Reviewer one states that “the main limitation, from the reviewer’s point of view, is the lack of information about the time and the simulations technical data.”. We are easily able to address this issue and include more information about elaboration time and technical details in the current paper. Furthermore, reviewer 1 says that “A simple single-compartment model able to reproduce some of these behaviours could be the strength of this work if the simulation of this model can be done in a reduced elaboration time.” Indeed our model is incredibly fast when compared to other works in the literature. It is not possible to compare our model to the most recent PC model by Zang and Sde Schutter as they don’t provide this information, but in the PC model described in Masoli et al., 2015 they can simulate 15-s of activity from six PCs in just under 40 min. We can easily get precise simulation times, but ours is considerably faster.

Reviewer 1:
Another limitation concerns the lack of data about the compartment (for example, is the soma represented as a sphere?) and about the experiments (which is the temperature considered in this simulation?).
[Methods]
In this Section authors describe the single-compartment models not specifying some compartment characteristics. Please, include some details about the compartment: is it a sphere? If yes, which is its radius or surface area? Moreover, which is the temperature considered in the simulation? Has it the same value of the one considered in the experiments? Is this not unnecessary for this model because it’s a point and so our units are essentially in /cm2 ?

[Methods]
In line 119, authors affirm that the model has been developed in Python language, using the scipy.integrate.ode package to solve differential equations. Which is the time step consider in the simulations? dt=0.001*ms

[Results]
In Figure 1 authors compare their results with the complex spikes presented in Davie et al. (2008). The main difference that the reviewer noticed in this comparison is the high amplitude of current injected in the soma in this work. In general (not only considering the comparison with Davie et al.), these current values seem very high (from 8 μA to 215 μA). Can the authors provide an explanation? I don’t really know what to say here other than that because we don’t model morphology we wouldn’t expect the injected current to be similar to experiment?

[Results]
In lines 167-174, authors affirm that the three-channel model is not capable of reproducing the pause (of ~50 ms) of the single spike activity after a complex spike event. Then, in lines 175-182, they affirm that the five-channel model is able to reproduce a pause of ~40 ms and they comment that “this pause was greater than expected if complex spikes and simple spikes are independent (simple spike interspike interval divided by two,…), unlike in the three channel model”. Which was the “expected” value? Why does the model reproduce a longer pause? The expected value would be simple spike ISI / 2 if the CS and SS are independent (can reference Xiao et al., 2014 for this) so in the model we would expect a pause of 12.5ms. Longer pause is due to the hyperpolarizing calcium-activated potassium channels.

[Discussion]
As a possible application of this model, authors affirm that “In the future these models will be useful as a component in a larger model of local cerebellar circuitry to identify the mechanisms

behind the experimentally observed covariation of complex spike waveform and simple spike activity.”.
From the authors’ point of view, is it possible to include the present version of the five-channel model in a cerebellar network linking this cell model to “real” parallel fibres and climbing fibres input, even if it is not able “to capture the more complicated interactions between complex spikes waveform changes and simple spike dynamics…”?
In other words, is the simple and complex spike activity, reproduced in this model, enough to integrate this work in a cerebellar network and to reproduce a correct network activity?

Can this model be used exploiting the NEURON software?

As previously stated, authors should better motivate the choice to use a simplified model, which can reproduce part of the Purkinje cells behaviours, instead of others detailed models present in other works. One reason could be the elaboration time that should be reported in the text. We can elaborate on the fact that the simplified model is good because it has a much faster simulation time, but can still generate complex spikes with the desired waveform and simultaneous simple spikes , which is lacking in previous simplified models.

Reviewer 2 | 10 Jul 2019 | 15:01
#1
A single compartmental model, with only 3 ionic channels can be seen as a strength, since it reduces the number of free parameters, the overall computational complexity and it can be focused on a specific behaviors.
At the same time, only the 5 channel model is actually good enough to deliver results when complex spikes are intermixed with single spikes (Authors -> line 172 and 173).
Is it not interesting in itself that you need the extra channels to capture these interactions – the channels responsible for generating CS shape are not the same as those that determine it’s relationship to SS.

The model are capable of simulate only simple and complex spikes, even thou with correct shapes, but it can be addressed as a limitation. There are integrate and fire models already capable of generating simple and complex spikes with, of course without a valid shape, but good enough for network simulations at a fraction of computational power(Luque and Arleo. 2019).

The ability of the five model to deliver some good results is a strength, maybe even with a low computational impact but was not provided any information about the computational power required or the time do complete a simulation. We can easily add this information

Another limitation is the resolution of the equations with Python / Scipy. Is it any better than, for example, NEURON?
Faster, more reliable?

On big limitation will be the necessity to build all the code to create a network, to link the models, deliver synaptic inputs, synaptic stimulation, etc.

Building a model that can do only partially realistic simple spikes (AIS missing) and complex spikes, even placed in a network, will miss 90% of the total behaviors of a real Purkinje cell. I don’t think I believe this. There is also a need for simple models that can be included in networks.

Line 61 "stands for the external input current, in what follows Ie this will be made up of a background current and a synaptic current entering the soma from the dendrite.

I think it need a little rewording. This can be done too.

Line 75 "and as such the Purkinje cell soma most likely receives the dendritic climbing fibre signal as a depolarisation plateau carried by calcium and non-inactivating sodium channels".

The absence of back propagation indicates a very low presence of sodium channels in the dendrites of Purkinje cell. Recordings from Purkinje cell in culture showed a complete absence or very small sodium currents in the dendrites compared to the soma, the AIS or the axon (Fry and Maue, 2007) We can delete to reference to sodium channels here, but these are mean to refer to just the passive sodium channels and in very small concentrations. Or add a good reference.

Line 109 " rate constant 0.02 kHz"

A biochemical rate constant is usually reported in Ms^-1 or M*s^-1, depending if is a first, second or third order. We can change the units here.

Line 119 "Simulations were run in Python".

Which python version, OS, version of Scipy, other modules? I'd need to check – it was Python 2.7, OS and I don't know which Scipy version.

Line 149 "In the absence of the sodium current, spikelets are abolished, as are simple spikes, and the resurgent sodium current is apparent after the initial spike of the complex spike, but spikelet generation fails."

The KO of sodium channels are, except in a very few cases, lethal for a neuron so it is normal to abolish the activity of a neuron. What is not clear is the part "the resurgent sodium current is apparent after the initial spike of the complex spike". If there is no sodium channel it sounds like a stimulation artifact. In the models we have two different types of sodium current, generated by the two different transient and resurgent sodium channels. This figure was included so that we could test the contributions of each in silico.

Line 223 "223 The multi-compartmental model developed in De Schutter and Bower (1994a,b,c)"

The latest model, from De Schutter's lab, was build specifically to simulate the shape of complex spike. (Zang and De Schutter, 2018) This is an impressive model and really cool work, but there is still a need for a simple model that is easy and fast to use.

Line 301 "These models clarify the relationship between channel dynamics and Purkinje cell spike generation."

The fact that Purkinje cell required sodium and potassium to generate action potential cannot be stated as a novelty of these models. Is at the basis of many Purkinje cell modelling effort.
For example, the single compartmental model (Akemann, Knopfel 2006) studies exactly the interplay between Kv3 and the Nav1.6 resurgent current.

Line 307 "The model was unable to capture the more complicated interactions between complex spike

waveform changes and simple spike dynamics, suggesting that these may result from mechanisms located outside of the soma, such as dendritic computations, synaptic plasticity or network effects"

Line 312 "The models presented here could be used to address a number of further questions including, but not limited to, the influence of synaptic plasticity at single synapses on Purkinje cell activity, the temporal significance of spike activity patterns, the contribution of individual channels to specific electrophysiological properties and how these are modulated by neurotransmission and intracellular pathways."

The Purkinje cell multi compartmental models published in the last 5 years are capable of many of these properties.

In figure 1 "from 8 uA (Bi) through to 215 uA" the current injection are way off physiological reality.
8 uA are 8000nA which over 1 thousand time stronger compared to actual experiments. Usually the upper limit for a current injection in the soma is 3nA. A little higher for dendritic stimulation like the experiments done in one of the cited papers "peak amplitude of 2-5 nA (Davie 2008).

Reviewer 2 | 10 Jul 2019 | 15:01
#1
The methods do not provide info about: temperature, the shape and dimensions of the "somatic" section, input resistance, the possibile age of the model since a P12 Purkinje cell behaves differently compared to a P21 or a P60 (McKay and Turner, 2005), on which type of CPU, OS, Python version, Scipy module version, equation integration time step, the length of the simulations (only in a case is defined under figure 4.) and how much time is required to do a simulation of each model, stimulation protocol. This last point is critical to understand if the model will perform well when placed in a large scale network as the authors intend to do.

In figure 1. "Simulated complex spike responses to increasing amplitudes of injected current. (from 100 nS (Ai) through to 500 nS"

Usually, a synaptic current, is defined in nA or pA and the conductance, which can be used to modulate the current, in Siemens (nanoS etc). Whoops, this is a mistake and should be uA

"(from 8 uA (Bi) through to 215 uA (Bvi))"

If the uA unit reported in the legend 1 and figure 1 is correct, the applied positive current injections are 1 thousand time stronger (8000nA to 215000 nA) than the one used in the experiments. Even in the case the unit is actually nA (8nA to 215nA) is still way out of the physiological range. On the contrary, with currents from 8 to 215pA, some results could have been obtained but only at the highest value. This critical information should have been provided in materials and methods since it puts the models outside the physiological ranges of a real Purkinje cell.

The presence of at least 3 sections could have improved the segregation of the action potential generation mechanism (AIS), the main calcium influx (dendrite) from the integrative part (soma). Similar approach was used in a 3 sections Inferior Olive model (De Gruijl and De Zeeuw, 2012).

" 310 In the future these models will be useful as a component in a larger model of local cerebellar circuitry".

The usage of an ODE solver, contained in external Python module, can be seen as an easy and good choice but, compared to dedicated simulation environment such as GENESIS, NEURON, MOOSE

or the recent Arbor, it will required the creation of an infrastructure to manage, distribute and link neurons together. A large scale network will require to simulate hundred thousand neurons on thousand cores of a cluster and such feat requires to scale very well with the node and core count.

The models were tested only for the simplex spike at "spontaneous firing" frequency. What about higher current injections? Purkinje cells are known to have a particular I/O relationship (Williams and Häusser, 2002). This can be seen useless in this specific case but, when the cell will receives a lot more synaptic inputs, from parallel fibers, ascending axon and/or climbing fiber, it will have to cope with bursts and simple spike modulation up to 250Hz.

"line 288 The simplified Purkinje cell models presented here do not include some of the channels known to be expressed in the Purkinje cell membrane."

All the missing channels are key for some behavior. The BK channel could have been added to the 5 ionic channel model since, in the soma, P-type, SK2 and BK have been seen to form clusters (Indriati and Shigemoto, 2013) and, even thou BK has a lower affinity to calcium, compared to SK2, and are slower to activate, when are KO from real cells, the neurons will be less active with an irregular firing and become, basically, ataxic (Sausbier et al., 2004 and Hoxha et al., 2018).

The importance of potassium channels in complex spikes has been already demonstrated as well as the criticality of dendritic tree in generating the varying shape of the complex spike. (Zang and De Schutter, 2018).
Having a single compartment able to reproduce similar results is good but a multi compartmental model, even with other types of limitations, it resolves them using an actual morphology what a single compartmental model want to achieve with only one.

In the Tables 1, the biochemical forward and backward rates are described in kHz (?) whereas in biochemistry are addressed as M^-1*S^-1 or M^-1 depending if they are first, second, third order. A B is missing in the scheme. OB is the actual OpenBlocked.