A Comprehensive Mathematical Framework for Modeling Intestinal Smooth Muscle Cell Contraction with Applications to Intestinal Edema*

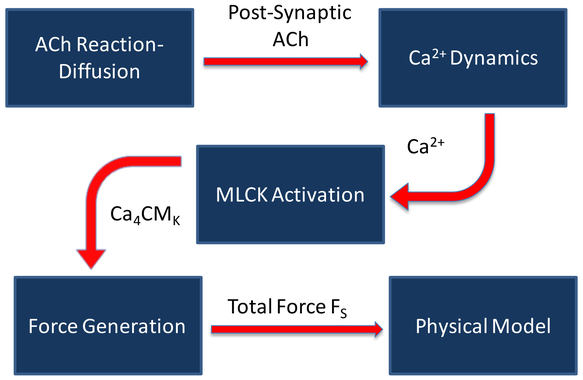
Muhammad Shamim and Jennifer Young Ph.D.
Department of Computational and Applied Mathematics, Rice University, Houston, Texas

Summary

- Contraction of intestinal smooth muscle cells (ISMCs) is a complex process, involving the enteric nerve system, membrane channels, and actin-myosin interactions.
- Motivating factor is to study ileus, decrease in ISMC contractility. Ileus correlates with edema, accumulation of interstitial fluid, but link remains unknown.
- Hypothesis: increased synapse size dilutes neurotransmitters, decreasing contraction response, causing ileus.
- Comprehensive model from enervation to contraction supports to causation relation between edema and ileus.
- Model successfully replicates data from animal studies.

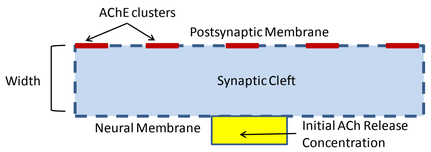
Biochemical Reactions

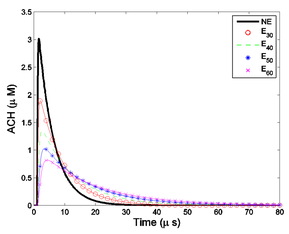
- Coupled chemical reactions



- Acetylcholine (Ach) diffusion modeled using reaction-diffusion model on two dimensional space

$$\frac{dc(\mathbf{x},t)}{dt} = \nabla \cdot D\nabla c(\mathbf{x},t) \qquad \mathbf{n}(\mathbf{x}) \cdot D\nabla c(\mathbf{x},t) = \begin{cases} -kc(\mathbf{x},t) & \text{on } \partial\Omega_{AChE} \\ 0 & \text{on } \partial\Omega - \partial\Omega_{AChE} \end{cases}$$

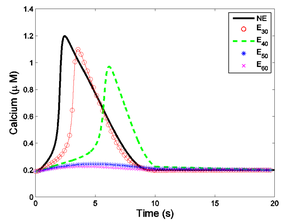




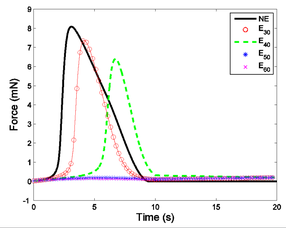
- Increasing cleft width decreases peak Ach concentration

Biochemical Reactions (Contd.)

- IP3 pathway allows Ach to alter membrane potential, which alters Ca^{2+} concentration. This in turn affects Actin-Myosin phosphorylation. These chemical reactions were modeled using nonlinear ODEs and solved using RK4.

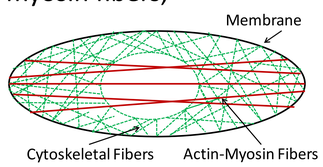


$$\frac{d\vec{y}}{dt} = f(\vec{y})$$



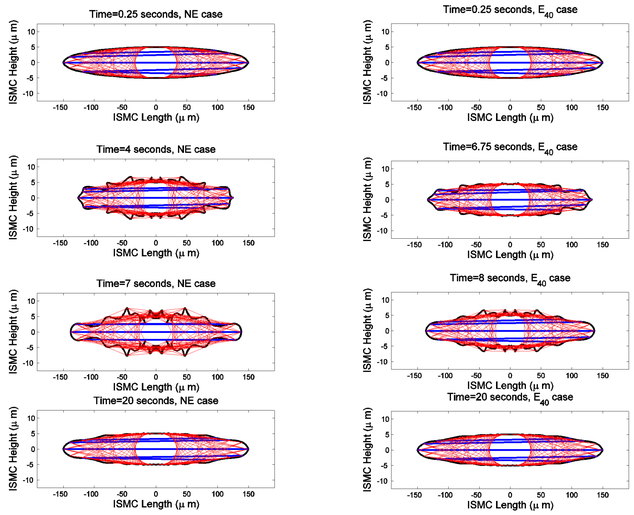
Physical Model

- Cell membrane, cytoskeleton, actin-myosin fibers, and cellular fluid drag modeled using two dimensional Hookean spring system.



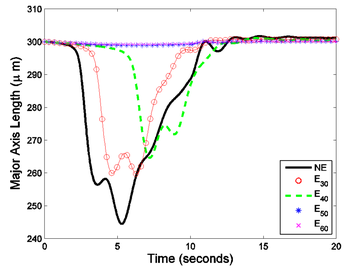
$$m_i\ddot{\mathbf{x}}_i = F_M^i(t) + F_C^i(t) + F_S(t) - \beta\dot{\mathbf{x}}_i$$

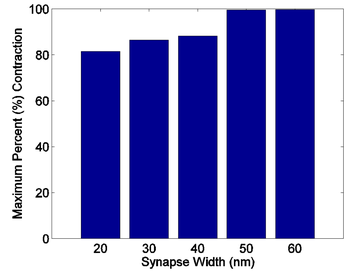
- Newton's Law ODE system solved using RK4.
- Figures below show ISMC contraction for two cases, cleft width is 20 nm on left, 40 nm on right. Figures on the right model edematous conditions with decreased contractility.



Results

- Increased synaptic cleft distance resulted in lower Ach and Ca^{2+} concentrations and decreased force generation and contraction.
- Unexpected sharp decline past cleft width of 40 nm





- Results match data from Texas Medical Center study of contraction in edematous intestinal muscle cells in rats.

Conclusion

- Increased synaptic cleft distance results in lower ISMC contractility.
- Comprehensive model successfully replicates edematous and non-edematous conditions in ISMCs, matching data from animal studies.
- Model supports causation relation between ileus and edema.
- Unexpected contractility threshold between 40-50 nm will be subject of future work.

References

1. Young, Shamim, et al. *A Comprehensive Mathematical Framework for Modeling Intestinal Smooth Muscle Cell Contraction with Applications to Intestinal Edema.* (Submitted) J BIOMECH 2012.
2. Gajendiran and Buist. *A quantitative description of active force generation in gastrointestinal smooth muscle.* INT J NUMER METHOD BIOMED ENG 2011.
3. Imtiaz et al. *A theoretical model of slow wave regulation using voltage-dependent synthesis of inositol-1,4,5-trisphosphate.* BIOPHYS J 2002.
4. Koenigsberger et al. *Ca^{2+} dynamics in a population of smooth muscle cells: modeling the recruitment and synchronization.* BIOPHYS J 2004.
5. Young and Mitran. *A numerical model of cellular blebbing: A volume-conserving, fluid-structure interaction model of the entire cell.* J BIOMECH 2010.

*This study was supported by NSF grant: DMS 0739420.