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Synchronization of regional contractions of human labor; direct effects of region size and tissue excitability

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ABSTRACT

The mechanisms used to coordinate organ-level contractions of human labor are not universally accepted. We previously proposed a dual mechanism, where electrical activity coordinates cellular contractions into tissue-level regional contractions, and mechanotransduction synchronizes the regional contractions into organ-level contractions. The simulation of this model successfully recapitulates the phasic pressure rises typical of human labor. In this work we extend the simulation to probe the effects of three critical parameters: electrical coupling (which defines functional regions within the uterine wall), enhancement of contractile responses during action potential bursts (action potential multiplier), and the threshold for mechanical recruitment of regional myometrial contractions (threshold). We test how changing the values of these parameters modulates the ability of the uterus to generate synchronized organ-level contractions. Simulations are performed using Mathematica and a non-classical cellular automaton program we recently published. At least 15 regions are necessary to generate physiologically relevant, synchronized contractions. Organ-level synchronization was improved using higher values for the action potential multiplier. At lower values of the action potential multiplier, synchronized contractions were inhibited when the number of regions was between 32 and 44, suggesting a critical level of electrical coupling is necessary at the onset of labor. Large numbers of low threshold regions resulted in contraction patterns suggestive of hyperstimulation. This work furthers support for the electrical–mechanotransduction mechanism for organ-level synchronization of uterine contractions. The mathematical simulation provides insight regarding how cellular- and tissue-level physiology converge to express synchronized contractions of human labor.

1. Introduction

The mechanisms used to coordinate organ-level uterine contractions of human labor are controversial (Young, 2007). It is clear that the ability of the myometrium to generate and propagate action potentials is crucial for recruiting myometrial tissue to participate in labor contractions (Garfield et al., 1988). However, it is likely that the action potential propagation is not sufficient as the *only* mechanism for synchronizing the contractions of all areas throughout the entire uterus (Young and Goloman, 2011). Recently we have proposed a second mechanism for organ-level, recruitment of regional contractions (Young and Barendse, 2014).

The complete mechanism, and the evidence used to develop the mechanism are presented in detail in Young and Barendse (2014). The fundamental basis of our proposed dual mechanism is that there exists a limit on the propagation distance of a single tissue-level action potential (Lammers et al., 2008). Thus, we proposed, electrical activity rapidly recruits and coordinates cellular and tissue-level contractions over short distances (on the order of centimeters), and this distance effectively defines functional regions. The more highly excitable regions contract first, which increases intrauterine pressure slightly. The increased pressure increases uterine wall tension, which directly initiates contractions of the next most excitable regions via a mechanotransduction mechanism that we have previously called the myometrial myogenic response (Young and Barendse, 2014). The contractions of those regions further increase intrauterine pressure. Using this dual electrical–mechanotransduction mechanism, a small population of relatively excitable regions can synchronize the contractions of all regions throughout the entire uterus.

The mathematical formulation of this model successfully produced many of the pressure–time curves commonly observed in women in labor. The input parameters of the simulation were, wherever possible, designed to directly relate to parameters clinically observable at the organ-level, or experimentally observable at the tissue-level. The key organ-level parameter is resting intrauterine pressure. Tissue-level

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parameters include the maximum duration of the action potential burst, the refractory period, and the enhancement of tissue contractility caused by electrical activity. Increasing electrical coupling between myocytes is thought to increase the distance action potentials can travel in tissue, hence sets the effective size of the regions.

In this paper, we focus on how uterine contractility changes as a function of three key parameters – the electrical coupling, the mechanotransduction threshold, and the enhanced contractility caused by electrical activity. Within the program, these parameters are simulated using the number of regions (electrical coupling), threshold distribution (mechanotransduction threshold) and the action potential multiplier (enhanced contractility caused by electrical activity).

1.1. Theoretical model

The primary goal of the model is to determine intrauterine pressure as a function of time. This was chosen specifically because phasic pressure rises define the character of human labor, and measuring pressure generation is the gold-standard method to determine if a patient is in-labor or not-in-labor.

In a closed sphere filled with an incompressible fluid, the tension contributes increasing intrauterine pressure through the Law of Laplace

$$P = 2T \times w/r \tag{1a}$$

where T is the maximum tension, P is the intrauterine pressure, w is wall thickness, r is the local radius of curvature. When a region experiences an action potential burst, tension is generated. As in the original program, we arbitrarily set the maximum numerical value for tension that each region can generate equal to 10. However, if the region resides at an anatomical location where the wall is thick and the local radius of curvature is small, the contribution of a region to the total pressure may be greater than 10.

While pressure is clinically quantified using Montevideo units, here we calculate the "impulse" by integrating the pressure over time. Here, "impulse" refers to the Newtonian impulse, not the action potential as an impulse. We also introduce a "synchronization parameter", which approximates the strength and degree of organ-level synchronization of contractions. We define synchronization based two criteria. For perfectly synchronized contractions: 1) Each region contracts in-phase with the other regions; 2) All regions are either contracting or in the refractory state, but not in the quiescent state. To quantify synchronization, we first examine the pressure–time plot to ensure the regional contractions occur in-phase, then we define:

Impulse: the integral of pressure–time curve averaged over the time studied.

Synchronization: the impulse observed/(maximum tension of one region *x* maximum possible time spent bursting).

Maximum possible time spent bursting: the burst duration/(refractory duration + burst duration).

To express the synchronization parameter as a percentage, we multiply by 100. Converting T to P requires considering w and r (Eq. 1a), so synchronization values can exceed 100. Values less than 20 indicate poor synchronization (or no contractions expressed), values over 50 indicate a moderate degree of synchronization, values over 75 a high degree of synchronization, and values over 100 indicate a very high degree of synchronization.

The contractile status of each region depends on the tension experienced by that region. Contraction of each region subsequently causes an incremental intrauterine pressure rise. Increased pressure, in turn, directly increases uterine wall tension throughout the entire uterine wall (Eq. 1a), which subsequently enhances the myogenic recruitment of less excitable regions.

In our model we vary the threshold for mechanically initiating a contraction for each region. The threshold value assigned to each region simulates the relative ability of that region to contract in response to wall tension. Thresholds are assigned based on pseudorandomly selected values from a Weibull distribution. If the regional tension exceeds the assigned threshold, the region will experience an action potential burst and the tension is then increased by applying a multiplier which we call the AP multiplier. A burst can only last a maximum time (maximum burst duration), after which a refractory period is applied. The refractory state is modeled by multiplying the tension by a number less than 1 for a maximum time (refractory duration).

Table 1
Input variables used in the program. The function, name within the program, and range of values corresponding to each variable are displayed.

Input variable	Function	Name in program	Range of values
Time steps	Defines iterations to run program	timesteps	50–500
average APdistance	Average distance an action potential can travel	aveAPdistance	3–13 cm
starting pressure	First pressure of simulation	initialpressure	0.1–3
minimum pressure	Lowest pressure allowed	minpressure	0.1–0.5
Maximum burst duration	Max iterations for bursting behavior	timeburst	5–15
refractory duration	Max iterations for refractory period	timerefractory	5–30
Action Potential Multiplier	Multiplier used to enhance force produced during a burst	burstmultiplier	1–10
refractory multiplier	Multiplier used to reduce force produced during the refractory period	refractorymultiplier	0–0.5
anatomy distribution curve shape	Shape of Weibull distribution	weibullvar1	1.2–3
anatomy distribution curve scope	Scope of Weibull distribution	weibullvar2	0.4–1.2
anatomy distribution curve lowest value	Lowest value of Weibull distribution	weibullvar3	0.1–0.6
anatomy pseudorandom number generator seed	Seed used to select numbers pseudorandomly from the distribution	random1	1000–2000
threshold distribution curve shape	Shape of Weibull distribution	weibullvar4	2–10
threshold distribution curve scope	Scope of Weibull distribution	weibullvar5	0.1–1
threshold distribution curve lowest value	Lowest value of Weibull distribution	weibullvar6	0.1–1
threshold pseudorandom number generator seed	Seed used to select numbers pseudorandomly from the distribution	random2	2000–3000
action potential distance distribution curve shape	Shape of Weibull distribution	weibullvar7	3–20
action potential distance distribution curve scope	Scope of Weibull distribution	weibullvar8	0.5–2
action potential distance distribution curve lowest value	Lowest value of Weibull distribution	weibullvar9	0.02–0.1
action potential distance pseudorandom number generator seed	Seed used to select numbers pseudorandomly from the distribution	random3	3000–4000

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