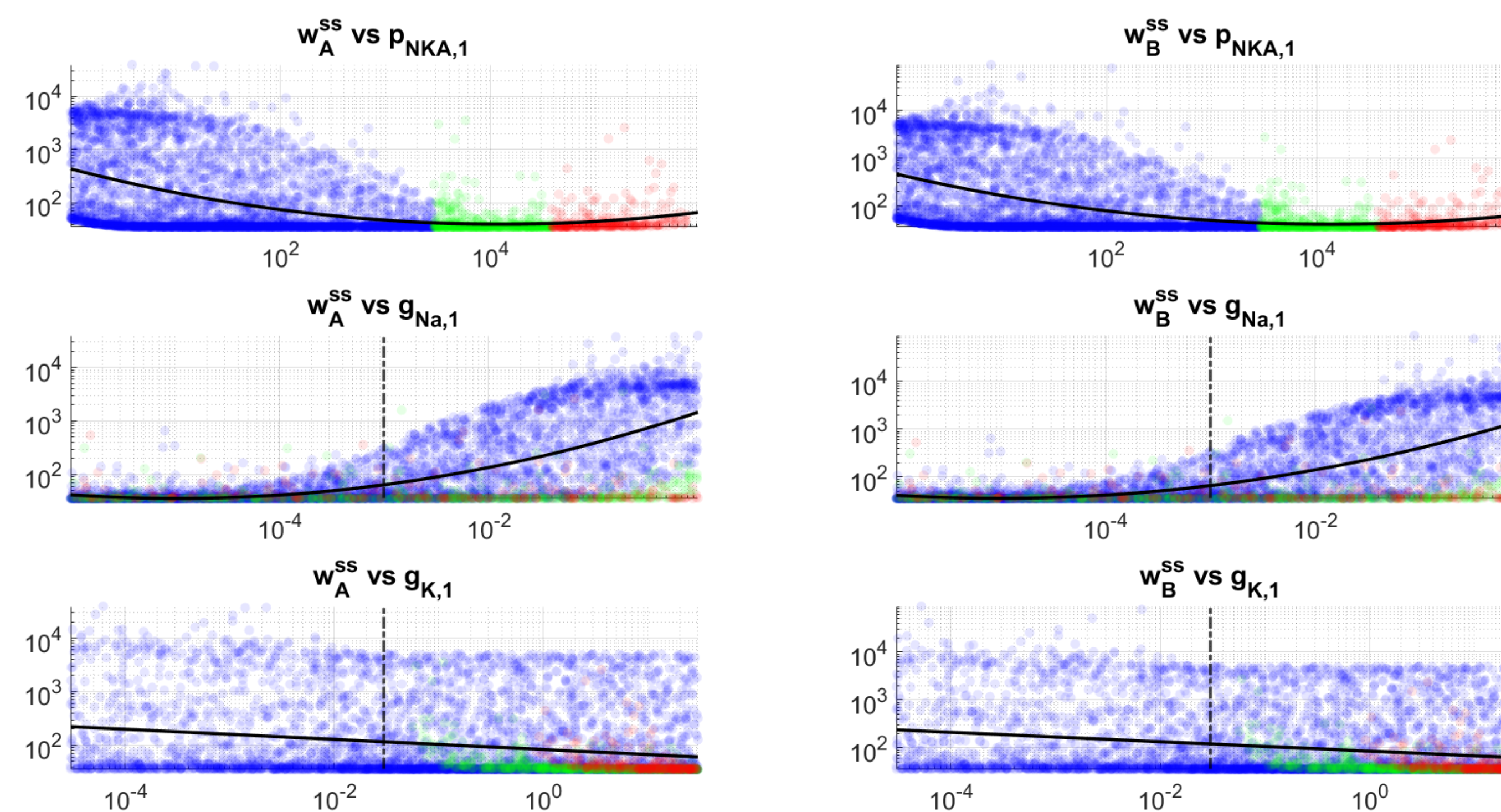
The steady state of the first configuration is plotted below as a function of the pump rate. The state variables of both compartments, at steady state, are plotted together. As the pump rate increases, volume will decrease in both A and B. Values do not differ considerably between compartments, though changes to compartment A proceed any in B. Volume begins to rapidly increase as the pump rate approaches a maximum value.



A schematic of the multi-compartment model with Na⁺/K⁺-pump on side 1, impermeant molecules in each compartment, and Na⁺, K⁺, and Cl⁻, and water channels on each side.

Sensitivity Analysis of Coupled PLE (side 1)

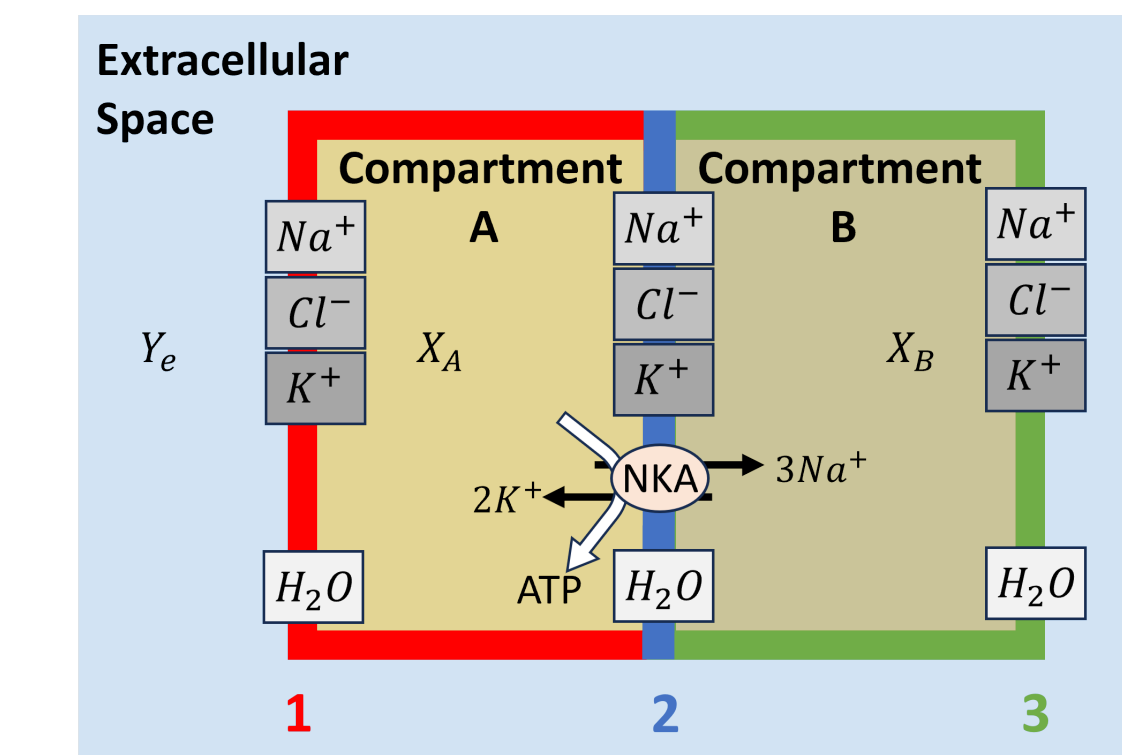
Sensitivity analysis can be used to study the effects of the pump rate and conductances. Plotted below is volume against the pump rate and the conductance on side 1. Varying these parameters leads to similar volume values. As seen above, increasing the pump rate will decrease volume. On the other hand, increasing Na⁺ conductance increases volume. Changes to K⁺ have a minor effect on volume. A second order polynomial is fitted to the datapoints (solid black curve). Nominal values are also provided (dashed vertical line).



References

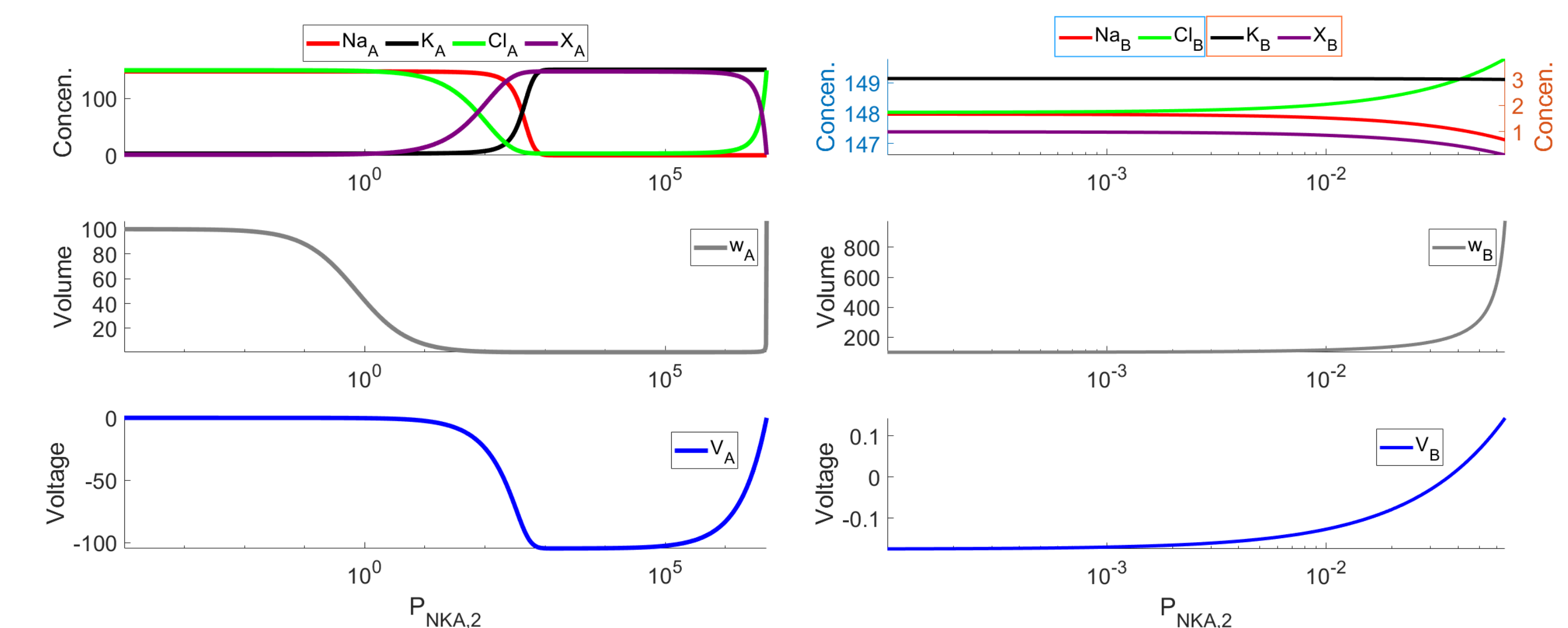
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- [2] Y. Mori. Mathematical properties of pump-leak models of cell volume control and electrolyte balance. *Journal of Mathematical Biology*, 65:875–918, 2012.
- [3] K. D. Tarrant, A. R. Kay, and Z. Aminzare. Mathematical modeling of multi-compartment ion transport and cell volume. [in progress].

Steady State Behavior of Coupled PLE with Pump on Side 2



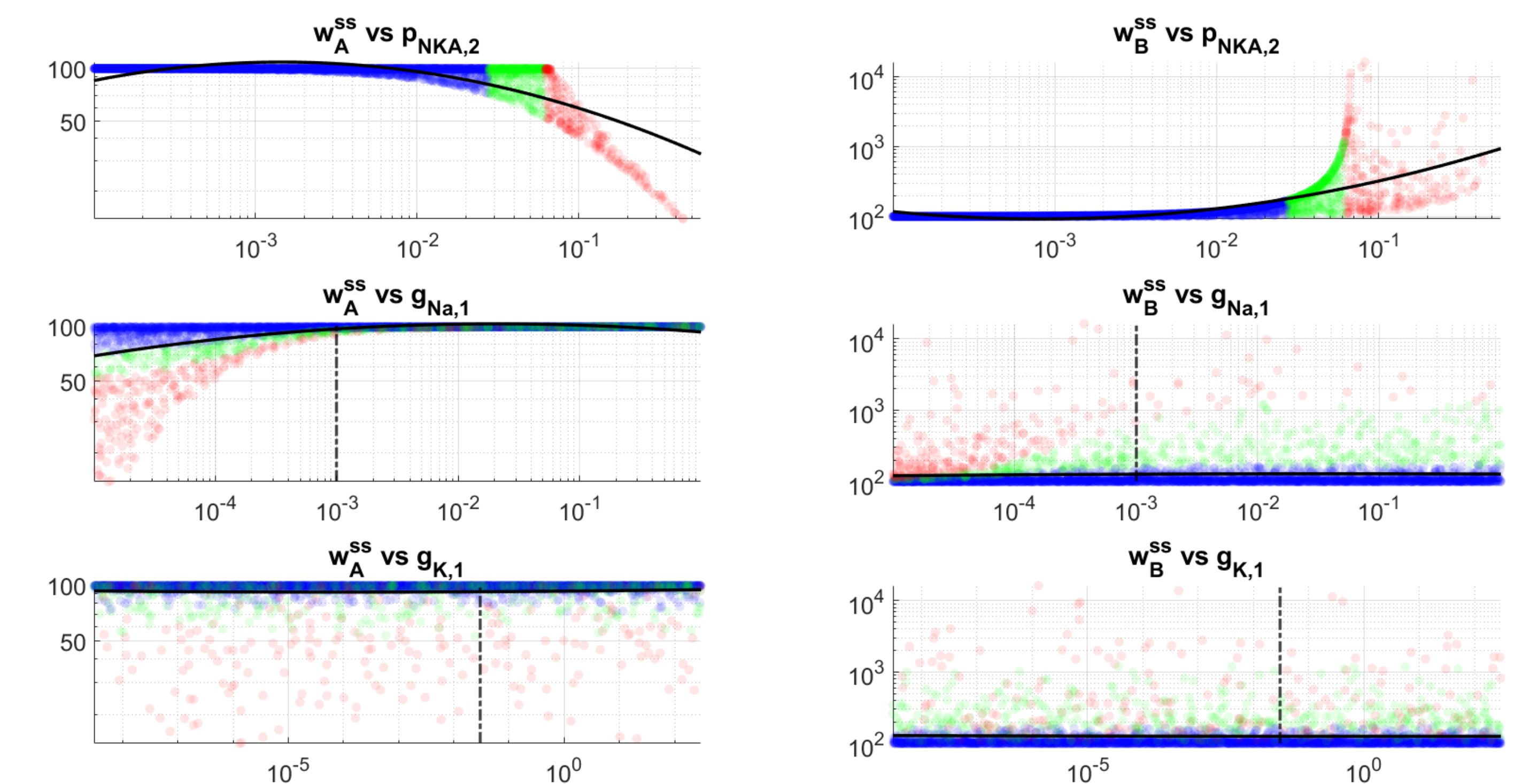
A schematic with Na⁺/K⁺-pump on side 2. In this configuration, for every hydrolysis of ATP, the Na⁺/K⁺-pump will transport 3 Na⁺ out of compartment A into B and 2 K⁺ into compartment A from B.

The steady state of this system is plotted as a function of the pump rate. The qualitative behavior of compartment A does not differ from the previous configuration. However, compartment B does change considerably. State variables of each compartment are plotted separately.



Sensitivity Analysis of Coupled PLE (side 2)

Sensitivity analysis shows the effects of pump placement and pump rate. As the pump rate is increased, the volume in compartment A decreases while B's increases. Volume in A will increase as Na⁺ conductance, along side 1, is increased. A similar trend appears in compartment B. K⁺ conductance has a negligible impact on both volumes.



Conclusions

This study extends the PLE to coupled systems, which are critical for modeling complicated biological structures such as epithelia. Analyzing the steady state behavior can provide valuable insights into the mechanisms effecting homeostasis in these systems. Furthermore, sensitivity analysis identifies key parameters influencing volume regulation.

The future directions include integrating transporters, such as KCC and NKCC, into the model to explore their interaction with the pump in regulating cell volume. In addition, we will explore the behavior of coupled systems for ion flux modeled by The Goldman-Hodgkin-Katz (GHK) equation and compare it with Ohm models explained here.