Models of VOR learning in MHC knockout mice

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Abstract

We see if we can model VOR gain increase and decrease learning in mice with a knockout in MHC as well as wild type.

Contents

1 The setup

sec:setup

1.1 Models of synapses

sec:synapse

We make the following assumptions:

- There are N identical synapses with M internal functional states.
- The states of different synapses are independent of each other.
- The synapses that are eligible for plasticity are chosen randomly.
- The potentiating/depressing plasticity event timings are distributed as Poisson processes with rates $rf^{\text{pot/dep}}$, where $f^{\text{pot}} + f^{\text{dep}} = 1$.

- Potentiation and depression are described by Markov processes with transition probabilities $\mathbf{M}^{\text{pot/dep}}$.

- The synaptic weights of the internal states are given by the column vector $\mathbf{w}$. This can only take two values that we can call ± 1.

The independence and identicalness of synapses means that the state of the system can be completely described by the probability distribution of the internal states, the row vector $\mathbf{p}(t)$.

The evolution of this probability is described by a forgetting matrix, $\mathbf{W}^{\text{F}}$:

$$\frac{\mathrm{d}\mathbf{p}(t)}{\mathrm{d}t} = r\mathbf{p}(t)\mathbf{W}^{\text{F}}, \qquad \mathbf{W}^{\text{F}} = f^{\text{pot}}\mathbf{M}^{\text{pot}} + f^{\text{dep}}\mathbf{M}^{\text{dep}} - \mathbf{I}. \tag{1}$$

eq:evolve

Eventually, this will settle into the equilibrium distribution:

$$\mathbf{p}^{\infty}\mathbf{W}^{\text{F}} = 0. \tag{2}$$

eq:eqprob

With only two possible synaptic weights, the distribution of synaptic weights is completely described by the mean, $\mathbf{p}(t)\mathbf{w}$.

1.2 Model of VOR learning experiment

ec:learning

Training the animal will not change the internal dynamics of a synapse under potentiation or depression. It will change the environment, will lead to a change in how often potentiation and depression occur. It could be manifested in a change in which synapses are potentiated/depressed, but this could not be captured in this type of model. We will model this by changing $f^{\text{pot/dep}}$, leaving r and $\mathbf{M}^{\text{pot/dep}}$ unchanged.

The untrained case will be described by $f^{\text{pot}} = f_0^{\text{pot}}$. Gain-increase training will be described by $f^{\text{pot}} = f_{\text{inc}}^{\text{pot}} < f_0^{\text{pot}}$, and gain-decrease training will be described by $f^{\text{pot}} = f_{\text{dec}}^{\text{pot}} < f_0^{\text{pot}}$. Note that the forgetting matrix (1) and the equilibrium distribution (2) depends on f^{pot}, which we will indicate with subscripts.

Before training, the synaptic distribution will in equilibrium with f_0^{pot}. During gain-increase training, it will evolve according to (1) with $f_{\text{inc}}^{\text{pot}}$:

$$\mathbf{p}(t) = \mathbf{p}_0^{\infty} \exp\left(rt\mathbf{W}_{\text{inc}}^{\text{F}}\right). \tag{3}$$

eq:nopre

On the other hand, if the gain-increase training follows gain-decrease pre-training for some time period, t_{pre}:

$$\mathbf{p}(t) = \mathbf{p}_0^{\infty} \exp\left(rt_{\text{pre}}\mathbf{W}_{\text{dec}}^{\text{F}}\right) \exp\left(r(t - t_{\text{pre}})\mathbf{W}_{\text{inc}}^{\text{F}}\right). \tag{4}$$

eq:withpre

We will describe the effect of training by the decrease in mean synaptic weight:

$$L(t) = \left(\mathbf{p}(0) - \mathbf{p}(t)\right)\mathbf{w}. \tag{5}$$

eq:learning

The behavioural output (VOR gain) will be some non-linear function of the synaptic weights, so the best we can hope for is to reproduce qualitative features of the experiment.

The MHC knockout has a lower threshold for depression. We can model this by changing $\mathbf{W}^{\text{dep}}_{\text{WT}}$ to $\mathbf{W}^{\text{dep}}_{\text{D}^{\text{b}}\text{K}^{\text{b}}\text{-/-}}$, which should have larger matrix elements.

QUESTION: Should $f^{\text{pot}}_{\text{WT}} = f^{\text{pot}}_{\text{D}^{\text{b}}\text{K}^{\text{b}}\text{-/-}}$?

If they are equal, this would change the mean synaptic weight in equilibrium. This seems like it would affect the ability of the network to perform its function, and one might expect adaptation to the environment to produce an equilibrium state that has the same performance. In any case, if the synaptic weights are different, the electrical activity will be different, and there will be no reason to expect the same statistics for potentiation or depression.

On the other hand, one could imagine adjusting $f^{\text{pot}}_{\text{WT}}$ and $f^{\text{pot}}_{\text{D}^{\text{b}}\text{K}^{\text{b}}\text{-/-}}$ so that $\mathbf{p}^{\infty}_{\text{WT}}\mathbf{w} = \mathbf{p}^{\infty}_{\text{D}^{\text{b}}\text{K}^{\text{b}}\text{-/-}}\mathbf{w}$. But, now that the synaptic weights are the same, the electrical activity will be the same, and there will be no reason to expect different statistics for potentiation or depression. If we did this for the multistate or two-state models, we'd remove all differences between the wild-type and $\text{D}^{\text{b}}\text{K}^{\text{b}}$-/- knockout.

2 Simulations

sec:sims

2.1 Models and parameters

We will look at three different models, the cascade model (see [1] and Figure 1a), the multistate model (see [2, 3] and Figure 1b) and the two-state model (which can be thought of as a special case of the previous two, see Figure 1c).

For the cascade model, we will use the same value for the parameter x (which controls the decay of transition rates, see [1]) for potentiation and depression in the wild-type as well as potentiation in the $\text{D}^{\text{b}}\text{K}^{\text{b}}$-/- mutant. We will use a larger value for x for depression in the $\text{D}^{\text{b}}\text{K}^{\text{b}}$-/- mutant.

For the multistate and two state models, we will use the same value for the transition probabilities, q for potentiation and depression in the wild-type as well as potentiation in the $\text{D}^{\text{b}}\text{K}^{\text{b}}$-/- mutant. We will use a larger value for q for depression in the $\text{D}^{\text{b}}\text{K}^{\text{b}}$-/- mutant.

In each case, we set $f^{\text{pot}}_0 = \frac{1}{2}$, $f^{\text{pot}}_{\text{inc}} = f^{\text{pot}}_0 + \Delta f$ and $f^{\text{pot}}_{\text{dec}} = f^{\text{pot}}_0 - \Delta f$. The values of all these parameters are listed in Table 1.

2.2 Results

sec:results

The features of the actual experiments that we'd like to capture are:

- Without pre-training, gain-increase learning is significantly faster in the wild-type than in the mutant.
- Gain-decrease pre-training is slightly faster in the wild-type, but not significantly so.

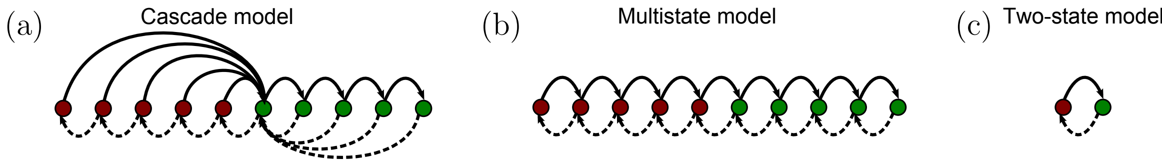

Figure 1: Transition probabilities for different models. (a) In the cascade model, the transition probabilities decay geometrically with a parameter x (see [1]). (b) In the multistate model the transition probabilities for potentiation/depression are all equal and it is parameterised by these two values. (c) The two-state model is parameterised by the two transition probailities. fig:models

Model	# states	pot,WT dep	D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- dep	Δf	rt_{train}	rt_{pre}
Cascade	10	$x = 0.25$	$x = 0.33$	-0.3	50	50
Cascade	10	$x = 0.25$	$x = 0.33$	-0.3	50	150
Multistate	10	$q = 0.6$	$q = 0.8$	-0.1	50	50
Multistate	10	$q = 0.6$	$q = 0.8$	-0.4	20	20
Two-state	2	$q = 0.4$	$q = 0.8$	-0.1	5	5

Table 1: Parameters used in simulations. tab:params

- After pre-training, gain-increase learning is significantly faster in the mutant than in the wild-type.
- For the wild-type, gain-increase learning is significantly faster without pre-training than with it.
- For the mutant, gain-increase learning is significantly faster with pre-training than without it.

We will try to gain some analytic insight to some of these models by looking at the slope of the learning curve at the start of gain-increase training. This is proportional to the net-flux between the $\mathbf{w} = +1$ states and the $\mathbf{w} = -1$ states, measuring using the transition probabilities for gain-increase but the equilibrium distribution for either untrained or gain-decrease, assuming that pre-training lasts long enough to reach the equilibrium distribution for gain-decrease.

2.2.1 Cascade

sec:cascade

2.2.2 Multistate

multistate

Consider the general uniform multistate model. Then the equilibrium distribution is given by

$$\mathbf{p}_i^\infty = \frac{1-\alpha}{1-\alpha^M}\,\alpha^{i-1}, \qquad \text{where} \quad \alpha = \frac{f^{\mathrm{pot}} q^{\mathrm{pot}}}{f^{\mathrm{dep}} q^{\mathrm{dep}}}. \tag{6}$$

eq:mutltieq

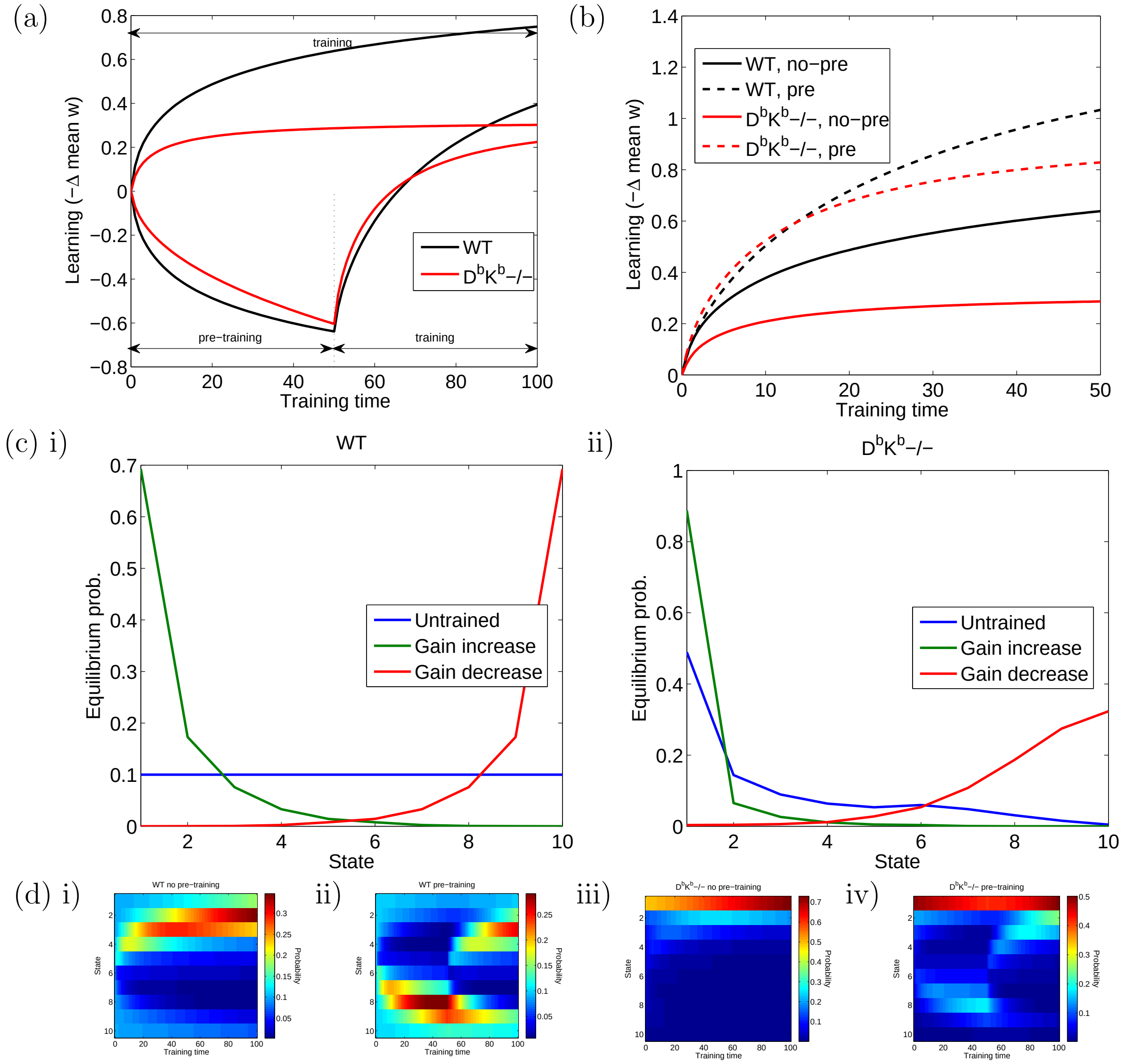

Figure 2: Simulation results for cascade model with short pre-training ($rt_{\mathrm{pre}} = 50$). (a) Learning curves for wild-type and D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout with and without pre-training. (b) Learning curves restricted to gain-increase training. (c) Equilibrium distributions without training or with gain-increase/decrease training for (ci) wild-type and (cii) D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout. (d) Evolution of probability distributions for (didii) wild-type and (diiidiv) D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout without (di,diii) and with (dii,div) pre-training. fig:cascade_

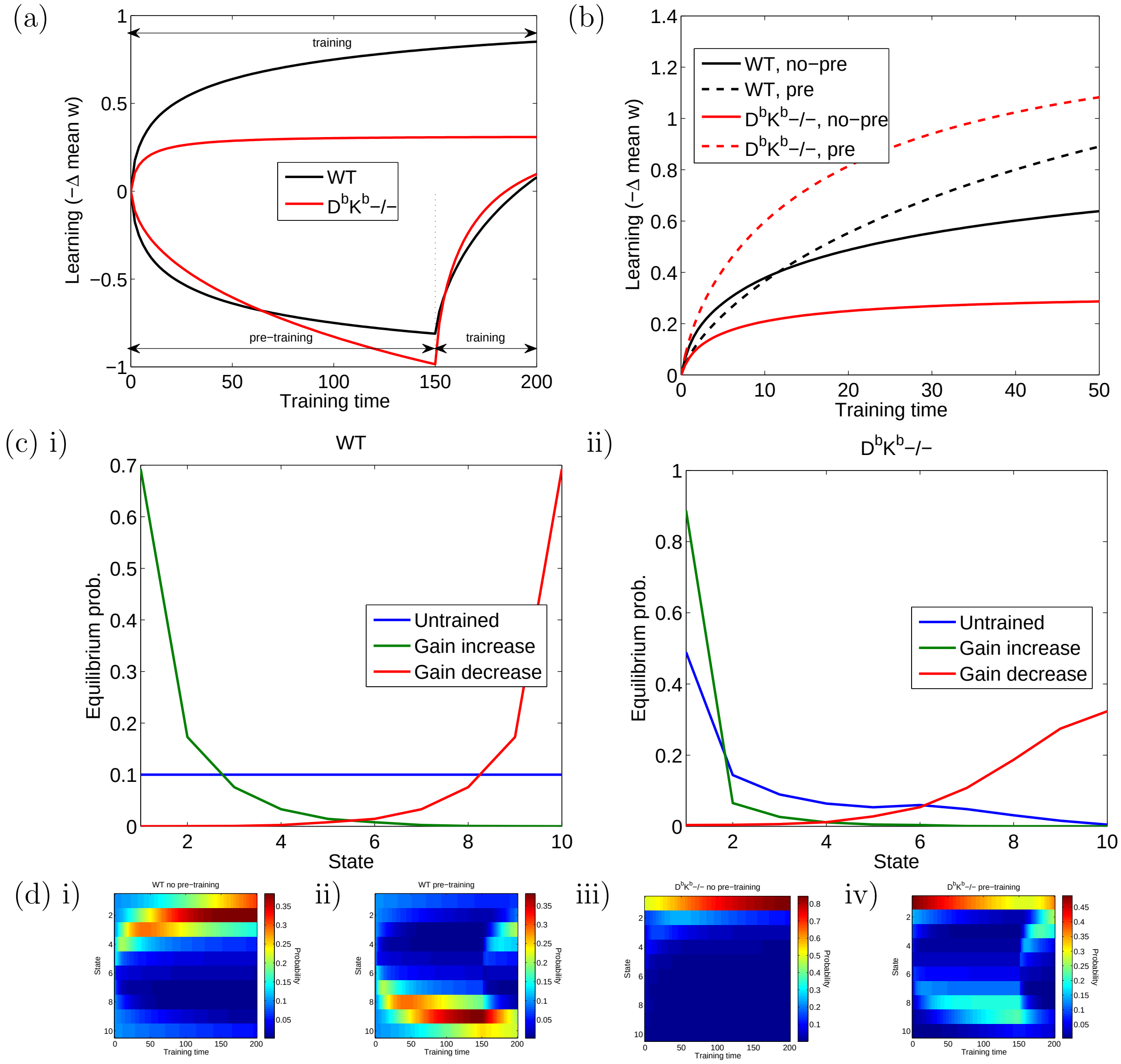

Figure 3: Simulation results for cascade model with long pre-training ($rt_{\mathrm{pre}} = 150$). (a) Learning curves for wild-type and $\mathrm{D^bK^b}$-/- knockout with and without pre-training. (b) Learning curves restricted to gain-increase training. (c) Equilibrium distributions without training or with gain-increase/decrease training for (ci) wild-type and (cii) $\mathrm{D^bK^b}$-/- knockout. (d) Evolution of probability distributions for (didii) wild-type and (diiidiv) $\mathrm{D^bK^b}$-/- knockout without (di,diii) and with (dii,div) pre-training.

fig:cascade_

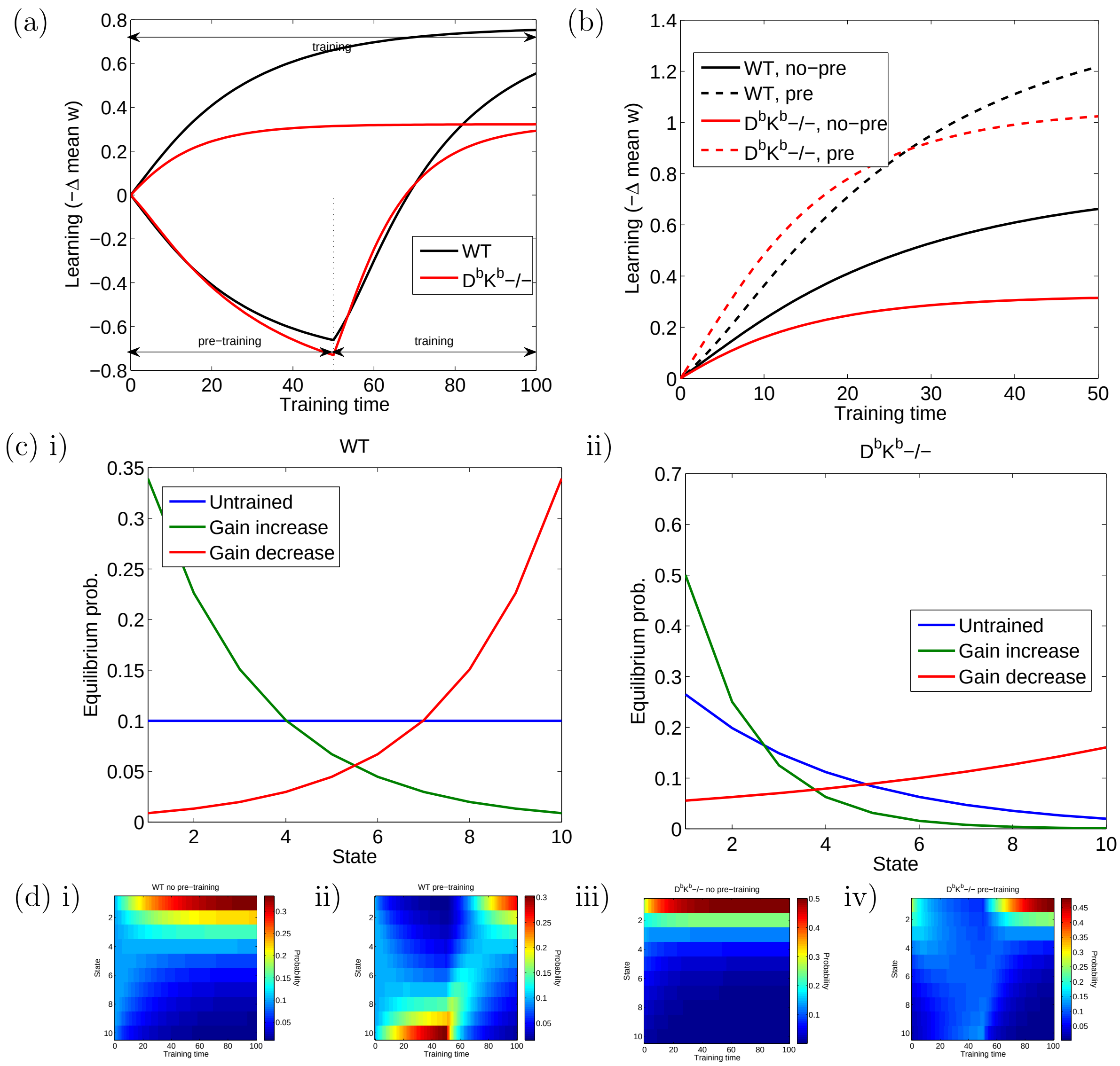

Figure 4: Simulation results for multistate model with weak training ($\Delta f = -0.1$). (a) Learning curves for wild-type and D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout with and without pre-training. (b) Learning curves restricted to gain-increase training. (c) Equilibrium distributions without training or with gain-increase/decrease training for (ci) wild-type and (cii) D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout. (d) Evolution of probability distributions for (didii) wild-type and (diiidiv) D$^{\mathrm{b}}$K$^{\mathrm{b}}$-/- knockout without (di,diii) and with (dii,div) pre-training. fig:multista

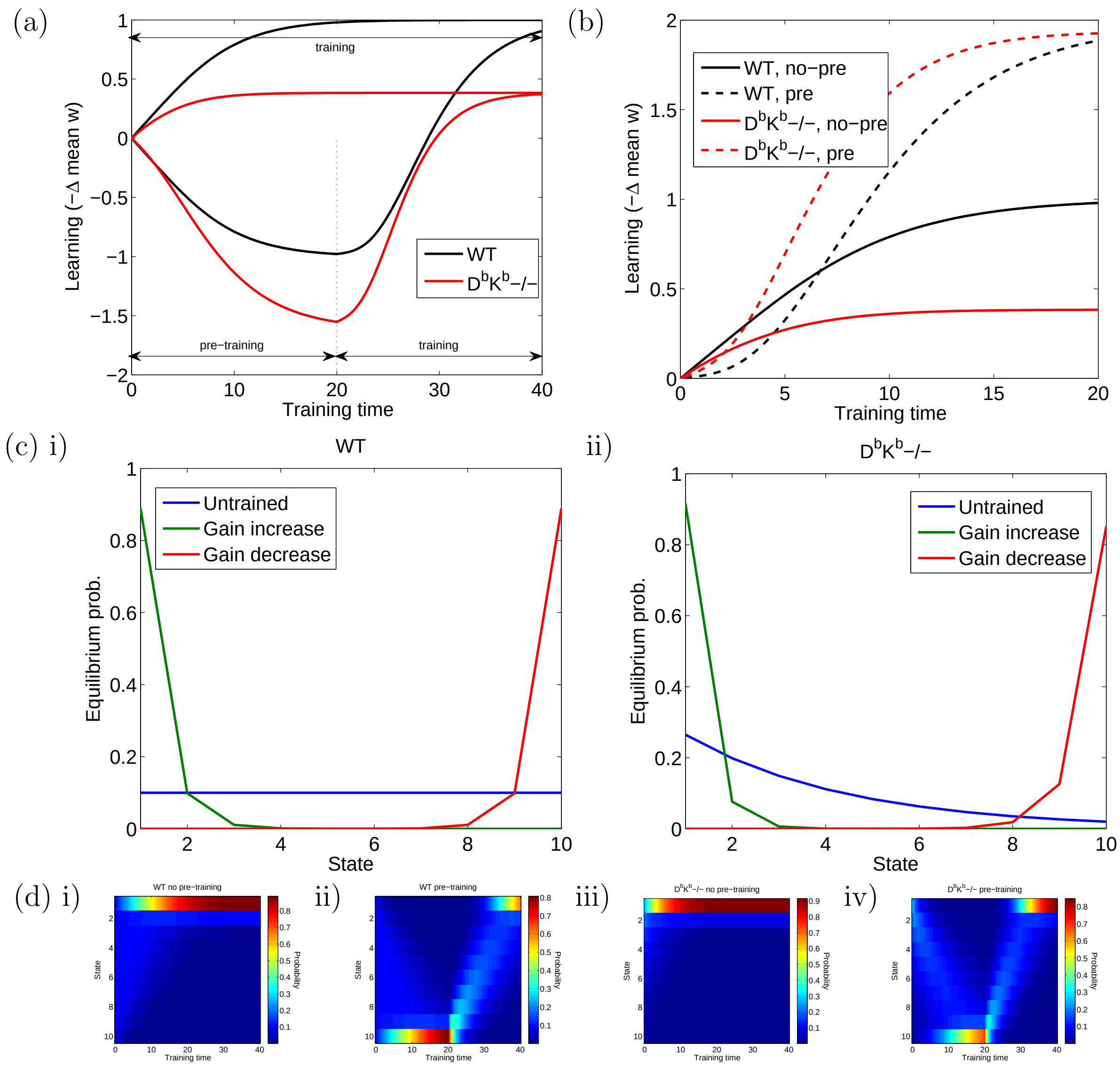

Figure 5: Simulation results for multistate model with strong training ($\Delta f = -0.4$). (a) Learning curves for wild-type and D^bK^b-/- knockout with and without pre-training. (b) Learning curves restricted to gain-increase training. (c) Equilibrium distributions with/without gain-increase/decrease training for (ci) wild-type and (cii) D^bK^b-/- knockout. (d) Evolution of probability distributions for (didii) wild-type and (diiidiv) D^bK^b-/- knockout without (di,diii) and with (dii,div) pre-training. fig:multista

If we take the limit $\alpha \to 1$, this becomes $\frac{1}{M}$.

The net-flux from the $\mathbf{w} = +1$ states to the $\mathbf{w} = -1$ states is:

$$\Phi = \mathbf{p}^{\infty}_{M/2+1} f'^{\text{dep}} q^{\text{dep}} - \mathbf{p}^{\infty}_{M/2} f'^{\text{pot}} q^{\text{pot}} = \frac{1-\alpha}{1-\alpha^M}\, \alpha^{M/2-1} \left(\alpha - \alpha'\right) f'^{\text{dep}} q^{\text{dep}}, \tag{7}$$ eq:multiflux

where primed values correspond to the new value of f^{pot}.

First, consider the wild-type, for which $q^{\text{pot}} = q^{\text{dep}} = q$. Without pre-training:

$$\Phi = -\frac{2\Delta f q}{M}, \tag{8}$$ eq:multiWTno

where it's worth remembering that $\Delta f < 0$. With pre-training:

$$\begin{aligned} \Phi &= 16(\Delta f)^2 q\, \frac{(1-2\Delta f)^{M/2-1}(1+2\Delta f)^{M/2-1}}{(1-2\Delta f)^M - (1+2\Delta f)^M} \\ &= -\frac{4\Delta f q}{M} + \mathcal{O}(\Delta f)^2. \end{aligned} \tag{9}$$ eq:multiWTpr

So, we see that pre-training will speed up learning when Δf is small. On the other hand, if Δf is close to $-\frac{1}{2}$, pre-training will initially slow down learning a lot.

Now, consider the mutant, for which $q^{\text{pot}} = \beta q^{\text{dep}} = q$, $\beta < 1$. Without pre-training:

$$\Phi = -\frac{2(1-\beta)\beta^{M/2-1}\Delta f q}{1-\beta^M}. \tag{10}$$ eq:multiKOno

With pre-training:

$$\Phi = -4\Delta f q\, \frac{(1-2\Delta f) - \beta(1+2\Delta f)}{(1-2\Delta f)^M - \beta^M(1+2\Delta f)^M}\, \beta^{M/2-1}(1-2\Delta f)^{M/2-1}(1+2\Delta f)^{M/2-1}. \tag{11}$$ eq:multiKOpr

sec:binary

2.2.3 Two-state

This model can be solved exactly:

$$\mathbf{p}^{\infty} = \frac{\left(f^{\text{dep}} q^{\text{dep}}, f^{\text{pot}} q^{\text{pot}}\right)}{\lambda}, \qquad \mathbf{p}(t) = \mathbf{p}^{\infty} + (\mathbf{p}(t) - \mathbf{p}^{\infty})\mathrm{e}^{-\lambda r t}, \\ \text{where} \quad \lambda = f^{\text{pot}} q^{\text{pot}} + f^{\text{dep}} q^{\text{dep}}. \tag{12}$$ eq:binarysol

But it is easier to just substitute $M = 2$ into the formulae in §2.2.2. In this case, the initial rate of change encapsulates the whole solution, as there is only a single exponential decay.

First, consider the wild-type, for which $q^{\text{pot}} = q^{\text{dep}} = q$. Without pre-training:

$$\Phi = -\Delta f q, \tag{13}$$ eq:binWTnopr

where it's worth remembering that $\Delta f < 0$. With pre-training:

$$\Phi = -2\Delta f q. \tag{14}$$ eq:binWTpre

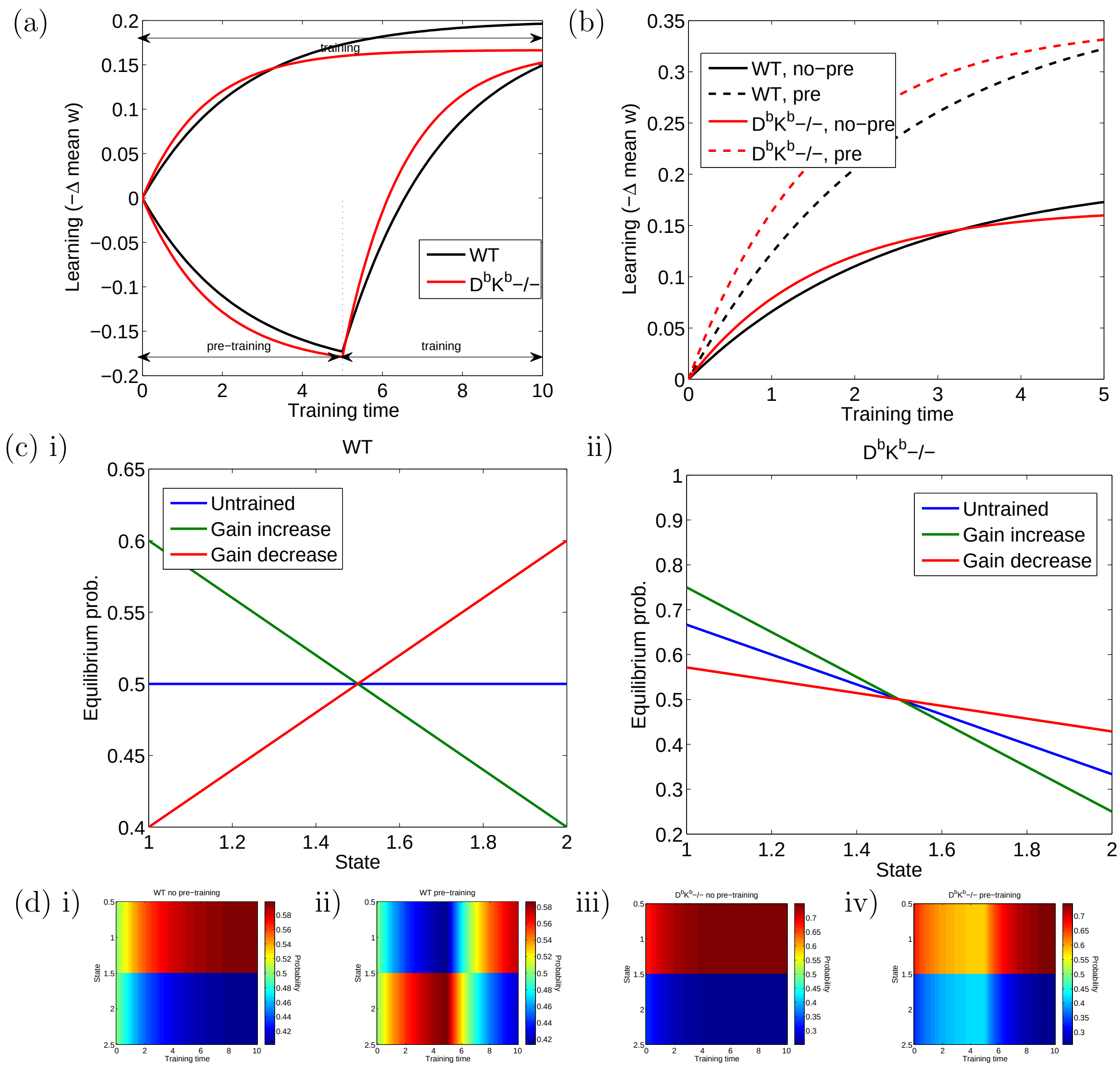

Figure 6: Simulation results for two-state model. (a) Learning curves for wild-type and D^bK^b-/- knockout with and without pre-training. (b) Learning curves restricted to gain-increase training. (c) Equilibrium distributions without training or with gain-increase/decrease training for (ci) wild-type and (cii) D^bK^b-/- knockout. (d) Evolution of probability distributions for (didii) wild-type and (diiidiv) D^bK^b-/- knockout without (di,diii) and with (dii,div) pre-training. fig:binary_r

So, we see that pre-training will always speed up learning.

Now, consider the mutant, for which $q^{\text{pot}} = \beta q^{\text{dep}} = q$, $\beta < 1$. Without pre-training:

$$\Phi = -\frac{2\Delta f q}{1+\beta}, \tag{15}$$

`eq:binKOnopr`

which is always larger that (13). With pre-training:

$$\Phi = -4\Delta f q \, \frac{(1-2\Delta f) - \beta(1+2\Delta f)}{(1-2\Delta f)^2 - \beta^2(1+2\Delta f)^2}. \tag{16}$$

`eq:binKOpre`

References

`2005cascade` [1] S. Fusi, P. J. Drew, and L. F. Abbott, "Cascade models of synaptically stored memories," *Neuron* **45** (Feb, 2005) 599–611, `PubMed:15721245`.

`94learning` [2] D. J. Amit and S. Fusi, "Learning in neural networks with material synapses," *Neural Computation* **6** (1994) no. 5, 957–982.

`multistate` [3] S. Fusi and L. F. Abbott, "Limits on the memory storage capacity of bounded synapses," *Nat. Neurosci.* **10** (Apr, 2007) 485–493, `PubMed:17351638`.