Ankle sprains are the most common musculoskeletal injury in sport and military physical activities requiring medical care, with estimated prevalence as high as 10–12% (Ruscio et al., 2010; Doherty et al., 2014). Among individuals who experience a first-time sprain, 40% will go on to develop chronic ankle instability, which can lead to recurrent sprains, time lost at work, and decreased quality of life (Doherty et al., 2016). Better preventative interventions are needed to reduce the burden of sprains on individuals and healthcare systems.

The most strongly recommended intervention to date for prevention of first-time or recurrent lateral ankle sprains is use of a semi-rigid brace during high-intensity physical activity (Newman et al., 2017; Martin et al., 2021). However, negative perceptions of ankle braces among users and prescribing clinicians exist, which influence use and abandonment, such as: interference with mobility, low satisfaction with comfort, and risks of dependency or decreased muscle strength over time (Gross and Liu, 2003; Denton et al., 2015; Dierker et al., 2017).
A framework to directly study sprain mechanics while rapidly testing different prophylactic strategies across varied users and movements could accelerate innovation. Direct measurement of sprain mechanics with injury potential is unethical, and thus sub-injury experiments on human subjects (e.g., “inversion platforms” (Ha et al., 2015)), or laboratory study on post-mortem models, have been the standard. However, such approaches do not fully represent sprain-causing motion and loads, or are time and cost intensive even with small sample sizes.

Computational simulation of musculoskeletal injury can supplement experiments to bridge these gaps (Seth et al., 2018). Forward dynamic, muscle-driven simulation has been used to isolate relative influences of foot positioning (Wright et al., 2000b), passive ankle flexibility (Wright et al., 2000a), and invertor/evertor muscular control on ankle sprain occurrence (DeMers et al., 2017). Modeling assumptions are often a primary limitation, although expected uncertainties can be incorporated with probabilistic techniques to increase confidence (Myers et al., 2015). Probabilistic simulations have been used to inform design of orthopaedic joint implants (Easley et al., 2007), quantify the influence of ankle-foot orthosis design on muscle mechanics in children with cerebral palsy (Hegarty et al., 2017), and to evaluate prophylactic roles of neuromuscular control versus movement strategy in sport knee injury (McLean et al., 2008). An efficient, probabilistic musculoskeletal simulation framework to study ankle sprain biomechanics that incorporates both intrinsic human factors and extrinsic factors has yet to be tested.

The primary purpose of this study was to extend a deterministic, subject-specific ankle sprain model for efficient, probabilistic simulation. Parameter sensitivities were characterized, and probabilistic predictions were validated against the original model and reports of real sprain occurrences.

**METHODS**

**Musculoskeletal Model**

A publicly-available musculoskeletal model was expanded upon for this study (DeMers et al., 2017) (Figures 1A). Briefly, the whole-body model (49 muscles, 21 degree-of-freedom) contained elastic foundation foot-ground contact (Seth et al., 2018) and lumped passive ankle stiffness represented by an uncoupled, rotation-only bushing (Chen et al., 1988). Joint motion was driven by custom stretch-reflex feedback muscle controllers. For baseline validation, the generic model anthropometry was scaled to a single human subject (female, 68 kg, 180 cm), and muscle control parameters optimized to track whole-body joint kinematics measured via 3D motion capture during a 40 cm drop onto a level surface. The model also had a landing platform that could be inclined to induce virtual inversion sprains. The
unmodified, subject-specific model was used as the mean baseline model for probabilistic simulations.

We also extended the baseline model with a representation of external, ankle-foot structural support (e.g., a brace, Figure 2). The rotation-only bushing representing passive anatomy was first duplicated, then scaled to represent adjustable magnitudes of bracing acting in parallel with passive anatomy. Specifically, angular displacement data was multiplied with a fixed factor (i.e., scaling flexibility (Wright et al., 2000a)), such that a brace with a 150% multiplier would be 50% less flexible than the model’s passive anatomy. This approach was chosen as ankle flexibility versus compliance (scaled torque at fixed displacements) –has been suggested to be more influential in sprain prevention (Wright et al., 2000a).

**Probabilistic Simulation**

After verifying reproducibility of the baseline deterministic simulation (DeMers et al., 2017), we assigned probabilistic distributions to 10 input parameters expected to influence sprain occurrence (Table 1). Mean values were kept equal to the baseline model, while assumed variances were relatively minor perturbations aimed to preserve validity of the baseline model (Table 1). Monte Carlo (MC) simulations with 1000 trials were instantiated with random sampling (NESSUS, v9.8.0, SwRI, San Antonio, TX) and executed via the MATLAB-OpenSim API (version 3.3). Six separate probabilistic simulations were generated with a level or 30-degree inclined landing surface; each using a common set of 7 parameter distributions and a combination of muscular co-activation, reflexive gain, and external bushing stiffness (Table 1).

**Data Analysis**

Rotational kinematics of the ankle were kept as defined in the baseline, generic OpenSim model. Briefly the model contained two body-fixed, anatomic axes (Inman, 1976; Delp et al., 1990). Talocrural motion (dorsiflexion (+)/plantarflexion) was defined as rotation of the talus around an oblique, talocrural axis fixed in the tibia (Figure 3). Subtalar motion (supination (+)/pronation) was defined as rotation of the calcaneus around an oblique, subtalar axis fixed in the talus (Inman, 1976). Kinematics were additionally resolved post-hoc to a joint coordinate system (JCS) for the combined ankle complex recommend by the International Society of Biomechanics (ISB) (Wu et al., 2002), which measures non-orthogonal rotations of the body-fixed calcaneus frame relative to the body-fixed tibia frame. The JCS sequence was per convention: dorsiflexion (+)/plantarflexion about a tibia-fixed Z-axis, which was identical to the talocrural anatomic axis; inversion (+)/eversion rotation around a floating axis; and internal (+)/external rotation around a body-fixed calcaneus y-axis (Grood and Suntay, 1983; Wu et al., 2002).

Peak subtalar supination angle was extracted as the primary outcome from probabilistic analysis, along with several complementary biomechanical metrics to aid interpretation and validation: peak talocrural angle, peak angular velocities, and moments borne by each passive bushing at the instant of peak supination. Bushing moments, expressed as vectors in the global reference frame by default, were orthogonally projected (i.e., dot products) onto each anatomic and JCS coordinate axis.

Cumulative distribution functions (CDF) of peak subtalar supination angle were computed from each MC simulation. The 5th, 50th, and 95th percentile values were extracted for comparison (Figures 1C). Sensitivity of the response to each independent parameter was characterized with standard Pearson correlation coefficients, and probabilistic sensitivity factors—which offer a unique assessment of how the mean and variance of the response are influenced by changes in either the mean or variance of each input (Easley et al., 2007).

**Advanced Mean Value Method**

We also tested the accuracy of the advanced mean value (AMV) probabilistic analysis method, a more computationally-efficient approach relative to traditional MC methods (Wu et al., 1990). Briefly, the AMV method approximates the numerical model

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**Table 1**: Probabilistic input parameters to six Monte Carlo simulations of single-limb drop landing. Each simulation was generated using 10 total parameters, where each had a fixed landing surface incline, a common set of 7 probabilistic parameters, and either fixed zero (0) or variable ranges of muscular co-activation, reflex gain, and brace flexibility.

| Input Parameter                              | Distribution               | Mean ± SD |
|----------------------------------------------|----------------------------|-----------|
| Landing surface incline (°, degrees)         | fixed                      | 0 ± 30    |
| Brace flexibility (% of passive anatomy flexibility) | normal                    | 0 ± 0     |
| Muscle co-activation (invertor/evertor, %)    | lognormal                  | 0 ± 60 ± 5|
| Muscle reflex gain (invertors, evertors)      | lognormal                  | 0 ± 10 ± 1|
| Muscle strength (invertor/evertor, % baseline) | normal                    | 100 ± 5   |
| Ankle passive flexibility (% baseline)        | normal                     | 100 ± 6   |
| Joint angle, talocrural at contact (?)       | normal                     | 34 ± 5    |
| Joint angle, subtalar at contact (?)         | normal                     | 0 ± 5     |
| Drop height (meters)                         | lognormal                  | 0.30 ± 0.05|
| Ground-foot contact modulus (MPa/meter)      | lognormal                  | 50 ± 5    |
| Ground-foot contact dissipation (sec/m)       | lognormal                  | 5 ± 1     |
(i.e., the sprain simulation) as a first-order Taylor series expansion to estimate the response gradient at specified probability levels. The AMV method requires only tens of trials to generate results, but can be sensitive to non-monotonic system behavior. Thus, we used our MC results as a gold standard to test if AMV predictions were similar at 5, 50, and 95% performance levels using the same inputs. Lastly, we evaluated AMV importance levels, which are the components of a unit vector pointing in the direction of the system response gradient. Thus, importance levels at each performance level have a root-mean-square sum of unity, and provide a more concise sensitivity analysis.

RESULTS

Cumulative distributions for the 6 MC studies are illustrated in Figure 4. Study #1, which simulated drop landing on a level surface, predicted the lowest values of peak supination angle among all studies but also had the largest uncertainty in response with a range of 17° between 5 and 95% bounds, driven by subtalar posture at landing (Table 2). Study #2 confirmed that with addition of a 30-degree incline, and still without brace protection or invertor/evotor muscle activity, the most severe peak supination angles were predicted, with a median response of 49° and 90% of trials falling in the range 45-52°. Response was decreased most strongly driven by passive anatomic stiffness, and moderately by subtalar supination posture at landing (Table 2).

Study #3 which added invertor/evotor muscular reflexes verified that strong reflexes only marginally reduced peak supination to 41° at the 50% response level. Sensitivities showed that despite presence of reflexes, response was most strongly increased by drop height, and moderately increased by subtalar supination posture at landing (Table 2). Study #4 which excluded muscular reflexes and added preparatory co-activation, predicted a large reduction in peak subtalar response to 30°, but also showed a relatively wide 90% confidence bound, ranging 16°. Response was most strongly increased by subtalar joint posture at landing and a weak/moderate negative association with co-activation (Table 2).

For both Study #3 and #4, probabilistic sensitivity factors highlighted that assumed increases in some input parameters influenced variance in peak subtalar response; specifically, increased mean ground contact dissipation decreased response variance, and increased mean talocrural joint posture at landing increased response variance (Table 2).

Study #5 and #6 which each incorporated added external structural support (i.e., a brace), showed similar reductions in peak subtalar response at 30° (Figure 4). However, Study #5 had tighter confidence bounds, with moderate, negative subtalar response sensitivity to talocrural angle at contact and to brace stiffness. In contrast, Study #6 that included a mix of all considered factors, showed response was primarily predicted by an increased subtalar angle at contact, and drop height (Table 2).
Lastly, the AMV method was successfully implemented by re-executing Study #6 (Figure 5). Only 14 simulation trials and 4-min processing time were required to reproduce 5, 50, and 95% response levels predicted with a 1000-trial MC study accurately and much more efficiently.

DISCUSSION

The primary aim of this study was to develop a probabilistic simulation of ankle inversion sprains for virtual study of prophylactic interventions. This was achieved by extending a validated deterministic model with several features. Firstly, a comprehensive set of 10 deterministic parameters were assigned probabilistic distributions such that confidence bounds on outputs were predicted, and underlying probabilistic sensitivities characterized. Secondly, an adjustable ankle-foot bushing was added to facilitate exploration of applied mechanical support (i.e., a brace) in parallel with anatomy. Lastly, code was included to report ankle biomechanics using the ISB-recommended joint coordinate system for the ankle complex, which will facilitate inter-study comparison. The extended probabilistic framework is made available for community use (https://simtk.org/projects/sprain-sim).

A breadth of prior human subject experiments report kinematics, kinetics, and muscle activity of the ankle complex during unilateral landing (Ha et al., 2015; Simpson et al., 2019). These observational studies describe cross-sectional differences between groups with and without ankle instability, characterized by altered neuromuscular

### TABLE 2
Correlations between probabilistic input parameters and peak subtalar supination angle within six Monte Carlo simulations. Input parameter distributions are provided in (Table 1). Probabilistic sensitivity factors were additionally computed to assess independent influences of input parameter mean and variance on response mean and variance, and generally agreed with correlations, with exception of (σ*) indicating an increase in the parameter mean increased (+) or decreased (-) variance in the response. Supplementary Figure S6, S7.

| Monte Carlo Study (#) | 1   | 2   | 3   | 4   | 5   | 6   |
|----------------------|-----|-----|-----|-----|-----|-----|
| Drop height          | 0.10| 0.36*| 0.61*| 0.34*| 0.65*| 0.61*|
| Ground contact compliance | -0.01| 0.19| 0.22| 0.16| 0.20| 0.12|
| Ground contact dissipation | -0.01| -0.38*| -0.07*| 0.01*| 0.00| 0.02|
| Muscle co-activation | -   | -   | -   | -0.37*| -   | -0.36*|
| Muscle reflex gain | -   | -   | -0.05| -   | -   | -0.01|
| Muscle strength, inv/evertor | 0.03| -0.08| -0.08| -0.21*| -0.05| -0.16|
| Talocrural joint plantarflexion at contact | -0.10| 0.18| 0.28 (σ*)| -0.02 (σ*)| -0.50*| 0.16|
| Subtalar joint supination at contact | 0.99*| -0.42*| 0.56*| 0.74*| 0.10| 0.57*|
| Passive anatomic stiffness | -0.06| -0.67*| -0.15| -0.07| -0.08| -0.03|
| External brace stiffness | -   | -   | -   | -   | -4.93| -0.13|

Correlation strength: weak, (r = 0.2–0.4), moderate (r = 0.4–0.6), strong (r = 0.6–1.0).

(σ*) identifies a probabilistic sensitivity factor that suggested increased input parameter MEAN, value led to increased (+) or decreased (-) variance in the response.

**FIGURE 5**
(A) Advanced Mean Value (AMV) probabilistic method in comparison to traditional Monte Carlo (MC) for Study #6 (Table 1). For 10 input parameters, the efficient AMV method required only 14 model evaluations to predict response probabilities (0, 5, 50, 95%) which agreed with a 1000-trial MC. The AMV method executed in 4 min processing time versus 13 hours for MC (laptop, Intel i7 CPU). (B) Probabilistic Importance Levels computed using the AMV method. Alpha values at each probability level are the components of a unit vector pointing in the direction of the response gradient (steepest ascent). The root-mean-square sum of alpha values is unity and thus establish a relative ranking of input parameters to which the response is most sensitive. For exemplary Study #6, only four of 10 input parameters had non-zero alpha values which suggested that drop height was the most influential, and showed increasing influence between 5 and 95% response levels, followed by talocrural/subtalar joint postures and muscle co-activation, the latter of which showed decreasing influence between 5 and 95% response levels.
control and passive joint laxity (Simpson et al., 2019). However, sub-

sprain experiments do not fully model injurious motion and loads,
nor can load sharing among structural elements (e.g., muscles, 
ligaments, bracing) be easily determined. Computational strain 
simulations have been used to explore underlying factors in 
spain occurrence; specifically, the influence of foot posture at 
landing (Wright et al., 2000b), passive ankle flexibility (Wright 
et al., 2000a), and muscular co-activation versus reflex strength 
(DeMers et al., 2017). However, no single framework has 
incorporated a breadth of human factors in combination with 
external factors and understood uncertainties. Additionally, a vast 
majority of biomechanical studies resolve ankle-foot mechanics 
using the ISB JCS (Wu et al., 2002), the axes of which differ 
from ankle internal anatomic axes, such as those implemented in 
OpenSim. Thus, our extended framework resolves ankle-foot 
mechanics in both anatomic and JCS conventions to facilitate 
comparison across studies.

Comparison With Baseline Deterministic 
Model

The original purpose of the validated deterministic model was to 
explore if muscular co-activation or reflexes could theoretically 
prevent a sprain (DeMers et al., 2017). Through uniform 
variation of preparatory invertor/evotor co-activation and reflex 
gain (20 total simulations), the authors of the prior study concluded 
that co-activation could prevent sprains, while reflexes could not; 
specifically, 60% co-activation reduced peak subtalar supination 
from 49 to 30°, while the strongest reflexes (gain of 10) produced 
an unsafe 41° supination. Our corresponding, probabilistic 
simulations - Study #3 with strong reflexes (gain 10 ± 1), Study 
#4 with strong co-activation (60 ± 5%) - aimed to verify if these 
conclusions held with added uncertainty across a breadth of sprain 
(factors (Table 1). Median response of each MC simulation matched 
deterministic predictions, although 90th percentile ranges were 
relatively wide (16°, Study #4, Figure 4). With co-activation only, 
our sensitivity results showed response variance was most strongly 
driven by subtalar posture at contact (r = 0.74, Study #4, Table 2), 
with only weak associations across co-activation, drop height, and 
muscle strength (r = −0.37, 0.34, −0.21). With reflexes only, 95% of 
our trials produced 35° or greater peak supination (Study #3, 
Figure 4), with response variance showing strong associations to 
drop height and subtalar posture at contact (r = 0.61, 0.55, Study #3, 
Table 2), but not to reflex gain. These findings corroborate prior 
conclusions that—even with added intrinsic and extrinsic uncertainty—the strongest reflexes could not prevent sprains for 
this specific subject and movement (DeMers et al., 2017).

Ankle Joint Mechanics

Our analysis of predicted ankle joint mechanics expressed in a JCS 
highlighted several points. Firstly, 35 ± 6° inversion has been 
suggested as a range within which lateral ligament damage beings 
to occur in cadaveric models (with foot 20° plantarfleked, 15° 
internally rotated), measured about an anterior-posterior axis 
parallel to the plane of the foot, through the talocrural joint 
(Aydogan et al., 2006). In this simulation, the generic subtalar 
joint axis is inclined 38° superior and 9° medial to anatomic 
directions of the foot (Figure 3). Thus, with 20° talocrural 
plantarfleked, 52° subtalar supination is required to yield 35° 
inversion in JCS coordinates, highlighting care needed when 
comparing across different conventions. As the ISB ankle 
complex JCS is more commonly used in human motion capture 
experiments, resolution of default OpenSim outputs to a JCS 
facilitates comparison. For example, one experiment had subjects 
drop land onto a 25° inclined platform, and captured 3D kinematics 
and kinetics of the JCS ankle complex during safe versus incidental 
sprain-causing trials in two female participants (Li et al., 2018). A 
range of 35–43° peak inversion in a JCS convention was measured 
during safe trials, and 55° during sprain trials. Our probabilistic 
simulations of a 30 cm drop onto a 30° incline predicted 11°–23° 
peak JCS inversion (Table 3); notably lower than observed injury 
ranges. Similarly, 600–900/second inversion velocities were 
measured during sprain trials, while our simulations predicted a 
lower 500–700/second (Li et al., 2018). More severe, virtual sprains 
could be achieved with a steeper platform incline, or higher drop 
height, in future applications requiring such.

Selected kinetics were also resolved to the non-orthogonal ankle 
complex JCS (Table 3). Simulated inversion torque resisted by the 
rotational bushing representing internal passive anatomy, peaked at 
24.5 ± 4.6 Nm in Study #2 in the worst-case of no invertor/evotor 
muscular contributions or external bracing, and decreased to 
4.8–5.3 Nm on average in MC Study’s #4–6 aimed to simulate 
near-injury scenarios. These latter predictions agree with 
measurements from the same cadaveric test data (Aydogan et al., 
2006); which observed anterior talofibular ligament damage initiation 
at 2.7–4.3 Nm external inversion torque and 35 ± 6° inversion.

Effect of Ankle Complex External 
Mechanical Support

Our addition of a second passive, rotational bushing was aimed to 
provide a simple means of estimating load sharing between 
internal anatomy and the net structural effect of a worn brace. 
Such human-device interactions are difficult or impossible to 
measure experimentally, but could be useful to inform 
mechanical design requirements for bracing. Torque-angle 
data used in the generic bushing definitions can be safely 
measured on humans with/without worn braces, to provide 
subject-specific inputs of passive flexibility and external 
bracing (Siegler et al., 1997; Crabtree and Higginson, 2009). For 
example, MC Study #5 suggested that - in the absence of 
invertor/evotor muscular contributions - a parallel, external 
brushing with a 240% scale factor (Figure 2) would be needed 
to achieve a similar supination reduction as with 60 ± 5% 
muscular co-activation alone (Study #4 Table 3). However, the 
complete absence of muscular contributions is unlikely, and such a 
rigid brace would likely be uncomfortable during typical ankle 
motions. Thus, we tested a more realistic scenario including low 
co-activation, moderate reflex gain, and applied bracing in 
combination (Study #6, Figure 4 and Table 3). Predictions 
suggested a more flexible 150% scaled bushing could provide 
similar protective effect (Figure 4). Future applications may use 
this framework to estimate design requirements on magnitudes of 
structural ankle support needed for sprain prevention, to achieve an
TABLE 3 | Predicted, peak ankle mechanics (mean ± standard deviation) across six, 1000-trial Monte Carlo simulations. Input parameter combinations are specified in (Table 1). Kinematics corresponding to subtalar and talocrural axes were extracted directly from the OpenSim model (Inman, 1976; Delp et al., 1990). Kinematics for a non-orthogonal joint coordinate system (JCS) of the tibia-calcaneus ankle complex were also resolved. Figure 3 (Wu et al., 2002). Peak moment borne by each passive bushing (anatomy, brace) at the instant of peak supination were computed as orthogonal projections of ground-referenced moments onto each anatomic and JCS axis.

| Monte Carlo Study (#) | 1       | 2       | 3       | 4       | 5       | 6       |
|-----------------------|---------|---------|---------|---------|---------|---------|
| **Subtalar Axis (Sup. +)** |         |         |         |         |         |         |
| Angle (°)             | 1 ± 5   | 49 ± 2  | 41 ± 3  | 29 ± 5  | 30 ± 1  | 29 ± 3  |
| Velocity (°/s)        | 135 ± 82| 886 ± 72| 878 ± 82| 671 ± 115| 911 ± 208| 799 ± 81|
| Moment (°)            | 0.7 ± 1.1| 31.0 ± 6.1| 15.1 ± 4.9| 4.3 ± 1.9| 4.9 ± 0.8| 4.3 ± 1.6|
| **Talocrural Axis (Dorsi. +)** |         |         |         |         |         |         |
| Angle (°)             | 17 ± 1  | 19 ± 2  | 19 ± 1  | 18 ± 2  | 21 ± 1  | 20 ± 2  |
| Velocity (°/s)        | 1650 ± 365| 1684 ± 356| 1644 ± 349| 1568 ± 337| 1728 ± 717| 1675 ± 365|
| Moment (°)            | 4.4 ± 0.7| -5.6 ± 1.8| -3.0 ± 1.0| 0.9 ± 1.0| 2.5 ± 0.5| 1.5 ± 0.5|
| **Sagittal (Dorsi. +)** |         |         |         |         |         |         |
| Angle (°)             | 19 ± 1  | 8 ± 1   | 8 ± 1   | 10 ± 2  | 13 ± 1  | 11 ± 1  |
| Velocity (°/s)        | 162 ± 347| 1641 ± 330| 1604 ± 326| 1532 ± 315| 2324 ± 743| 1641 ± 348|
| Moment (°)            | 4.4 ± 0.7| 1.0 ± 0.5 | 0.9 ± 0.7 | 1.2 ± 0.9 | 2.6 ± 0.5 | 1.6 ± 0.4|
| **Frontal (Inv. +)**  |         |         |         |         |         |         |
| Angle (°)             | -9 ± 4  | 23 ± 1  | 19 ± 2  | 11 ± 3  | 12 ± 1  | 11 ± 2  |
| Velocity (°/s)        | 103 ± 62| 650 ± 57 | 652 ± 60 | 501 ± 88 | 702 ± 167 | 599 ± 62 |
| Moment (°)            | 0.3 ± 0.9| 24.5 ± 4.6 | 13.2 ± 3.8 | 4.8 ± 1.6 | 5.3 ± 0.8 | 4.8 ± 1.4|
| **Transverse (Int. +)** |         |         |         |         |         |         |
| Angle (°)             | 7 ± 3   | 39 ± 2  | 33 ± 3  | 24 ± 3  | 25 ± 1  | 24 ± 2  |
| Velocity (°/s)        | 77 ± 48 | 572 ± 58 | 537 ± 55 | 398 ± 68 | 520 ± 117 | 471 ± 48 |
| Moment (°)            | 0.3 ± 0.5| 10 ± 1.6  | 5.5 ± 1.6 | 1.9 ± 0.9 | 2.0 ± 0.7 | 2.0 ± 0.7|

effective but minimally-restrictive brace design (Dierker et al., 2017). Conversely, structural flexibility of a prototype brace and of a user’s ankle complex can be measured (Siegler et al., 1997), and input to this framework to safely predict probability of a sprain.

**Probabilistic Simulation**

An additional aim of this study was to characterize model sensitivities. Standard input-response Pearson correlations generally agreed with probabilistic sensitivity factors computed from MC results (Table 2); moderate and strong correlations corresponded with probabilistic sensitivities that suggested input parameter means drove peak subtalar supination. Increasing variance in correlated parameters also led to increased variance in the response. However, a unique feature of probabilistic sensitivity factors is identification of input-output relationships beyond linear correlation. For example, in MC studies #3 and #4, increased mean ground contact dissipation decreased variance in the response. Similarly, increased plantarflexion at contact increased variance in the response. These relationships are physically sensible and increase confidence in model validity. Specifically, in the absence of external bracing, increased foot-ground damping created a less variable subtalar response, while greater plantarflexion has potential to increase response variance through variance in location of foot-ground contact and moment arms of primary evertors (e.g., peroneus, extensor digitorum). Of note, invertor/evertor muscle strength showed no association with peak subtalar supination across all scenarios. This agrees with clinical studies that have found no predictive relationship between evertor weakness and lateral ankle sprain occurrence (de Noronha et al., 2006; Martin et al., 2021).

Lastly, while probabilistic analysis is a powerful supplement to forward dynamic musculoskeletal simulation, it is often not feasible due to time constraints of traditional techniques. For this reason, we tested the efficient AMV method on Study #6, which included all 10 probabilistic inputs, and found AMV accurately replicated MC predictions at the 5, 50, and 95% levels (Figures 5A). Only 14 simulations were required for the AMV analysis (4 min processing time, laptop Intel i7 CPU), in contrast to the high computational cost of MC (1000 trials, 13 h). Another added benefit of the AMV method relative to MC are probabilistic importance levels, which provide a more succinct, relative ranking of sensitivities at each probability level. For example, importance levels for Study #6 revealed that drop height was the most influential, with increasing effect between 5 and 95% response probability, followed by talocrural and subtalar joint postures, and muscle co-activation, the latter of which showed decreasing influence between 5 and 95% probability levels (Figures 5B).

**Limitations and Future Work**

The probabilistic framework and study findings must be considered with several limitations. The experimental data used to validate the baseline model was limited to one subject (female, 68 kg, 180 cm), and one motion (40 cm unilateral drop landing onto a level surface). Therefore, conclusions should not be generalized to substantially different contexts of use without further validation (Viceconti et al., 2020). Comparison to experimental data of persons with varied anthropometry, landing on inclined surfaces, with/without ankle instability could broaden future utility. An added challenge is the definition of injury thresholds to internal anatomic structures via externally-measured joint kinematics or kinetics. Therefore, we chose not to assume a fixed injury threshold, as the primary focus of this study was on
incorporating appropriate input uncertainties and characterizing the most influential sensitivities.

**CONCLUSION**

This study successfully developed an efficient probabilistic, subject-specific simulation of ankle inversion sprains during drop landing. This was accomplished through extensions to an open-source, validated deterministic model with probabilistic inputs, characterizing sensitivities, and evaluating confidence bounds on extended predictions. Additionally, ankle joint mechanics were resolved in both default anatomic joint conventions, and in ISB-recommended conventions to facilitate interstudy comparisons (Wu et al., 2002). Lastly, a method was added to estimate load sharing between internal anatomy versus external structural ankle support (e.g. ligaments versus bracing), aimed to accelerate virtual testing of future brace concepts. The extended model and all associated code are made available for open-source use (https://simtk.org/projects/sprain-sim).

**DATA AVAILABILITY STATEMENT**

Publicly available datasets were analyzed in this study. This data can be found here: https://simtk.org/projects/sprain-sim.

**REFERENCES**

Aydogan, U., Glisson, R. R., and Nunley, J. A. (2006). Extensor Retinaculum Augmentation Reinforces Anterior Talofibular Ligament Repair. *Clin. Orthop. Relat. Res.* 442, 210–215. doi:10.1097/01.blo.0000183737.43245.26

Chen, J., Siegler, S., and Schneck, C. D. (1988). The Three-Dimensional Kinematics and Flexibility Characteristics of the Human Ankle and Subtalor Joint-Part II: Flexibility Characteristics. *J. Biomechanical Eng.* 110 (4), 374–385. doi:10.1115/1.3108456

Crabtree, C. A., and Higginson, J. S. (2009). Modeling Neuromuscular Effects of Ankle Foot Orthoses (AFOs) in Computer Simulations of Gait. *Gait & Posture* 29 (1), 65–70. doi:10.1016/j.gaitpost.2008.06.004

de Noronha, M., Refshauge, K. M., Herbert, R. D., Kilbreath, S. L., and Hertel, J. (2006). Do voluntary Strength, Proprioception, Range of Motion, or Postural Sway Predict Occurrence of Lateral Ankle Sprain? *Commentary*. *Br. J. Sports Med.* 40 (10), 824–828. discussion 828. doi:10.1136/bjsm.2006.029645

Delp, S. L., Loan, J. P., Hoy, M. G., Zaice, F. E., Topp, E. L., and Rosen, J. M. (1990). An Interactive Graphics-Based Model of the Lower Extremity to Study Orthopaedic Surgical Procedures. *IEEE Trans. Biomed. Eng.* 37 (8), 757–767. doi:10.1109/10.29791

DeMers, M. S., Hicks, J. L., and Delp, S. L. (2017). Preparatory Co-activation of the Ankle Muscles May Prevent Ankle Inversion Injuries. *J. Biomech.* 52, 17–23. doi:10.1016/j.jbiomech.2016.11.002

Denton, J. M., Waldhelm, A., Hacke, J. D., and Gross, M. T. (2015). Clinician Recommendations and Perceptions of Factors Associated with Ankle Brace Use. *Sports Health* 7, 267–269. doi:10.1177/1941738115572984

Dierker, K., Levay, E., Brosky, J. A., and Topp, R. V. (2017). Comparison between Rigid Double Upright and Luce-Up Ankle Braces on Ankle Range of Motion, Functional Performance, and User Satisfaction of Brace Characteristics. *Jphr* 1. doi:10.26036/jphr2017.1.1.dierker

Doherty, C., Bleakley, C., Hertel, J., Caulfield, B., Ryan, J., and Delahunt, E. (2016). Recovery from a First-Time Lateral Ankle Sprain and the Predictors of Chronic Ankle Instability. *Am. J. Sports Med.* 44 (4), 995–1003. doi:10.1177/0363546516628870

**AUTHOR CONTRIBUTIONS**

AY adjusted musculoskeletal models and wrote code for automated batch simulations. AY and AP conferred on the probabilistic analysis methods. AY performed the probabilistic data analysis and AP performed all kinematic/kinetic data analysis. AY drafted the manuscript with contributions from AP. All authors discussed and revised the manuscript, and all authors approved the final version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fbioe.2021.765331/full#supplementary-material

Doherty, C., Delahunt, E., Caulfield, B., Hertel, J., Ryan, J., and Bleakley, C. (2014). The Incidence and Prevalence of Ankle Sprain Injury: a Systematic Review and Meta-Analysis of Prospective Epidemiological Studies. *Sports Med.* 44 (1), 123–140. doi:10.1007/s12202-013-0102-5

Easley, S. K., Pal, S., Tomaszewski, P. R., Petrera, A. J., Radhakrishna, P. J., and Laz, P. J. (2007). Finite Element-Based Probabilistic Analysis Tool for Orthopaedic Applications. *Computer Methods Programs Biomech.* 85 (1), 32–40. doi:10.1016/j.cmpb.2006.09.013

Grood, E. S., and Suntay, W. J. (1983). A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. *J. Biomechanical Eng.* 105, 136–144. doi:10.1115/1.3158397

Gross, M. T., and Liu, H.-Y. (2003). The Role of Ankle Bracing for Prevention of Ankle Sprain Injuries. *J. Orthop. Sports Phys. Ther.* 33, 572–577. doi:10.2521/jospt.2003.33.10.572

Ha, S. C.-W., Fong, D. T.-P., and Chan, K.-M. (2015). Review of Ankle Inversion Sprain Simulators in the Biomechanics Laboratory. *Asia-Pacific J. Sports Med. Arthrosc. Rehabil. Technology* 2, 114–121. doi:10.1016/j.asmart.2015.08.002

Hegarty, A. K., Petrera, A. J., Kurz, M. J., and Silverman, A. K. (2017). Evaluating the Effects of Ankle-Foot Orthosis Mechanical Property Assumptions on Gait Simulation Muscle Force Results. *J. Biomechanical Eng.* 139 (3), 031009. doi:10.1115/1.4035472

Inman, V. (1976). *The Joints of the Ankle*. Baltimore: Williams & Wilkins.

Li, Y., Ko, J., Zhang, S., Brown, C. N., and Simpson, K. J. (2019). Biomechanics of Ankle Giving Way: A Case Report of Accidental Ankle Giving Way during the Drop Landing Test. *J. Sport Health Sci.* 8, 494–502. doi:10.1016/j.shs.2018.01.002

Martin, R. L., Davenport, T. E., Fraser, J. J., Sawdon-Bea, J., Garcia, C. R., Carroll, L. A., et al. (2021). Ankle Stability and Movement Coordination Impairments: Lateral Ankle Ligament Sprains Revision 2021. *J. Orthop. Sports Phys. Ther.* 51 (4), CPG1–CPG80. doi:10.2521/jospt.2021.03002

McLean, S. G., Huang, X., and van den Bogert, A. J. (2008). Investigating Isolated Neuromuscular Control Contributions to Non-contact Anterior Cruciate Ligament Injury Risk via Computer Simulation Methods. *Clin. Biomech.* 23 (7), 926–936. doi:10.1016/j.clinbiomech.2008.03.072

Myers, C. A., Laz, P. J., Shelburne, K. B., and Davidson, B. S. (2015). A Probabilistic Approach to Quantify the Impact of Uncertainty Propagation in...
Musculoskeletal Simulations. *Ann. Biomed. Eng.* 43 (5), 1098–1111. doi:10.1007/s10439-014-1181-7

Newman, T. M., Gay, M. R., and Buckley, W. E. (2017). Prophylactic Ankle Bracing in Military Settings: A Review of the Literature. *Mil. Med.* 182, e1596–e1602. doi:10.7205/milmed-d-16-00160

Ruscio, B. A., Jones, B. H., Bullock, S. H., Burnham, B. R., Canham-Chervak, M., Rennix, C. P., et al. (2010). A Process to Identify Military Injury Prevention Priorities Based on Injury Type and Limited Duty Days. *Am. J. Prev. Med.* 38 (1 Suppl.), S19–S33. doi:10.1016/j.amepre.2009.10.004

Seth, A., Hicks, J. L., Uchida, T. K., Habib, A., Dembia, C. L., Dunne, J. J., et al. (2018). OpenSim: Simulating Musculoskeletal Dynamics and Neuromuscular Control to Study Human and Animal Movement. *Plos Comput. Biol.* 14 (7), e1006223. doi:10.1371/journal.pcbi.1006223

Siegler, S., Liu, W., Sennett, B., Nobilini, R. J., and Dunbar, D. (1997). The Three-Dimensional Passive Support Characteristics of Ankle Braces. *J. Orthop. Sports Phys. Ther.* 26, 299–309. doi:10.2519/jospt.1997.26.6.299

Simpson, J. D., Stewart, E. M., Macias, D. M., Chander, H., and Knight, A. C. (2019). Individuals with Chronic Ankle Instability Exhibit Dynamic Postural Stability Deficits and Altered Unilateral landing Biomechanics: A Systematic Review. *Phys. Ther. Sport* 37, 210–219. doi:10.1016/j.ptsp.2018.06.003

Viceconti, M., Pappalardo, F., Rodriguez, B., Horner, M., Bischoff, J., and Mussamba Tshinamudzi, F. (2021). In Silico trials: Verification, Validation and Uncertainty Quantification of Predictive Models Used in the Regulatory Evaluation of Biomedical Products. *Methods* 185, 120–127. doi:10.1016/j.ymeth.2020.01.011

Wright, I. C., Neptune, R. R., van den Bogert, A. J., and Nigg, B. M. (2000a). The Effects of Ankle Compliance and Flexibility on Ankle Sprains. *Med. Sci. Sports Exerc.* 32, 260–265. doi:10.1097/00005768-200002000-00002

Wright, I. C., Neptune, R. R., van den Bogert, A. J., and Nigg, B. M. (2000b). The Influence of Foot Positioning on Ankle Sprains. *J. Biomech.* 33, 513–519. doi:10.1016/S0021-9290(99)00218-3

Wu, G., Siegler, S., Allard, P., Kurtley, C., Leardini, A., Rosenbaum, D., et al. (2002). ISB Recommendation on Definitions of Joint Coordinate System of Various Joints for the Reporting of Human Joint Motion-Part I: Ankle, Hip, and Spine. *J. Biomech.* 35, 543–548. doi:10.1016/S0021-9290(01)00222-6

Wu, Y.-T., Millwater, H. R., and Cruse, T. A. (1990). Advanced Probabilistic Structural Analysis Method for Implicit Performance Functions. *AIAA J.* 28 (9), 1663–1669. doi:10.2514/3.25266

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