The Implications of Sodium and Potassium on Muscle Fatigue: Literature Review and Dynamic Mathematical Model Using STELLA® Software.

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Logan College of Chiropractic

JMPT TITLE PAGE

ARTICLE INFORMATION	
Article Title	The Implications of Sodium and Potassium on Muscle Fatigue: A Dynamic Mathematical Model Using STELLA® Software and Literature Review.
Key Words – only use **MeSH** terms that are found at http://www.nlm.nih.gov/mesh/meshhome.html Do not use non-MeSH key words	Action Potential; Fatigue; Electrolyte Balance; Sodium; Potassium; Resting Membrane Potential; Membrane Potential; Excitability; Skeletal Muscle
Running head - no more than 40 letters/ spaces	SODIUM AND POTASSIUM AFFECTING FATIGUE
Word count for structured abstract (approx 250 words or less)	
Word count for text (excludes abstract, acknowledgments, figure legends, and references);	
Practical Applications Three to 5 short sentences that highlight findings of the study. These statements should relate directly to the study findings.	There is a significant amount of evidence that supports that electrolyte balance of sodium and potassium does play a significant role in muscle fatigue. This information has not been cohesively brought together into an interactive model that has the potential to predict and project an athlete's short term fatigue due to the change of electrolytes that occurs during repeated muscle stimulation. This has enormous application beyond muscle as well, and could be later adapted to neural function, cardiac function, and any other excitable tissue.
Human Subjects If human subject data were used, state the name of the IRB/Ethics review board that reviewed this study in the Methods and here.	No human subjects were used; all modeling data came from existing literature.
Clinical Trial Registry If the study was a clinical trial, please include clinical trial registration number in the Methods and here.	The paper is a literature review with an accompanying dynamic model that has data from said reviewed literature.
Permission to Acknowledge	Robert Davidson, PhD. helped with the conception of the idea, guidance in developing the model, and

State the names of people who you are acknowledging and specifically how they contributed to the study. A signed letter of permission from *each* person and/or entity stating they give permission to the JMPT to print their name must be uploaded to the website at the initial time of submission.	with formatting of the paper. Amanda Anderson, DC helped with paper formatting.
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Conflicts of interest List any present or potential conflict s of interest for all authors. Include those listed in the ICMJE form.	There are no conflicts at this time.

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Abstract

Objective
Electrolyte imbalance has been reported to be a factor in muscle fatigue, namely the two main electrolytes, sodium and potassium, which are needed for generation of electrical potentials in the membrane of the muscle. The excitability of muscle membrane is absolutely essential for the contraction of muscle, thus if it is not excitable, contraction cannot occur. The purpose of this study is to describe muscle fatigue looking only at the shifts of electrolytes that occur during repeated muscle stimulation, and the effects, if any, on muscle contraction and fatigue.

Methods
The literature was systematically searched in PubMed and Google Scholar. Search terms included Muscle, Fatigue, Muscle Fatigue, Sodium, Potassium, Electrolytes, Membrane Potential, Resting Membrane Potential, Excitability, and Action Potential. Articles were excluded if they were irrelevant, or if there was a duplicate publication; articles published in non–peer-reviewed literature were also excluded. Included articles were filtered by being written in English.

Results
68 potentially relevant studies were read, and after review using inclusion and exclusion criteria, 29 articles were selected as being relevant to the effects of intracellular and extracellular levels of sodium and potassium ions on muscle force generation and fatigue.

Conclusion
Plasma electrolyte levels definitely appear to have a correlation with the muscle force generation and the rate of fatigue. However, the final evaluation of this hypothesis awaits more detailed modeling as well as the integration of some of the more specialized channels that affect the levels of intracellular and extracellular potassium and sodium, which have less of an effect on the resting membrane potential, but definitely introduce some error since these are excluded from the model. More refinement of the model is needed as well as more extensive testing of the model using human subjects and along with experimental data. It is however, clear that the diameter of the muscle fibers, the rate of the sodium-potassium ATPase, and the extensiveness of the t-tubular network play a significant role in skeletal muscle fatigue due to electrolyte imbalance and have a major impact on muscle excitability and thusly contraction.

Key Indexing Terms
Action Potential; Fatigue; Electrolyte Balance; Sodium; Potassium; Resting Membrane Potential; Membrane Potential; Excitability; Skeletal Muscle

Background

By definition, muscle fatigue is characterized by a loss of muscle power that results from a decline in both force and velocity of contraction (1). To distinguish fatigue from muscle weakness or damage, it is crucial to note that the loss of contraction force associated with fatigue is reversible by rest. Loss of membrane excitability due to electrolyte imbalance has serious utility in fields of athletic performance, cardiac function, kidney function, and neural function if the model is adapted to these other tissues. In fact, every living cell maintains its internal electrolyte balance within very narrow limits, while the kidneys and diet also maintain extracellular levels within narrow limits as well (1). Age and training status together with nutritional status modify muscle K^+ content as well as the abundance of Na^+-K^+ pumps (2). Despite modifying factors coming into play during muscle activity, the K^+ and Na^+ shifts with high-intensity exercise likely contribute substantially to fatigue in skeletal muscle (1). For example, the factors causing fatigue during high-intensity exercise are distinctively different from those precipitating fatigue during prolonged activity. The challenge is further complicated since muscle fatigue not only results from multiple factors acting at various sites, but in many cases effects are synergistic of two or more factors (19).

The purpose of this review is to describe the functional changes to the muscle cell membrane and the composition of sodium and potassium inside and outside the cells after periods of activity to fatigue. Other factors such as central fatigue, neuromuscular fatigue, muscular structural damage, and energy substrate depletion will be omitted from this review.

The following are the physiological steps of muscle contraction beyond the level of the nervous system to the muscle itself. In resting muscle cells, sodium and potassium are maintained within narrow limits both inside cells and outside the cells (15). The level of K^+

inside of resting muscle cells is on average about 159mM and outside of cells is about 4.5mM (21). This difference from outside versus inside of the myocyte creates a concentration gradient that tends to force potassium out of myocytes. Sodium is normally at a concentration of about 142mM outside of cells and about 9mM inside of cells at rest (21). This difference causes a concentration gradient that tends to force sodium into myocytes. These levels of electrolytes maintain a normal resting membrane potential of around -90mV (1). During an action potential, sodium floods into the muscle cell as voltage gated channels open when the muscle is stimulated and instantly thereafter, potassium is released in an effort to regain the -90mV membrane potential (15). With every action potential there is a small amount of potassium lost from the cell, and a small amount of sodium gained (1). It is easy to see that with high intensity stimulation of the muscle, the levels of sodium and potassium will be disturbed, which will in turn affect the membrane potential of the cell (21). Action potentials are absolutely essentially requisite before any muscle contraction can occur. This is why the levels of sodium and potassium are very important for muscle membrane excitability and thusly muscle fatigue.

Immediately after an action potential penetrates deep into the muscle cell, it stimulations receptors on the sarcoplasmic reticulum (the calcium storage organelle of the muscle cells), which causes a massive release of calcium into the cytoplasm of the muscle cell. This increase in intracellular calcium causes the mechanical cycle of contraction to begin (1). It is proposed that as muscle experiences "action potential degradation," the amount of calcium released per stimulation also is reduced (25). If there is a reduction of action potential amplitude affecting the receptors that release calcium, there will indeed be less calcium released per stimulation. If there is reduced calcium, there will be less activation of troponin by the binding of calcium. Troponin is the muscle protein that acts as a hinge which holds tropomyosin, a filamentous protein in front

of the two functional proteins, actin and myosin (1). When calcium is present in high concentration in the cytoplasm, troponin changes shape and moves the separating protein, tropomyosin out from in between actin and myosin (1). As long as the binding sites of actin are exposed to myosin, contraction will occur (1). However, if there is muscle fatigue due to action potential degradation, there will then be decreased release of calcium, and thusly an incomplete exposure of actin to myosin. This will cause a loss in power that is reversible by rest, which is fatigue (1).

If any one point of the chain of events that eventually leads to the union of actin and myosin is disturbed, this will lead to a loss of power (15). However, this review primarily looks at the action potential generation as prerequisite to all of the steps to contraction.

Methods

Several searches in PubMed were performed. The first search words used were sodium AND potassium AND " skeletal muscle" AND fatigue. The limits were set to human only, published in the last 30 years, written in English, and appeared to be credible sources. This search brought 115 results, 12 of which were relevant.

The second search was in PubMed and words used were "membrane excitability" AND "action potential" AND "skeletal muscle" AND fatigue. This search brought 10 results, 2 of which were relevant. The limits were set to human only, published in the last 30 years, written in English, and appeared to be credible sources.

The third search was in Google Scholar and words used were "goldman equation" AND "membrane excitability." This search yielded 52 results, 5 of which were relevant. There were no limits set for this search, only critical inspection of abstracts.

The fourth search was in Google Scholar and words used were "muscle fatigue" AND "electric stimulation" AND "action potential." This search yielded 183 results, 10 of which were relevant. There were no limits set for this search, only critical inspection of abstracts.

The medical search headings (MeSH) and their corresponding tree numbers were “muscle fatigue” G11.427.550, “skeletal muscle” A02.633, fatigue C23.888.369, sodium D01.268.549.750, potassium D01.268.549.550, electric stimulation E05.723.402, and action potential G04.580.100. The terms “membrane excitability,” “Goldman Equation,” and excitability did not have corresponding medical search headings.

Abstracts from all search results were reviewed for potentially relevant clinical studies on sodium and potassium levels affecting muscle fatigue. The following inclusion criteria were applied: the study had to have either sodium or potassium values before or after muscle contraction, and there could be no medications involved. The studies had to serve the function of building the mathematical model, which included important physiological data such as normal extracellular, intracellular, and plasma levels of sodium and potassium as well as other important information about the physical structure and rates of change of sodium and potassium during activity and recovery. We excluded all studies that were literature reviews, letters to the editors, abstracts, and non-English studies.

Additionally, Guyton & Hall Textbook of Medical Physiology 10^{th} edition was used along with some of the original sources for the book. The sources that came from these textbooks include animal studies and articles some of which are more than 70 years old cited in Guyton’s Physiology.

Results

Abstracts of 98 potentially relevant studies were read, and after review using inclusion and exclusion criteria, 29 articles were selected as relevant to the affect of serum electrolytes on muscle force generation. As of July 2012, a search using PubMed retrieved 98 potential articles. The rest were excluded for the following reasons. 35 were excluded because the study measured something other than potassium or sodium as the primary effect of the muscle force generation. 28 were excluded because they were letters, reviews, or only the abstract was available. 6 were excluded because there was not an attainable document.

The Changes of Sodium and Potassium Composition During Contraction/Stimulation

In resting muscle cells, concentrations of sodium and potassium are maintained within narrow limits. The level of K^+ inside of resting muscle cells is on average about 159mM and outside of cells is about 4.5mM (21). This difference from outside versus inside of the myocyte creates a concentration gradient that tends to drive potassium out of myocytes. Sodium is normally at a concentration of about 142mM outside of cells and about 9mM inside of cells at rest (21). This difference causes a concentration gradient that tends to drive sodium into myocytes. When an action potential is propagated along a myocyte, voltage gated sodium channels open and allow sodium to follow its concentration gradient inward.

The Causes of imbalance of Potassium and Sodium

T-tubules are a functionally important structure in muscle fibers that propagates action potentials deep into the cells to the sarcoplasmic reticulum where a release of calcium is then seen. According to Shorten et. Al, the tortuous nature of the highly branched space-filling t-tubule network significantly impedes the diffusion of material through the network. The effective diffusion coefficient for K^+ is equal to 19-27% of its value in free solution (3). A

similar decrease is seen for sodium. The t-tubule network impedes diffusion of potassium out of the muscle fibers and impedes sodium from entering muscle fibers as the muscles are being stimulated. This will lead to an accumulation of potassium in the T-tubule network, and a lack of sodium in the T-Tubule network during the most rapid of stimulation of the membrane (3). This is also demonstrated in the mathematical model created in STELLA. The authors determined that larger fibers are more vulnerable to accumulation of potassium than smaller diameter fibers, since a larger fiber an effectively farther distance that ions must diffuse to exit the muscle fiber (3). Therefore, the size of the fibers being analyzed is important to fatigability. The size of muscle fibers ranges from 5 to 100 microns in diameter, according to Shorten et al (3). In Guyton and Hall's Medical Textbook of Physiology, is seen that the larger diameter fibers, which are the fast twitch fibers also demonstrate the shortest time to fatigue which is in contrast to the small diameter slow twitch fibers (1), therefore this is consistent with the current knowledge of fiber type and fatigue time. It would likely be safe to assume that fast twitch muscles are more vulnerable to electrolyte related fatigue than slow twitch fibers.

Since there is an accumulation of potassium in the t-tubules and diffusion out of muscle is impaired by the t-tubule network, the Na^+-K^+ ATPase must work over-time to try to restore the imbalance caused by repeated stimulation of the muscle fibers (22). It is seen that the Na^+-K^+ ATPase will significantly increase its activity during muscle activity (22). However, it is clear that the stimulation rate can overcome the two main restorative mechanisms, diffusion and the Na^+-K^+ ATPase.

The relation of repeated stimulation to excitability

According to Bouclin et al., the effects of sodium and potassium together on membrane excitability are in fact synergistic (6). They found that the concomitant effect of an increased K^+

concentration in the extracellular space along with a decreased Na^+ in the extracellular space significantly cause a decrease in muscle membrane excitability and caused the membrane to become more depolarized overall (6). As the membrane becomes more depolarized, this will decrease the reactivity of voltage gated sodium channels (6), which makes the membrane unresponsive to signals from the motor neuron.

The Relation of Excitability to Force Generation and Fatigue

There has been a definite relationship between the force generated by muscle and its ability to generate action potentials for decades (20). It has been shown that if the muscle is impaired in its ability to propagate action potentials, this has a linear impairment of calcium release and thusly force generation (25, 13). According to Cairns et al., there is a decrease of force production as the membrane becomes more and more globally depolarized due to disturbances of electrolytes from high intensity stimulation (21). At the membrane potential of -55mV, the muscle produces 0% of its original tetanic force seen at -90mV (the normal membrane potential at rest) (21).

Logic in creation of the model

In this section, the data included in the model will be disclosed as well as the thought processes behind the various mechanisms of the model. To get a big picture view of how the model is put together, it is important to view the model first generally, and then it can be viewed in specific terms. All starting values that are included in the model are normal resting values for sodium and potassium in three compartments: intracellular, extracellular (t-tubular), and plasma. All rates of ion flow are calculated in terms of individual ions. All diffusion occurs from high

concentration to low concentration just as in real life. Stimulation is determined as hertz, which is cycles per second.

A very important input for the model includes the weight of the active muscle which is used to calculate the amount of intracellular and extracellular water, the amount of working Na^{+}-K^{+} ATPase, and the amount of working voltage gated sodium and potassium channels. Another important input is the body weight of the exercising person, which is used to calculate plasma volume.

Then, once we have all of the fluid compartments accounted for in specific volumes, we can use our normal values for electrolytes which are always seen as concentration values. These are usually in millimolar (mM) concentration values. These concentrations are then used to in conjunction with the volume to get a specific amount of moles of potassium and sodium for each compartment. These numbers are then converted using Avagadro's number to individual ions, which is a necessary step because the rates of the voltage gated channels and Na^{+}-K^{+} ATPase are given in flows of individual ions per pump per unit of wet weight of tissue. We have our starting values which are in units of individual ions, now we can watch the flows of these ions based on stimulation factors.

According to Sejersted et al., the Na^{+}-K^{+} ATPase has an in vivo maximum pumping rate of 450 Na^{+} and 300 K^{+} ions per second per pump, and the amount of Na^{+}-K^{+} ATPase on skeletal muscle is about 300 pmol/g of wet tissue weight (2). These two pieces of data along with the weight of the active muscle are used to determine the flow rate of the Na^{+}-K^{+} ATPase, which is crucial in determining how rapidly the electrolyte levels are restored.

Another crucial piece of information that determines the buildup and removal of sodium and potassium is the diffusion rate of the two electrolytes through the t-tubular network.

According to Shorten et al., the diameter of the t-tubules is approximately 18nm and the diameter of skeletal muscle fibers range from 5 to 200nm (3). They state that because of the extensive nature of the t-tubular network, the diffusion rate through the skeletal muscle is about 21% of each electrolyte's original rate of diffusion in free solution. They found that the apparent diffusion coefficient of sodium is 3.11×10^{-6} cm^2/s in the muscle t-tubules and is 14.8×10^{-6} cm^2/s in free solution. They also found that the apparent diffusion coefficient of potassium is 3.8×10^{-6} cm^2/s in the muscle t-tubules and is 18.3×10^{-6} cm^2/s in free solution (3). These two apparent diffusion coefficients in the t-tubular matrix were used to calculate the linear flow time of each electrolyte.

To determine the rate of diffusion of the electrolytes in T-tubules, we need to determine the mean cell diameter to determine an average rate of diffusion into the blood system. We are using 100micrometers (30) as the diameter for the skeletal muscle fibers. If this is the case, using πr^2, we can determine the area inside a cross section of the skeletal muscle cell, and thusly determine the time to diffuse out of the cell to the interstitial space outside of the t-tubular network once the ions are out of the t-tubules, they are free to enter the plasma.

πr^2=cross sectional area
$(50\text{micrometers})^2(3.14)$=7850micrometers^2 (this number is the cross sectional area of the myocyte)
7850 $\text{micrometers}^2 = 78.5 \times 10^{-6}$ cm

Cross sectional area/apparent diffusion coefficient for each ion = linear diffusion time
K+ time $=78.5 \times 10^{-6}$ $cm^2/3.8 \times 10^{-6} cm^2/sec$= 20.66 sec
Na+ time $=78.5 \times 10^{-6}$ $cm^2/3.11 \times 10^{-6} cm^2/sec$= 25.24 sec

These two time values are then input into the model in the form of half-lives using the half-life equation (29). This determines the rate of diffusion through the t-tubular space from high concentration to low concentration of each specific ion.

According to Sacco et al., 30 Hz of stimulation is well within the normal range of motor unit firing rates recorded from voluntary contractions of skeletal muscle (12). Therefore, when testing the model, we used 45Hz as our stimulation frequency to simulate elevated intensity contractions. We did not use 100Hz as our stimulation frequency, because according to Sejersted et al., skeletal muscle only achieves stimulation rates of 100 Hz for very brief periods and is not normally seen in muscle stimulated by motor neuron alone (2).

Another important rate is the rate in which sodium enters the cell and potassium exits the cell when the muscle is stimulated. According to Sejersted et al., both Na^+ and of K^+ will be 4–6 nmol * action potential^{-1} * g wet wt^{-1} in skeletal muscle (2). In other words, there is 4-6 nmol of both sodium and potassium exchanged per hz of stimulation per gram of wet weight. A value of 5 nmol per Hz per gram of wet weight was used in the model. This was a crucial data input for the model and was coupled with the stimulation selection of the muscle. The user can determine the various frequencies and thusly the magnitude that the ions are perturbed. By estimating the stimulation profile of the muscle, one can then watch the disturbance of the ions occur, and can see its effect on the membrane potential.

With stimulation in Hz, the rate of the Na^{+}-K^+ ATPase, rate of voltage gated channels, and rate of diffusion through the t-tubules one can then calculate the instantaneous values for the membrane potential using the Goldman-Hodkin-Katz equation (11). This is a well-known equation in the field of physiology. According to Cairns et al., the membrane potetial can be calculated for muscle fibers in exercising humans using the Goldman–Hodgkin–Katz (GHK) equation (described for 37◦C) which is (21):

$$E_m = 61.5 \log_{10}([[K+]I + \alpha[Na+]I + \gamma[Cl-]i]/[[K+]i + \alpha[Na+]i + \gamma[Cl-]I])$$

This equation then gives the voltage in mV of the membrane based on the levels of sodium and potassium. Chloride can be ignored, because its impact on the membrane potential is apparently very minimal (21).

The last piece of data was taken as a graphical expression input into the model demonstrating loss of force at a depolarized membrane potential that occurs during fatigue. This graph was taken from Cairns et al. (21).

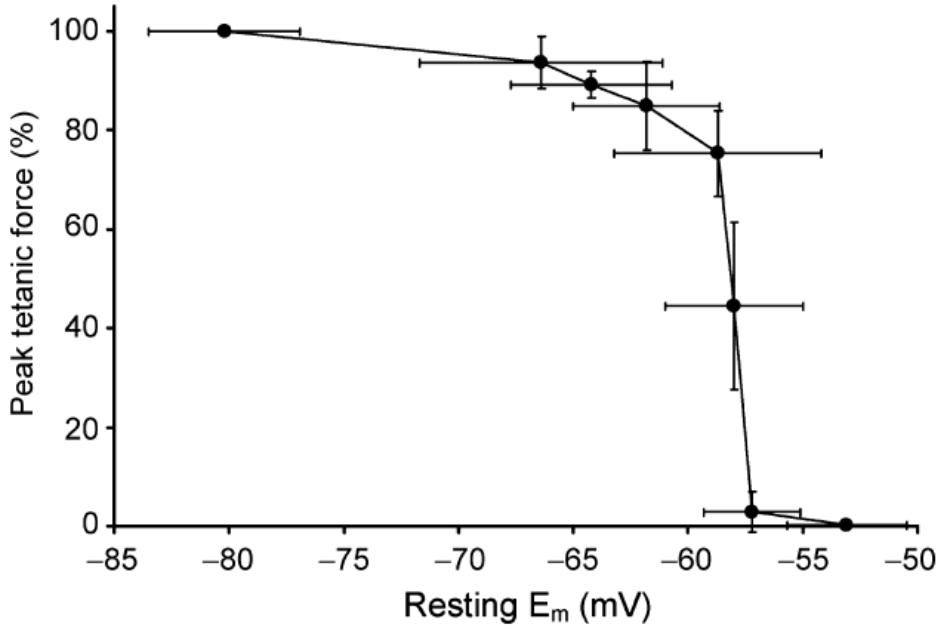


Figure 2. The influence of reduced transarcolemmal K^+ gradient on contractile force is mediated via depolarization of the resting E_m in isolated mouse extensor digitorum longus (EDL) muscle

Instantaneous data in the STELLA model of the membrane potential calculated from the Goldman-Hodgkin-Katz equation was input into this graphical function to give a determined percentage of the peak tetanic force (21).

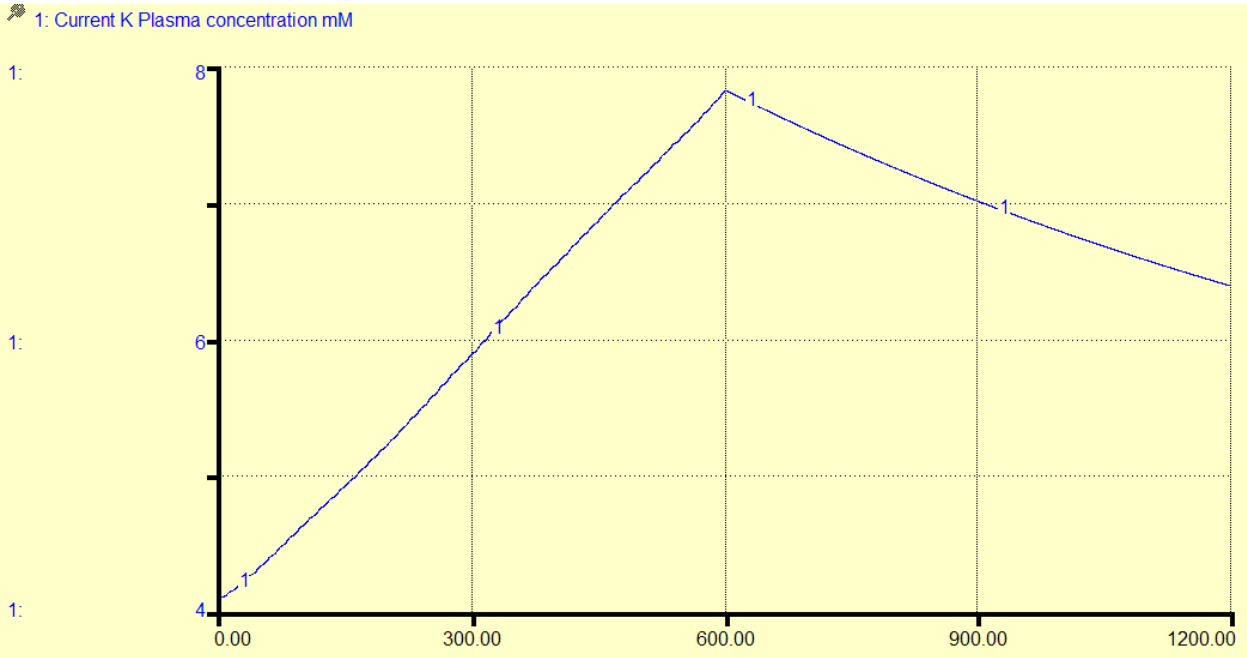
Summary of Data from the Literature Used in the Model

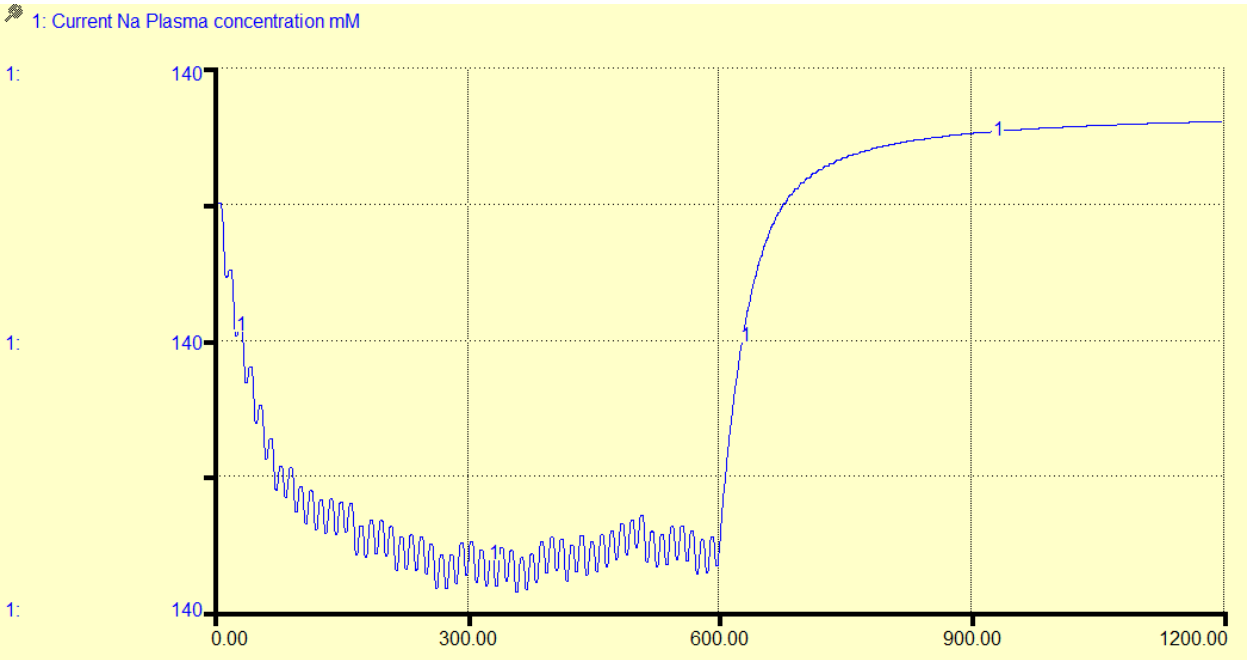
Numerical Value and Units	Application in the Model (source cited)
72.5%	This is a percentage of muscle which is water by mass (5).
9%	This is a percentage used to calculate the mass of extracellular fluid around a muscle (2).
20%	This is a percentage, which is the percent of body weight in kg that is plasma volume in L (1).
300 potassium ions per pump per second	The rate that the Na^{+}-K^{+} ATPase pumps potassium per pump (2).
450 sodium ions per pump per second	The rate that the Na^{+}-K^{+} ATPase pumps sodium per pump (2).
320 pmol/g of wet weight of tissue	The density of Na^{+}-K^{+} ATPase pumps in skeletal muscle tissue (2).
5 to 200 micrometers	The range of diameters of the skeletal muscle fiber (3).
3.11 x 10-6 cm2/s	The apparent diffusion coefficient for sodium (3).
3.8×10^{-6} cm^2/s	The apparent diffusion coefficient for potassium (3).
30Hz	Stimulation frequency for moderately strenuous exercise native to the motor neuron

	(12).
4–6 nmol * action potential^{-1} * g wet wt^{-1}	The amount of both sodium and potassium exchanged per hz of stimulation per gram of wet weight (1).
E m = 61.5 log10([[K+]I + α[Na+]I + γ[Cl−]i]/[[K+]i + α[Na+]i + γ[Cl−]I])	Goldman-Hodgkin-Katz Equation used to calculate membrane potential (21).

Data in Support of the Current Model

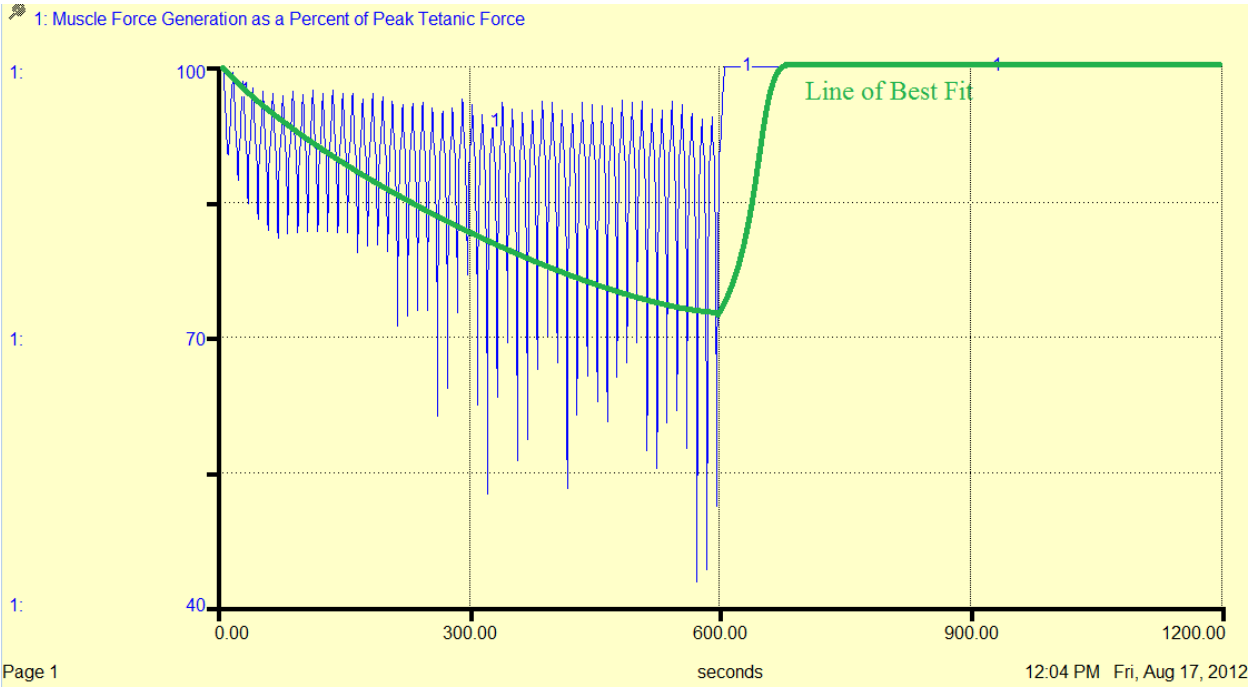
In most studies, the plasma and interstitial K^+ concentration reaches between 9 and 13.7 mM in human and mammalian muscle at exhaustion. This is increased far above the normal values of 4.3 to 5 mM seen at rest (9). Also, according to Bouclin et al., the changes of plasma Na^+ are very minimal in comparison increase seen with potassium (6). Also, active muscle mass will have a direct relationship with the changes in the electrolytes seen. Both of these points are seen in the model.





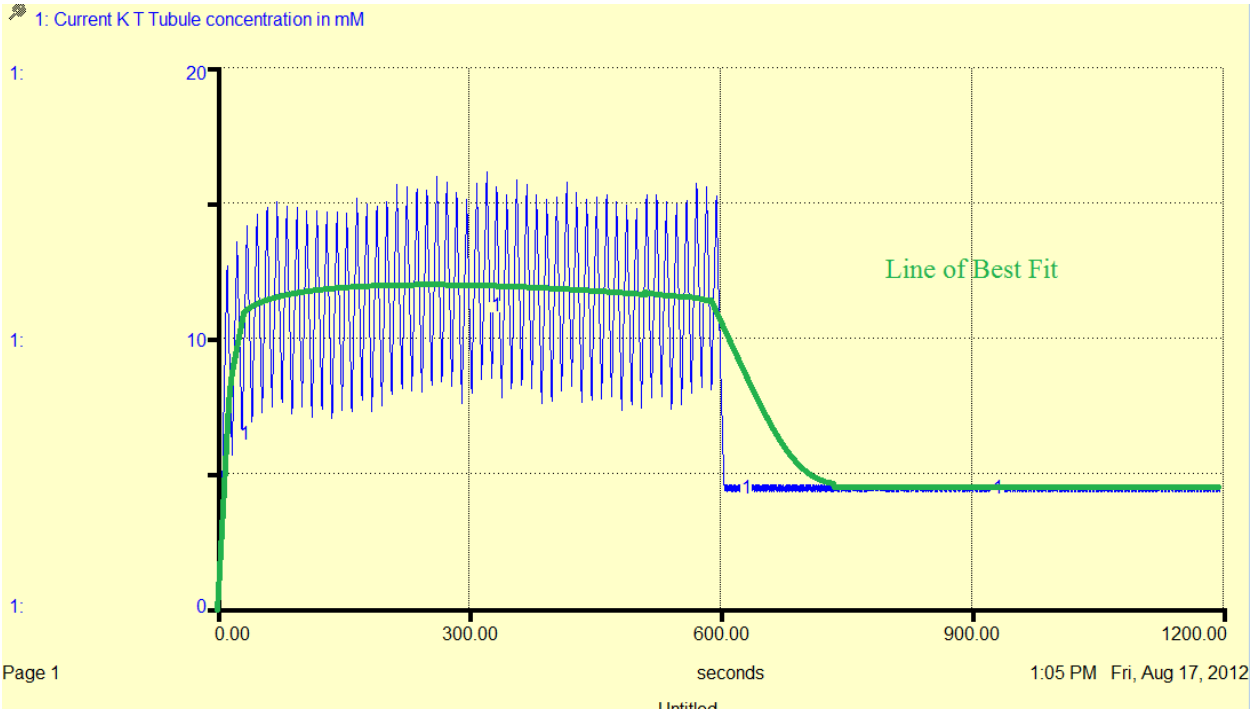
This pattern of increased changes of plasma potassium and minimal change in plasma sodium is seen at all scales of simulation run in the model in STELLA. The first graph shows changes in potassium in the model with the Na^+-K^+ ATPase at 100% capacity, with 4.2kg of

muscle active, with a total body weight of 70kg, and with an activity pattern of 50 total stimulations at 45Hz with a stimulation period of 3 seconds and a rest period of 3 seconds in between each stimulation, over a total time period of 600 seconds, or ten minutes. The peak plasma sodium concentration is just under 8 mM. This is consistent with experimental values recorded by Bouclin et al. as well as those seen by Cairns et. al (6, 9). The latter graph shows very minimal changes of plasma sodium level, which is also consistent with experimental values (6).



This figure shows the decrease in force generation of the muscle mass over the ten minute period. The current model shows an instantaneous recovery from the trough of force generation, this is because of many factors, one being that because of the complexity of the Na^+-K^+ ATPase, it is difficult to model its dynamics perfectly. The current version of the model shows rapid on off pulses of the Na^+-K^+ ATPase which are seen as very jagged highs and lows in the graphs, but if a line of best fit is draw, it is seen that the there is a smoother, more realistic graph of

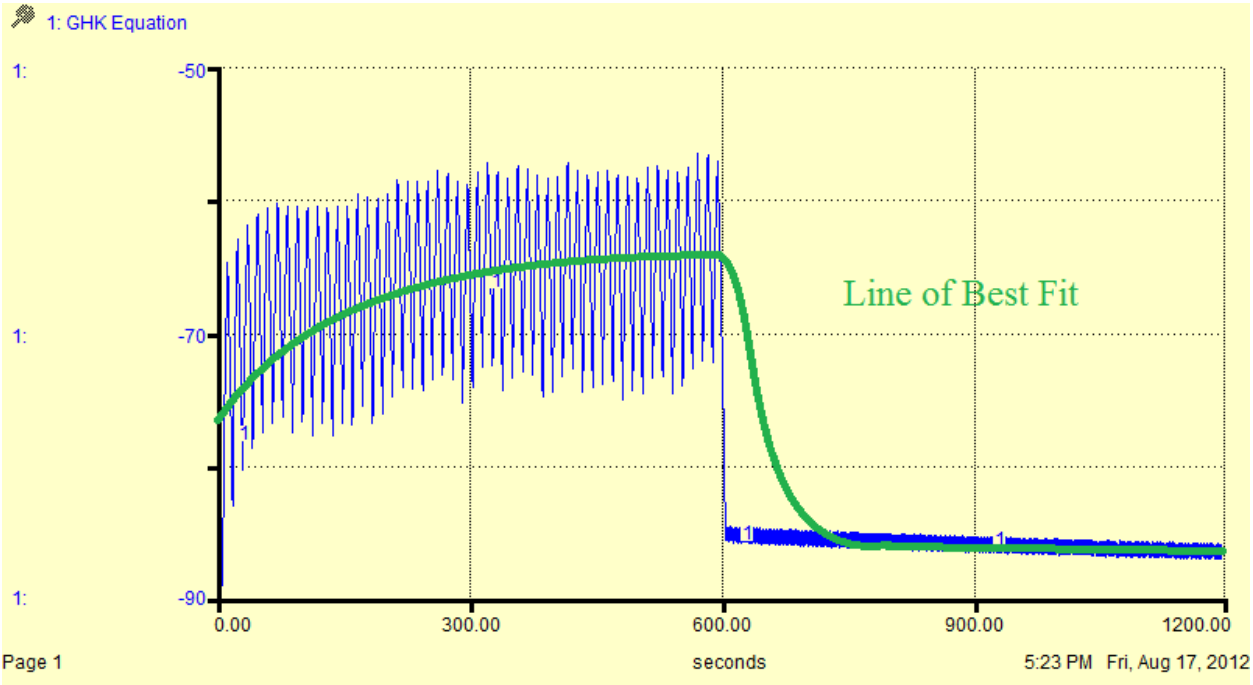
decreasing force generation. The recovery time on the line of best fit matches experimental values of 60 seconds of recovery time for electrolyte as well. This demonstrates a diminished power of contraction over time, which also demonstrates fatigue.



The two graphs above are from a trial of the model run with the Na^+-K^+ ATPase at 100% capacity, with 4.2kg of muscle active, with a total body weight of 70kg, and with an activity pattern of 50 total stimulations at 45Hz with a stimulation period of 3 seconds and a rest period of 3 seconds in between each stimulation, over a total time period of 600 seconds, or ten minutes.

The graph above demonstrates t-tubular potassium levels during the trial run. The average T-tubular potassium concentration during the trial was about 11mM, which is very close to data collected by Cairns et al. They have found that on average, extracellular K^+ is 10.5mM during intense exercise and the range of values during intense exercise is 9 to 13.7mM (21). The

peak levels of extracellular potassium are seen as about 15mM, while the valley is seem to be around 7.5mM in the simulation. This is very close to values seen in real life experimental values.



Limitations of the current version of the model

The current model has no regulation of the Na^+-K^+ ATPase outside of all on and all off. In real life, there is a smooth demand/output relationship that is allosterically modified based on specific demands placed on the enzyme (1). This is currently lacking from the model, which creates very jagged graphs that have highs and lows that fluctuate around the true value.

Another limitation of the current model is that blood flow to the muscle is not modeled at all. A complete tetanus to a muscle will greatly decrease blood flow to a few percentage points of its original amount of flow (18). This will lead to changes of ion composition that is different

than what is currently seen in the model, because the lumens of the t-tubular network become narrowed with every contraction (7). During normal exercise however in which there is not complete sustained tetany for long periods of time, also sympathetic activation and increased cardiac output during normal exercise causes the blood flow to be above normal resting flow with only brief impedances of flow during contraction (1, 10, 18). So for purposes outside of complete sustained tetany, the current model does not have large amounts of error without modeling blood flow if we assume instant mixing of plasma as is what the current model does.

Another factor that is not included in the model is the kidneys, diet, and perspiration affecting the plasma levels of the electrolyte. We excluded this from the model, because we primarily looked at short-term, high intensity exercise. In a period of 10 minutes, we concluded, it is unlikely that plasma electrolyte levels will have much time to fluctuate beyond caused by active muscle. However, more sustained activity will have a significant effect on the levels of the electrolytes of the muscles, and this will definitely have long term implications. This model is limited to predicting short term changes in electrolytes rather than changes over periods of hours or more.

The effect of age on the amount of Na^+-K^+ ATPase has been documented qualitatively, but consistent quantitative data on this is currently lacking (23). Another important piece of information is the effect of training on muscle Na^+-K^+ ATPase, efficiency of ATP production, circulation and other changes that occur that make the model not only more realistic but also more predictive of real life situations (1). Another variable lacking from the model is the substrates required for muscle contraction that definitely has an effect on the Na^+-K^+ ATPase, the Ca^{2+} active transporters on the sarcoplasmic reticulum, and last but certainly not least the functional proteins of the muscle themselves require ATP. There are also other channels other

than the Na^{+}-K^{+} ATPase and voltage gated channels that can affect the levels of potassium and sodium (17). If a more cohesive model was put together that could input all of these factors, one could predict the fatigability of virtually anyone.

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Appendix: Equations of the Model

Current_Potassium_Intracellular(t) = Current_Potassium_Intracellular(t - dt) + (K_Atpase - Voltage_Gated_K_Channels) * dt

INIT Current_Potassium_Intracellular = {Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1413 CONVERTED TO INDIVIDUAL POTASSIUM IONS IN MUSCLE USING THE WEIGHT OF THE MUSCLE}Normal_K_ions_Intracellular

INFLOWS:

K_Atpase =

IF(Current_K_T_Tubule_concentration_in_mM)>(Normal_K_Extracellular_Conc_in_mM) THEN(Current_K_ATPase_Rate) ELSE 0

OUTFLOWS:

Voltage_Gated_K_Channels = { Place right hand side of equation here... }IF GHK_Equation < -95 THEN 0 ELSE Na_and_K_ions_released_per_second_at_given_Stim_Frequency

Current_Potassium_Plasma(t) = Current_Potassium_Plasma(t - dt) + (K_Dif_Out - K_Dif_In_1) * dt

INIT Current_Potassium_Plasma = {Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1420}Normal_K_ions_Plasma

INFLOWS:

K_Dif_Out = { Place right hand side of equation here... } IF

(Current_K_T_Tubule_concentration_in_mM)>(Current_K_Plasma_concentration_mM)THEN

(((Current_Potassium_T_Tubule) - (Normal_K_ions_Extracellular_Muscle)) *

K_elimination_rate_constant) ELSE 0

OUTFLOWS:

K_Dif_In_1 = IF

(Current_K_Plasma_concentration_mM)>(Current_K_T_Tube_conc_in_mM)THEN

(((Maximum_K_Permissible_to_Enter) - Current_Potassium_T_Tubule) *

K_elimination_rate_constant) ELSE 0

Current_Potassium_T_Tubule(t) = Current_Potassium_T_Tubule(t - dt) + (K_Dif_In_1 +

Voltage_Gated_K_Channels - K_Dif_Out - K_Atpase) * dt

INIT Current_Potassium_T_Tubule = { Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1420}

Normal_K_ions_Extracellular_Muscle

INFLOWS:

K_Dif_In_1 = IF

(Current_K_Plasma_concentration_mM)>(Current_K_T_Tube_conc_in_mM)THEN

(((Maximum_K_Permissible_to_Enter) - Current_Potassium_T_Tubule) *

K_elimination_rate_constant) ELSE 0

Voltage_Gated_K_Channels = { Place right hand side of equation here... }IF GHK_Equation < -

95 THEN 0 ELSE Na_and_K_ions_released_per_second_at_given_Stim_Frequency

OUTFLOWS:

K_Dif_Out = { Place right hand side of equation here... } IF

(Current_K_T_Tubule_concentration_in_mM)>(Current_K_Plasma_concentration_mM)THEN

(((Current_Potassium_T_Tubule) - (Normal_K_ions_Extracellular_Muscle)) *

K_elimination_rate_constant) ELSE 0

K_Atpase =

IF(Current_K_T_Tubule_concentration_in_mM)>(Normal_K_Extracellular_Conc_in_mM)

THEN(Current_K_ATPase_Rate) ELSE 0

Current_Sodium_Intracellular(t) = Current_Sodium_Intracellular(t - dt) +

(Voltage_Gated_Na_Channels - Na_ATPase) * dt

INIT Current_Sodium_Intracellular = {Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1425 CONVERTED TO INDIVIDUAL

POTASSIUM IONS IN MUSCLE USING THE WEIGHT OF THE

MUSCLE}Normal_Na_ions_Intracellular

INFLOWS:

Voltage_Gated_Na_Channels = { Place right hand side of equation here... }IF GHK_Equation

>= 55 THEN 0 ELSE Na_and_K_ions_released_per_second_at_given_Stim_Frequency

OUTFLOWS:

Na_ATPase = {Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1424}

IF(Current_Na_Intracellular_concentration_mM)>(Normal_Na_Conc_Intracellular_mM)

THEN(Current_Na_ATPase_Rate) ELSE 0

Current_Sodium_Plasma(t) = Current_Sodium_Plasma(t - dt) + (Na_Diff_Out_1 -

Na_Diff_In_1) * dt

INIT Current_Sodium_Plasma = { Place initial value here... }Normal_Na_ions_Plasma

INFLOWS:

Na_Diff_Out_1 = { Place right hand side of equation here... } IF

(Current_Na_T_Tubule_concentration_in_mM)>(Current_Na_Plasma_concentration_mM)

THEN (((Current_Sodium_T_Tubule -

Normal_Na_ions_Extracellular_Muscle))*Na_elimination_rate_constant) ELSE 0

OUTFLOWS:

Na_Diff_In_1 = IF

(Current_Na_T_Tubule_concentration_in_mM)<(Current_Na_Plasma_concentration_mM)THE

N (((Maximum_Na_Permissible_to_Enter - Current_Sodium_T_Tubule)) *

Na_elimination_rate_constant) ELSE 0

Current_Sodium_T_Tubule(t) = Current_Sodium_T_Tubule(t - dt) + (Na_Diff_In_1 +

Na_ATPase - Na_Diff_Out_1 - Voltage_Gated_Na_Channels) * dt

INIT Current_Sodium_T_Tubule = Normal_Na_ions_Extracellular_Muscle

INFLOWS:

Na_Diff_In_1 = IF

(Current_Na_T_Tubule_concentration_in_mM)<(Current_Na_Plasma_concentration_mM)THE

N (((Maximum_Na_Permissible_to_Enter - Current_Sodium_T_Tubule)) *

Na_elimination_rate_constant) ELSE 0

Na_ATPase = {Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1424}

IF(Current_Na_Intracellular_concentration_mM)>(Normal_Na_Conc_Intracellular_mM)

THEN(Current_Na_ATPase_Rate) ELSE 0

OUTFLOWS:

Na_Diff_Out_1 = { Place right hand side of equation here... } IF

(Current_Na_T_Tubule_concentration_in_mM)>(Current_Na_Plasma_concentration_mM)

THEN (((Current_Sodium_T_Tubule -

Normal_Na_ions_Extracellular_Muscle))*Na_elimination_rate_constant) ELSE 0

Voltage_Gated_Na_Channels = { Place right hand side of equation here... }IF GHK_Equation

>= 55 THEN 0 ELSE Na_and_K_ions_released_per_second_at_given_Stim_Frequency

Activity_End_Time = { Place right hand side of equation here... }1

Activity_Selector = { Place right hand side of equation here... }0

Activity_Start_Time = { Place right hand side of equation here... }0

Amount_Of_Na_K_ATPase_Pumps_in_pmol = {Dynamics and Consequences of Potassium

Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1424}

(Muscle_Weight_in_wet_grams)*(Concentration_of_Pumps_Per_wet_g)

Avogadro's_Number_conv_for_individual_NA_K_ATPase_Pumps_channels = { Place right

hand side of equation here... } (pmol_to_mol)*(6.0221415)*(10^23)

Body_Weight_in_kg = { Place right hand side of equation here... }1

Concentration_of_Pumps_Per_wet_g = { Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

Constant_Stim_Hz_Slider = { Place right hand side of equation here... }0

Cross_Sectional_Area_Calculation_in_micrometers_squared = { Place right hand side of equation here... } (Fiber_Radius_in_micrometers^2) * 3.14159

Cross_Sectional_Area_in_cm_squared = { Place right hand side of equation here... }

Cross_Sectional_Area_Calculation_in_micrometers_squared * ((.0001)^2)

Current_K_ATPase_Rate = { Place right hand side of equation here... }

(Avogadro's_Number_conv_for_individual_NA_K_ATPase_Pumps_channels)*(Maximum_K_ATPase_Rate)*(Percent_of_Maxiumum_Na_K_ATPase_Rate)

Current_K_Extracellular_Dry_Grams = {Is this a believable amount of Potassium??}

(Current_Potassium_T_Tubule/((6.0221415)*(10^23)))*19

Current_K_Intracellular_concentration_mM =

(Current_K_Intracellular_in_mmol)/(Muscle_Intracellular_Volume_of_Water_in_L)

Current_K_Intracellular_in_mmol = { Place right hand side of equation here... }

(Current_Potassium_Intracellular/((6.0221415)*(10^23)))*1000

Current_K_Plasma_concentration_mM = { Place right hand side of equation here... }(Current_K_Plasma_in_mmol)/(Whole_Body_Plasma_Volume_in_L)

Current_K_Plasma_in_mmol = { Place right hand side of equation here... }(Current_Potassium_Plasma/((6.0221415)*(10^23)))*1000

Current_K_T_Tube_conc_in_mM = { Place right hand side of equation here... }(Current_K_T_Tube_mmol)/(Muscle_Extracellular_Fluid_in_L)

Current_K_T_Tube_mmol = { Place right hand side of equation here... }(Current_Potassium_T_Tubule/((6.0221415)*(10^23)))*1000

Current_K_T_Tubule_concentration_in_mM = { Place right hand side of equation here...

}(Current_K_T_Tubule_in_mmol)/(Muscle_Extracellular_Fluid_in_L)

Current_K_T_Tubule_in_mmol = { Place right hand side of equation here...

}(Potassium_T_Tube_Sum/((6.0221415)*(10^23)))*1000

Current_Na_ATPase_Rate = { Place right hand side of equation here... }

(Avogadro's_Number_conv_for_individual_NA_K_ATPase_Pumps_channels)*(Maximum_Na_

ATPase_Rate)*(Percent_of_Maxiumum_Na_K_ATPase_Rate)

Current_Na_Extracellular_Dry_Grams = {Is this a believable amount of Sodium??}

(Current_Sodium_T_Tubule/((6.0221415)*(10^23)))*23

Current_Na_Intracellular_concentration_mM =

(Current_Na_Intracellular_in_mmol)/(Muscle_Intracellular_Volume_of_Water_in_L)

Current_Na_Intracellular_in_mmol = { Place right hand side of equation here... }

(Current_Sodium_Intracellular/((6.0221415)*(10^23)))*1000

Current_Na_Plasma_concentration_mM = { Place right hand side of equation here...

}(Current_Na_Plasma_in_mmol)/(Whole_Body_Plasma_Volume_in_L)

Current_Na_Plasma_in_mmol = { Place right hand side of equation here...

}(Current_Sodium_Plasma/((6.0221415)*(10^23)))*1000

Current_Na_T_Tube_conc_mM = { Place right hand side of equation here...

}(Current_Na_T_Tube_mmol)/(Muscle_Extracellular_Fluid_in_L)

Current_Na_T_Tube_mmol = { Place right hand side of equation here...

}(Current_Sodium_T_Tubule/((6.0221415)*(10^23)))*1000

Current_Na_T_Tubule_concentration_in_mM = { Place right hand side of equation here...

}(Current_Na_T_Tubule_in_mmol)/(Muscle_Extracellular_Fluid_in_L)

Current_Na_T_Tubule_in_mmol = { Place right hand side of equation here...

}(Sodium_T_Tube_Sum/((6.0221415)*(10^23)))*1000

Current_Plasma_Potassium_Dry_Grams = {Is this a believable amount of Potassium??}

(Current_Potassium_Plasma/((6.0221415)*(10^23)))*19

Current_Sodium_Intracellular_Dry_Grams = {Is this a believable amount of Sodium??}

(Current_Sodium_Intracellular/((6.0221415)*(10^23)))*23

Diff_K_In_Conv_to_mol = { Place right hand side of equation here... } .001 *

Current_K_Plasma_concentration_mM * Muscle_Extracellular_Fluid_in_L

Diff_Na_In_Conv_to_mol = { Place right hand side of equation here... } .001 *

Current_Na_Plasma_concentration_mM * Muscle_Extracellular_Fluid_in_L

Duration_of_Stimulation_Rest_Cycles = { Place right hand side of equation here... }0

E_K = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } -60*LOG10

(K_in/K_out)

E_Na = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } -60*LOG10

(Na_in/Na_out)

Fiber_Diameter_in_micrometers = { Place right hand side of equation here... } 0

Fiber_Radius_in_micrometers = Fiber_Diameter_in_micrometers/2

GHK_Equation = { 21. Cairns, S. P. and Lindinger, M. I. Do multiple ionic interactions

contribute to skeletal muscle fatigue? The Journal of Physiology. 2008; 586 (16): 4039-54.

(page 4042)} 61.5 * LOG10(((Current_K_T_Tubule_concentration_in_mM + (.01 *

Current_Na_T_Tube_conc_mM)))/((Current_K_Intracellular_concentration_mM + (.01 *

Current_Na_Intracellular_concentration_mM))))

g_K = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } 10 +

PULSE(K_Amplitude, K_Interval, Reciprocal_K)

g_Na = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } 1 +

PULSE(Na_Amplitude, Na_Interval, Reciprocal_Na)

ions_of_Na_and_K_in_1nmol = { Place right hand side of equation here... }

0.000000001*(6.0221415)*(10^23)

K_Amplitude = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } 10

K_Diff_Half_Life_in_seconds = { (Anomalous ion diffusion within skeletal muscle transverse tubule Networks Paul R Shorten* and Tanya K Soboleva) }

Cross_Sectional_Area_in_cm_squared / (3.8 * (10^-6))

K_elimination_rate_constant = { Place right hand side of equation here... } LOGN(2) /

K_Diff_Half_Life_in_seconds

K_in = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Current_K_Intracellular_concentration_mM

K_Interval = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Reciprocal_K + .005

K_Intracellular_in_dry_grams = {Is this a believable amount of

Potassium??}(Current_Potassium_Intracellular/((6.0221415)*(10^23)))*19

K_out = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Current_K_T_Tubule_concentration_in_mM

Maximum_K_ATPase_Rate = {Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1424 {The number 300 is given as ions of Potassium per second per pump.} 300

Maximum_K_Permissible_to_Enter = { Place right hand side of equation here... }

Diff_K_In_Conv_to_mol * ((6.0221415)*(10^23))

Maximum_Na_ATPase_Rate = {Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1424 {The number 450 is given as ions of Potassium per second per pump.} 450

Maximum_Na_Permissible_to_Enter = { Place right hand side of equation here... }

Diff_Na_In_Conv_to_mol * ((6.0221415)*(10^23))

Membrane_Potential_mV = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } E_K * (g_K/(g_K+g_Na)) + E_Na * (g_Na/(g_Na+g_K))

Muscle_Extracellular_Fluid_in_L = {Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1448}

(Muscle_Weight_in_wet_grams)*.09/1000

Muscle_Intracellular_Volume_of_Water_in_L = { Body Water Spaces and Cellular Hydration during Healthy Aging

P. RITZa AND INVESTIGATORSb,c p. 477} (Muscle_Weight_in_wet_grams/1000)*.725

Muscle_Weight_in_wet_grams = { Place right hand side of equation here... }1000

Na_Amplitude = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } 10

Na_and_K_ions_released_per_second_at_given_Stim_Frequency = { Place right hand side of equation here... }

(Muscle_Weight_in_wet_grams)*(Release_of_Na_and_K_in_nmol_Per_Stim_per_g_of_wet_wt)*(Stimulation_Frequency_Hz)*(ions_of_Na_and_K_in_1nmol)

Na_Diff_Half_Life_in_seconds = { (Anomalous ion diffusion within skeletal muscle transverse tubule Networks Paul R Shorten* and Tanya K Soboleva) }

Cross_Sectional_Area_in_cm_squared / (3.11 * (10^-6))

Na_elimination_rate_constant = { Place right hand side of equation here... } LOGN(2) / Na_Diff_Half_Life_in_seconds

Na_in = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Current_Na_Intracellular_concentration_mM

Na_Interval = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Reciprocal_Na

Na_ions_Plasma_dry_grams = {Is this a believable amount of Sodium??}

(Normal_Na_ions_Plasma/((6.0221415)*(10^23)))*23

Na_out = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

Current_Na_T_Tubule_concentration_in_mM

Normal_K_Conc_Intracellular_mM = { Place right hand side of equation here... }

((Normal_K_ions_Intracellular)*1000)/((Muscle_Intracellular_Volume_of_Water_in_L)*(6.0221415)*(10^23))

Normal_K_Conc_Plasma_in_mM = {Converting the Data back to Concentration in mM to check the math, and for plugging it into Goldman-Hodgkins-Katz Equation}((Normal_K_ions_Plasma)*1000)/((Whole_Body_Plasma_Volume_in_L)*(6.0221415)*(10^23))

Normal_K_Extracellular_Conc_in_mM = {Converting the Data back to Concentration in mM to check the math, and for plugging it into Goldman-Hodgkins-Katz Equation}((Normal_K_ions_Extracellular_Muscle)*1000)/((Muscle_Extracellular_Fluid_in_L)*(6.0221415)*(10^23))

Normal_K_Extracellular_Dry_Grams = {Is this a believable amount of Potassium??}(Normal_K_ions_Extracellular_Muscle/((6.0221415)*(10^23)))*19

Normal_K_Extracell_mM = { Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040 } 4.5

Normal_K_Intracellular_in_dry_grams = {Is this a believable amount of Potassium??}(Normal_K_ions_Intracellular/((6.0221415)*(10^23)))*19

Normal_K_Intracell_mM = { Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040 } 159

Normal_K_ions_Extracellular_Muscle = {Na+ and K+ effect on contractility of frog sartorius muscle: implication for the mechanism of fatigue R. BOUCLIN, E. CHARBONNEAU, AND J. M. RENAUD C1528}

((Muscle_Extracellular_Fluid_in_L)*(Normal_K_Extracell_mM)*(6.0221415)*(10^23))/1000

Normal_K_ions_Intracellular = {Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1413 CONVERTED TO INDIVIDUAL POTASSIUM IONS IN MUSCLE USING THE WEIGHT OF THE MUSCLE}

((Muscle_Intracellular_Volume_of_Water_in_L)*(Normal_K_Intracell_mM)*(6.0221415)*(10^23))/1000

Normal_K_ions_Plasma = {Na+ and K+ effect on contractility of frog sartorius

muscle: implication for the mechanism of fatigue R. BOUCLIN, E. CHARBONNEAU, AND J. M. RENAUD C1528}

((Whole_Body_Plasma_Volume_in_L)*(Normal_K_Plasma_mM)*(6.0221415)*(10^23))/1000

Normal_K_Plasma_mM = { Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040} 4.1

Normal_Na_Conc_Intracellular_mM = { Place right hand side of equation here... }

((Normal_Na_ions_Intracellular)*1000)/((Muscle_Intracellular_Volume_of_Water_in_L)*(6.02 21415)*(10^23))

Normal_Na_Conc_Plasma_in_mM = {Converting the Data back to Concentration in mM to check the math, and for plugging it into Goldman-Hodgkins-Katz Equation}((Normal_Na_ions_Plasma)*1000)/((Whole_Body_Plasma_Volume_in_L)*(6.022141 5)*(10^23))

Normal_Na_Extracellular_Conc_in_mM = {Converting the Data back to Concentration in mM to check the math, and for plugging it into Goldman-Hodgkins-Katz Equation}((Normal_Na_ions_Extracellular_Muscle)*1000)/((Muscle_Extracellular_Fluid_in_L) *(6.0221415)*(10^23))

Normal_Na_Extracell_mM = {Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040} 142

Normal_Na_Intracell_mM = { Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040} 9

Normal_Na_ions_Extracellular_Muscle = {Na+ and K+ effect on contractility of frog sartorius

muscle: implication for the mechanism of fatigue R. BOUCLIN, E. CHARBONNEAU, AND J. M. RENAUD C1528}

((Muscle_Extracellular_Fluid_in_L)*(Normal_Na_Extracell_mM)*(6.0221415)*(10^23))/1000

Normal_Na_ions_Intracellular = { Dynamics and Consequences of Potassium Shifts in Skeletal Muscle and Heart During Exercise OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1425 CONVERTED TO INDIVIDUAL POTASSIUM IONS IN MUSCLE USING THE WEIGHT OF THE MUSCLE }

((Muscle_Intracellular_Volume_of_Water_in_L)*(Normal_Na_Intracell_mM)*(6.0221415)*(10^23))/1000

Normal_Na_ions_Plasma = {Na+ and K+ effect on contractility of frog sartorius muscle: implication for the mechanism of fatigue R. BOUCLIN, E. CHARBONNEAU, AND J. M. RENAUD C1528}

((Whole_Body_Plasma_Volume_in_L)*(Normal_Na_Plasma_mM)*(6.0221415)*(10^23))/1000

Normal_Na_Plasma_mM = { Do multiple ionic interactions contribute to skeletal muscle fatigue? S. P. Cairns and M. I. Lindinger p. 4040 } 140

Percent_of_Maxiumum_Na_K_ATPase_Rate = { Place right hand side of equation here... }0

pmol_to_mol = (Amount_Of_Na_K_ATPase_Pumps_in_pmol)*((10)^(-12))

Potassium_Current = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 } g_K * (Membrane_Potential_mV - E_K)/ 1398

Potassium_T_Tube_Sum = { Place right hand side of equation here... }

Current_Potassium_T_Tubule

Reciprocal_K = { Place right hand side of equation here... }1 / Stimulation_Frequency_Hz

Reciprocal_Na = { Place right hand side of equation here... }1/Stimulation_Frequency_Hz

Release_of_Na_and_K_in_nmol_Per_Stim_per_g_of_wet_wt = { Dynamics and Consequences of Potassium Shifts

in Skeletal Muscle and Heart During Exercise

OLE M. SEJERSTED AND GISELA SJ¯GAARD p. 1436 (4 - 6 nmol of both Na and K released per AP per gram of wet weight, we will use the value of 5 nmol per AP per gram of wet weight)} 5

Selected_Stimulation_Frequency_Pattern_in_Hz = { Place right hand side of equation here... }

IF TIME > Activity_Start_Time AND TIME <Activity_End_Time THEN (Stimulation) ELSE 1

Selected_Stimulation_Intensity_in_Hz = { Place right hand side of equation here... }1

sinewave = { Place right hand side of equation here... }SINWAVE(.5, 2* (Duration_of_Stimulation_Rest_Cycles))

Sodium_Current = { Hargrove, James L. Dynamic Modeling in the Health Sciences p.27 }

g_Na * (Membrane_Potential_mV - E_Na)/ -1398

Sodium_T_Tube_Sum = { Place right hand side of equation here... }Current_Sodium_T_Tubule

Stimulation = { Place right hand side of equation here... }Selected_Stimulation_Intensity_in_Hz * Time_Switch + 1

Stimulation_Frequency_Hz = { Place right hand side of equation here... } IF Activity_Selector = 0 THEN Constant_Stim_Hz_Slider ELSE Selected_Stimulation_Frequency_Pattern_in_Hz

Time_Switch = { Place right hand side of equation here... } IF sinewave > 0 THEN 1 ELSE 0

Total_Activity_Time = { Place right hand side of equation here... }Activity_End_Time - Activity_Start_Time

Total_Stimulations = { Place right hand side of equation here... }Total_Activity_Time / (Duration_of_Stimulation_Rest_Cycles * 2)

Whole_Body_Plasma_Volume_in_L = {Textbook of Medical Physiology. Guyton & Hall, ed.10 Ch 25 p. 265-266}Body_Weight_in_kg*.2

Potential_Force_Generation_as_a_Percent_of_Peak_Tetanic_Force = GRAPH({ 21. Cairns, S. P. and Lindinger, M. I. Do multiple ionic interactions contribute to skeletal muscle fatigue? The Journal of Physiology. 2008; 586 (16): 4039-54. (page 4041) }GHK_Equation)

(-100, 100), (-94.9, 100), (-89.7, 100), (-84.6, 100), (-79.5, 98.0), (-74.4, 96.0), (-69.2, 92.0), (-64.1, 90.0), (-59.0, 78.0), (-53.8, 5.00), (-48.7, 0.00), (-43.6, 0.00), (-38.5, 0.00), (-33.3, 0.00), (-28.2, 0.00), (-23.1, 0.00), (-17.9, 0.00), (-12.8, 0.00), (-7.69, 0.00), (-2.56, 0.00), (2.56, 0.00), (7.69, 0.00), (12.8, 0.00), (17.9, 0.00), (23.1, 0.00), (28.2, 0.00), (33.3, 0.00), (38.5, 0.00), (43.6, 0.00), (48.7, 0.00), (53.8, 0.00), (59.0, 0.00), (64.1, 0.00), (69.2, 0.00), (74.4, 0.00), (79.5, 0.00), (84.6, 0.00), (89.7, 0.00), (94.9, 0.00), (100.0, 0.00)