Investigation for

[1] Questions: (1) What parameters affect the peak and (2) decaying phase, given Gto, V, and Ek

[2] The maximum conductance does not affect the “shape”, decaying phase in another word, but the peak

|  |  |
| --- | --- |
| Gto = 0.4067 | Gto = 4.067  A screenshot of a cell phone  Description automatically generated |

[3] ato

* At the resting potential, ito has to be 1 and decreases o
* nce clamp voltage is applied.
* ato and ito are bounded by [0, 1]
* The maximum Ito = Gto(V-Ek)
* Initial ato had been almost 0 but rapidly reached steady-state value at 50 mV, meaning small tau=0.316 (i.e., alpha=3.16, beta=0.0027)
* Steady-state value of ato is almost 1, because alpha is relatively much bigger than beta
* Time constants tau\_a=0.2293 / tau\_i=54.0387

|  |  |
| --- | --- |
| A screenshot of a social media post  Description automatically generated | A screenshot of a cell phone  Description automatically generated |

* For voltage steps between -20 and 50 mV, the smaller voltage steps, the lower and more elongated the peak and current trace, at which the difference between beta and alpha is not big

|  |  |
| --- | --- |
| At 50 mV  A screenshot of a social media post  Description automatically generated | Over varying voltages  A screenshot of a map  Description automatically generated |
|  | A picture containing mirror  Description automatically generated |

Iter 1 | Voltage: -70 | Peak: 0.000006 | Tau 5000.000000

Iter 2 | Voltage: -60 | Peak: 0.000164 | Tau 5000.000000

Iter 3 | Voltage: -50 | Peak: 0.003658 | Tau 5000.000000

Iter 4 | Voltage: -40 | Peak: 0.064585 | Tau 5000.000000

Iter 5 | Voltage: -30 | Peak: 0.750306 | Tau 5000.000000 | 0.3133 | 0.9823

Iter 6 | Voltage: -20 | Peak: 4.473935 | Tau 286.250255 | 0.5475 | 0.9426

Iter 7 | Voltage: -10 | Peak: 12.902327 | Tau 153.499703

Iter 8 | Voltage: 0 | Peak: 22.891657 | Tau 122.631793

Iter 9 | Voltage: 10 | Peak: 31.707188 | Tau 113.330063

Iter 10 | Voltage: 20 | Peak: 38.831791 | Tau 109.989202

Iter 11 | Voltage: 30 | Peak: 44.756906 | Tau 107.926318

Iter 12 | Voltage: 40 | Peak: 49.998904 | Tau 106.965022

Iter 13 | Voltage: 50 | Peak: 54.865764 | Tau 106.331899

[4] ito

* The shape of Ito is dominated by ito

|  |  |
| --- | --- |
| A screenshot of a cell phone  Description automatically generated | A screenshot of a cell phone  Description automatically generated |
| A screenshot of a cell phone  Description automatically generated | A screenshot of a cell phone  Description automatically generated |

* Roles of steady-state values of alpha and beta are flipped: alpha decreases and beta increases, as voltage increases
* Alpha and beta are relatively smaller than the case of ato, which results in large tau (1/(alpha+beta)), so that ito changes slower than ato
* We can control steady-state values with alpha, while maintaining large tau by keeping beta small
* Make it sure ito is near 1 (inactivated) under low voltages by having large alpha and small beta

|  |  |
| --- | --- |
| A screenshot of a cell phone  Description automatically generated | A picture containing screenshot  Description automatically generated |

[5] Compare ato and ito

* At the peak, when t=51.973, ato=0.99722 and ito=0.96413
* Once clamp voltage is applied, ato increases very quickly from the initial value, almost 0, to the steady-state value of ato, 0.9991 under 50 mV, while ito decreases relatively slowly from almost 1 to the steady-state value of ito
* To make it happen, alpha and beta of ito should be small so that tau becomes large
* alpha\_i and beta\_i are bounded, while alpha\_ and beta\_a are not

|  |  |
| --- | --- |
| A screenshot of a social media post  Description automatically generated | A close up of a map  Description automatically generated |
| A screenshot of a social media post  Description automatically generated | A screenshot of a map  Description automatically generated |
| A screenshot of a cell phone  Description automatically generated | A screenshot of a cell phone  Description automatically generated |

* alpha\_i and beta\_i are S-curved. Note that beta\_i is a sigmoid function, while alpha\_i is a little bit deviated from the sigmoidal form as offset voltage in numerator and denominator are different (13.5 and 33.5 respectively)
* beta\_i has a middle point at -33.5 mV

[6] Time constants

* tau\_a has the peak around -20 mV
* It coincides with the fact that Kv generates a normal trace with clamp voltage greater than -20 mV

|  |  |
| --- | --- |
| A close up of a device  Description automatically generated | A screenshot of a cell phone  Description automatically generated |
| Peak: 0.750306 | Tau: 5000.000000 |  Peak time: 62.496118|  a\_peak: 0.313255 | i\_peak: 0.982271 |  ass: 0.313480 | iss: 0.525415  tau\_a: 1.735388 | tau\_i: 328.645682 | A screenshot of a cell phone  Description automatically generated  Peak: 4.473935 | Tau: 286.250255 |  Peak time: 62.265243|  a\_peak: 0.547529 | i\_peak: 0.942592 |  ass: 0.549216 | iss: 0.073706  tau\_a: 2.126091 | tau\_i: 191.782544 |

[7] How to make the peak low?

* Check Ito.txt
* Case 1. Decrease ato\_ss
  + Decrease alpha\_a -> correct
* Case 2. Decrease tau\_i so that ito decrease faster
  + Increase beta\_i -> correct

[8] Elongate trace

* Check Ito txt
* Case 3. Increase tau\_i
  + Decrease beta\_i -> correct
  + Decrease alpha\_i

[9] Hypotheses

* Activation state variable reaches the steady-state value much faster than the inactivation state variable
  + Because alpha\_a and beta\_a are larger than alpha\_i and beta\_i
  + Therefore, the peak is more affected by a\_ss
  + Inactivation state variable is not reduced to the steady-state value at the peak time
  + **How to enforce this relationship during the optimization?**
* The decaying phase is dominated by the inactivation state
  + The activation state already reached the steady-state value at the very beginning
  + The remaining part of a current trace is dominated by the slowly changing inactivation state variable
* i\_ss determines the thickness of the tail
* tau\_i stretches or contracts the trace
* Current trace has a sigmoidal activation phase and exponential decaying phase

|  |  |
| --- | --- |
| A screenshot of a cell phone  Description automatically generated | A screenshot of a cell phone  Description automatically generated |
| A screenshot of a cell phone  Description automatically generated |  |

[10] Default

|  |
| --- |
| Peak: 54.865764 | Tau: 106.331899 | Peak time: 51.973156| a\_peak: 0.997215 | i\_peak: 0.964125 | ass: 0.999148 | iss: 0.000001 | tau\_a: 0.316256 | tau\_i: 54.043738  alpha\_a = 3.1593 / beta\_a = 0.0026934 / alpha\_i = 1.7465e-08 / beta\_i = 0.018504  A screenshot of a cell phone  Description automatically generated |